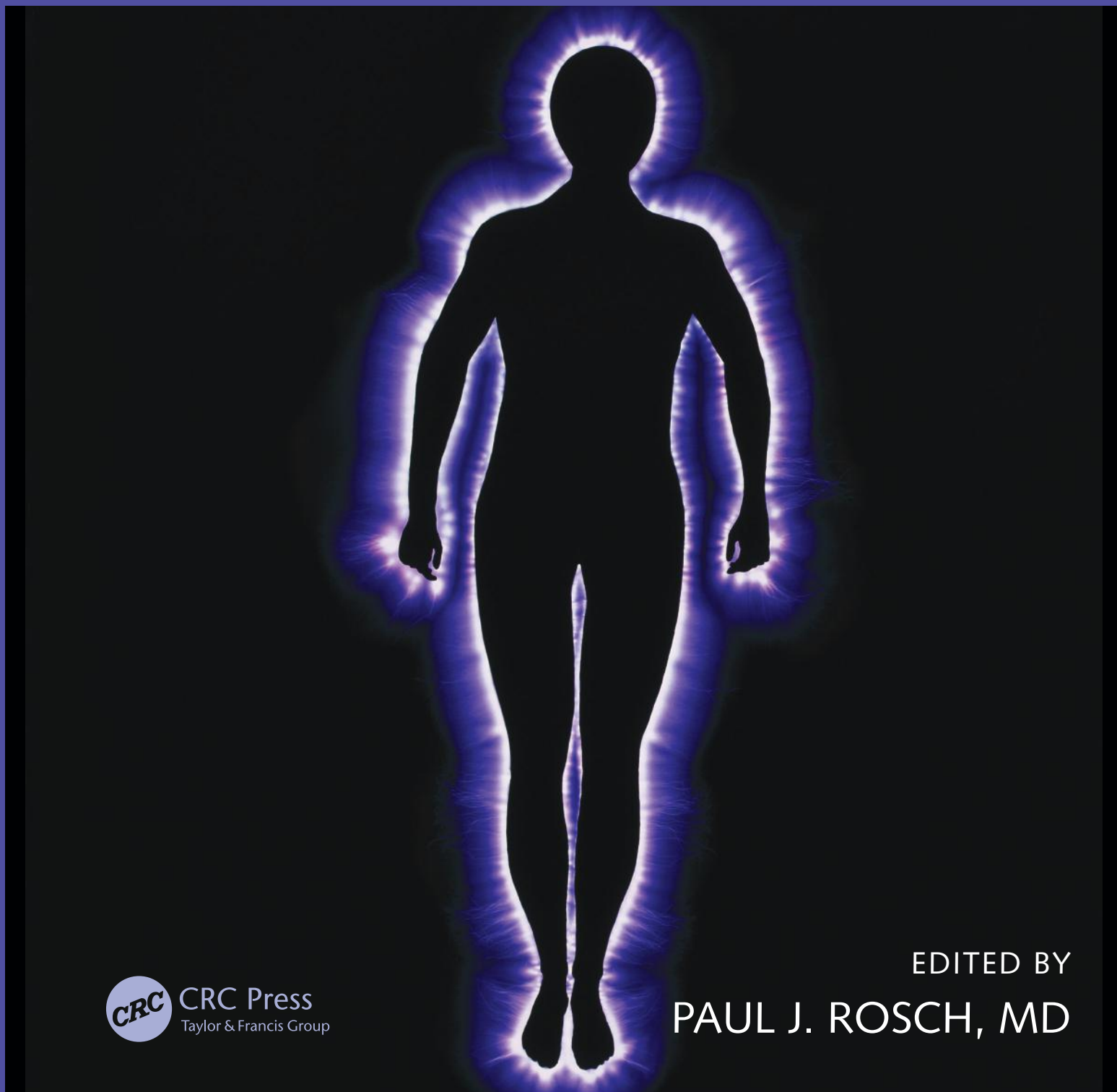
BIOELECTROMAGNETIC AND SUBTLE ENERGY MEDICINE

SECOND EDITION



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EDITED BY
PAUL J. ROSCH, MD

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This book is dedicated to Marguerite, my late wife, without whose constant support I could not have embarked on this venture.

Contents

SECTION VII Environmental Influences

SECTION VIII Mechanisms of Action and Hypotheses

SECTION IX Electromagnetic Field Safety and Hazards

SECTION X Looking Back, the Current FDA Fiasco, and a Peek into the Future

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Section I

Preface

1 Preface: Why and How This Book Was Assembled

*Paul J. Rosch**

CONTENTS

WHY THE NEED FOR THIS SECOND EDITION?

There have been so many dramatic advances since the publication of the first edition more than a decade ago that chapters must be updated and new ones added for it to continue to be the gold standard in this field. Certain important chapters have been reproduced because their authors are no longer with us including:

- Therapeutic Applications of Nonthermal Electromagnetic Fields—W. Ross Adey
- EMFs: The Interface between Matter and Function—Jacques Benveniste
- Is There an Electrical Circulatory System?—Björn Nordenström
- Magneto-Metabolic Therapy for Advanced Malignancy and Cardiomyopathy—Demetrio Sodi Pallares

Also reproduced are William Tiller's state of the art "Electromagnetism Versus Bioelectromagnetism" and "Subtle Energies and Their Roles in Bioelectromagnetic Phenomena" because they are so pertinent to the subtle energy focus of this volume.

SAFETY CONCERNS OVER CELL PHONES AND ELECTROMAGNETIC POLLUTION

There were topics we would have liked to discuss but could not because of space constraints and/or the inability to provide accurate and unbiased information. The most important issue was the adverse health effects of cell phones, which I tried to explain in the Preface to the first edition as follows:

> Another issue that has caused wariness about bioelectromagnetic therapies are safety concerns about possible increased risk of certain malignancies and birth defects resulting from proximity to high power lines, cell phones, microwave ovens and electric blankets. It is not surprising that electromagnetic fields, like many other therapies can be two-edged swords. For example, all the modalities we use to treat cancer, including radiation, chemotherapy and hormonal interventions can also cause cancer. Such effects may depend upon dosage, duration of exposure, genetic and other influences. It is not likely that any clear conclusion about adverse electromagnetic effects can be reached until more information has been obtained from long term studies that focus on these factors. For this reason, we have refrained from participating in this debate other than to devote a chapter on the importance of dosimetry and to emphasize that no such adverse effects have been observed or seem likely in the therapies presented in this book. Indeed, those that have been proposed and implemented by Demetrio Sodi Pallares and Björn Nordenström and confirmed by others have shown stunning success in treating various malignancies. Many of the chapters in this book are based on presentations at the annual International Congress on Stress over the past decade or so and additional information on these events can be obtained at www.stress.org

The massive Interphone study involving scientists from 16 study centers in 13 countries that began in 1999 was designed to determine whether cell phones posed any health hazards when it concluded in 2006. However, there was so much disagreement and confusion, that the final results, which were not published until 2010, shed more heat than light on the subject. The only conclusion reached after spending over $24 million evaluating some 13,000 participants was that this rancorous controversy will continue.

There has been an explosion in cell phone sales over the past decade, and there are now over 7.3 billion, or more than the number of people on the planet. There are 100 countries where the number of cell phones exceeds the population, Russia, has 1.8 times more active cell phone accounts than people and Brazil has 1.2 times as many. In addition, there has been a steady proliferation of electromagnetic pollution from thousands of communication satellites in outer space, millions of cell phone towers and antennas emitting radio-frequency signals, WiMax towers that can cover 3000 square miles, Wi-Fi in homes and offices, and Bluetooth devices. There is also exposure to dirty electricity from transformers,

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microwave ovens and other common household appliances as well as lighting fixtures. The above issues are thoroughly and objectively discussed by leading authorities in the following chapters: "Electromagnetic Field Effects on Cells and Cancer Risks from Mobile Communication" (Igor Belyaev), "Mobile and Cordless Phone Use and Brain Tumor Risk" (Lennart Hardell and Michael Carlberg) and "Dirty Electricity" (Samuel Milham). Most of us are oblivious to this 24/7 bombardment, although it is clear that some individuals who are extremely electrosensitive have objective proof of their symptoms. In other instances, complaints of headaches, dizziness, fatigue, or difficulty sleeping, that were attributed to stress or aging, have vanished when the electromagnetic field (EMF) source has been removed. This subject is comprehensively reviewed in "Electrosensitivity: Sources, Symptoms, and Solutions" by Andrew Tressinger and Michael Bevington.

Quis Custodiet Ipsos Custodes? (Who Is Watching The Watchman?)

An equally important topic not previously addressed is the flawed regulatory system for evaluating the safety of electrical devices in the U.S. Most standards are established by the wireless industry, which is like having the fox guard the chicken coop. The only two enforceable EMF emissions standards are for microwave ovens set by the Food and Drug Administration (FDA) and for cell phones, which are established by the Federal Communications Commission (FCC). However, neither of these agencies monitor possible health effects or compliance with standards. The Russian safety limit for microwave radiation is 0.01 mW/cm^2, but our current limit established in 1993 is 1 mW/cm^2, 100 times higher. Prior to that, it was a thousand times higher! Although cell phones emit radiofrequency energy in the microwave range, there was no safety testing prior to their availability in 1983. In point of fact, cell phones are the only radiation emitting devices that have ever been sold without pre-market safety testing.

The reason for this is that the FCC contracted to have the safety standards written by an engineering society with strong ties to telecommunication and cell phone companies and there was scant or no input from physicians or health authorities. The FCC has little expertise in biology, therefore, it accepted as gospel that the only harm that could come from cell phone radiofrequencies would be from a thermal or heating effect, and as there was no evidence of this, there was no need for any objective safety testing. Nor are things likely to improve with the recent appointment of Thomas Wheeler as FCC Commissioner. Wheeler chaired the Cellular Telecommunications and Internet Association (CTIA), which represents the interests of the U.S. wireless industry and includes Verizon, AT&T, Sprint, and T-Mobile. He has numerous close industry ties, which may explain his ability to raise over $1 million for Obama's presidential campaign.

Preserving the status quo is worth billions of dollars, and anyone who questioned the entrenched doctrine that nonthermal radiation was perfectly safe, was subjected to severe retribution. Ross Adey was the first to prove that this dogma was erroneous, and later warned there may be no lower limit for EMF effects on health. Despite his stature in the field, he was one of these victims, as was Dr. Robert Becker, who was twice nominated for the Nobel Prize. In his 1985 *The Body Electric* and other books and papers, Becker emphasized the dangers of electropollution and particularly living near overhead high power transmission lines. As a result, his laboratory was shut down because funding suddenly disappeared and he was persecuted by powerful vested interests that he described in detail in the last chapter of *The Body Electric,* entitled "Postscript: Political Science Part One." Nevertheless, his repeated protests were largely responsible for the New York State power line project directed by David Carpenter, which convincingly confirmed prior studies linking these high-voltage lines to childhood leukemia. Other examples of refusal to accept proof of harmful effects of cell phone and other EMF pollution by regulatory authorities can be found in the cutting edge chapters by Lennart Hardell, Igor Belayev, and Samuel Milham previously noted.

The FDA has similarly been criticized because its drug approval process is heavily influenced by powerful pharmaceutical companies, whose clout extends to Congress and academia. According to the following March 20, 2014, *Washington Post* article:

> Based on critical information gathered from hundreds of leaked emails, pharmaceutical companies have doled out hundreds of thousands of dollars over the years to attend private meetings with the FDA, many of which were geared towards the regulation and approval of painkiller drugs. Drug companies would reportedly shell out upwards of $25,000 or more per meeting to have their voices heard, a small price to pay for direct access to the $9 billion American painkiller market.
>
> According to reliable sources, officials from both the FDA and the U.S. National Institutes of Health (NIH) would regularly meet with pharmaceutical representatives in private to discuss regulatory protocols, co-write scientific papers and collaborate on various ways to help streamline the drug approval process. And the only parties who actually paid to attend such meetings were the drug companies, a fact that one official from the NIH expressed serious concerns about in an email, referring to the whole scheme as a "pay to play" process.

Industry employees and consultants frequently sit on advisory panels despite a ban on anyone with a conflict of interest, and in other instances, the recommendations of such panels may be rejected if they are not in favor of a manufacturer's new drug. This also applies to the Center for Devices and Radiological Health (CDRH), which has the responsibility of approving and classifying medical devices based on an objective assessment of safety and efficacy. CDRH's lack of transparency and arbitrary and capricious decisions triggered several Congressional investigations, especially after whistleblowers were fired because they documented and reported various abuses. I personally witnessed some of these at a docket hearing to reclassify cranial electrotherapy stimulation (CES) devices, which was more of a "kangaroo court." Despite a superb safety record for over three decades and the fact that they do not require a prescription in other

countries, it was obvious that a decision had already been made, as valuable testimony and comments in support of making a change was not allowed.

Studies have shown that CES is effective for posttraumatic stress disorder (PTSD), and unlike drugs, has no adverse side effects or addictive tendencies. This is a threat to pharmaceutical companies that do not want to lose the hundreds of millions of dollars from the VA and Armed Services for products that are not only useless, but many feel may be contributing to the rising rates of suicides in veterans with PTSD not related to combat, but rather difficulty in adjusting to civilian life and dealing with bureaucratic bungling. Further details on the flawed FDA approval and classification process can be found in the chapter by Kirsch and Kirsch.

The first edition of *Bioelectromagnetic Medicine* was limited to 900 pages as any additional chapters would have necessitated two volumes of this 10-inch tall book and made its price prohibitive. This space restriction was an even more serious problem when attempting to draw up a tentative Table of Contents for this update, as deciding what to include from the 50 chapters in the first edition and select from among the many new contributions was difficult and often exasperating. I had planned to concentrate on breakthrough advances and background information that would be of particular value for clinicians and health care practitioners as opposed to basic science researchers. I used this benchmark to whittle away my list and gave the highest priority to chapters that would appeal to both groups. As indicated previously, those from Ross Adey, Jacques Benveniste, William Tiller, Björn Nordenström, and Demetrio Sodi Pallares best satisfied these criteria and they have been reproduced as they originally appeared.

I used the same standards to decide which chapters to update. Brain stimulation seemed to attract the greatest clinical interest with over 10,000 PubMed transcranial magnetic stimulation (TMS) citations and another 1000 dealing with transcranial direct current stimulation (tDCS). What was even more impressive were the 600+ registered clinical trials for TMS and 200+ for tDCS. There is also increased interest in other types of brain stimulation, such as CES, chronic deep brain stimulation, and vagal stimulation. We had devoted chapters to all of the above modalities from leading authorities, all of whom have now provided updates, which include noninvasive vagus and trigeminal nerve stimulation, noninvasive deep brain stimulation, and the latest indications for rTMS. New chapters dealing with cranial ultrasound stimulation have also been added.

ACUPUNCTURE, HOMEOPATHY AND BIOLOGICAL OR EXCLUSION ZONE (EZ) WATER

Deciding what new chapters or topics to include was even more challenging because of the embarrassment of riches from which to choose. Space constraints had precluded any discussion of acupuncture, which is widely practiced throughout the world and has persisted for thousands of years. Acupuncture is based on the belief that an intangible and invisible energy called *Qi* (chi) circulates through the body in an orderly fashion through specific pathways (meridians) to maintain health. Illness occurs when the flow of *Qi* is blocked or there is a disturbance in the balance between its complementary *yin* and *yang* components. Similar forces are also thought to represent a "vital energy," "life force," or "spirit" in other cultures, such as *prana* (Hinduism), *mana* (Hawaii), *lüng* Tibetan Buddhism, and *ruah* (Hebrew).

Dynamic internal and environmental energies analogous to *Qi* have also resurfaced over the centuries in Western medicine. The medieval physician and alchemist, Paracelsus postulated that a vital force called *archeus* sustains life by utilizing the *vis medicatrix naturae* (healing power of nature). Isaac Newton, the seventeenth century mathematician-philosopher borrowed some of these ideas in his concept of a mysterious cosmic "aether" that pervaded all space. Two centuries later, Franz Mesmer postulated an invisible "universal fluid" with magnetic properties that circulated throughout the body to provide energy. Disease occurred when this flow was blocked, but health could be restored by swallowing iron filings and applying magnets to the affected area. The magnets were soon discarded, as Mesmer believed the cures were due to the power of his "animal magnetism" when he touched or moved his hands over the patient. Other physicians subsequently proposed analogous healing energies, such as the Odic force of Baron Karl von Reichenbach, Oscar Brunler's biocosmic energy, and Wilhelm Reich's orgone. Although all of these disappeared, followers of Mesmer were responsible for developing hypnotherapy, osteopathy and chiropractic as professions, as well as Christian Science, which favors faith healing rather than drugs.

In contrast, acupuncture and traditional Chinese medicine have not only stood the test of time, but are experiencing a resurgence of interest, especially in the U.S. Some of the reasons for this are explained in "Basic Science and Evidence-Based Support for Acupuncture: The Crucial Importance and Biology of Acupuncture Points" by Richard Niemtzow, Editor of *Medical Acupuncture*. Further support comes from "Bioelectricity Circulation and Bioelectric Resonance Therapy: The Bridge Between Traditional Chinese and Western Medicine" by Yuling Wang and colleagues. Her research and therapy program had their roots in Björn Nordenström's theory of an electrical circulatory system and his success in treating metastatic lung and other malignancies. Nordenström's treatment protocol is still utilized for these and other disorders in China, as detailed in "Electrochemical Therapy of Tumors" by Jing-hong Li and Yuling Xin.

Homeopathy was created in 1796 by Samuel Hahnemann, a German physician, and is based on the premise that "*like cures like*;" 300 years earlier, Paracelsus wrote that "small doses of what makes a man ill also cures him" and homeopaths believe a substance that causes the symptoms of a disease in healthy people will cure sick people with similar symptoms. They accomplish this by administering highly diluted doses of anything that mimics the patient's complaints. Homeopathy quickly spread to other countries, and by 1900, the U.S. had 22 homeopathic medical schools, 100

homeopathic hospitals and 15,000 homeopathic practitioners (one in five medical doctors). However, like many other medical practices at the time, there was little regulation, and fraud was so frequent that the teaching of homeopathy was banned following the 1910 Flexner report, and homeopathic practitioners have been accused of quackery ever since. In contrast, hundreds of millions of people in more than 80 other countries now use homeopathy. It is part of the national health system in the UK, Germany, France, India, Pakistan, Sri Lanka, Brazil, and Mexico, and it is reimbursed in Switzerland and other countries, where homeopathic physicians are licensed after several years of training and passing an examination. There is no national licensure in the U.S., states have very different certification requirements, and although the FDA recognizes homeopathic prescriptions as medicines or drugs it does not evaluate them for safety or efficacy.

One reason for this may be that any active ingredients were so diluted they could not possibly have any effect, good or bad. Many feel strongly that homeopathy should be banned, and as recently noted in one prominent U.S. journal "Homeopathy is among the worst examples of faith-based medicine. These axioms of homeopathy are not only out of line with scientific facts but also directly opposed to them. If homeopathy is correct, much of physics, chemistry, and pharmacology must be incorrect." Last year, the new Government Chief Scientific Adviser and head of the Government Office for Science in the UK stated: "My view scientifically is absolutely clear: homoeopathy is nonsense, it is non-science. My advice to ministers is clear: that there is no science in homoeopathy. The most it can have is a placebo effect—it is then a political decision whether they spend money on it or not." This may seem strange, as the Royal Family has embraced homeopathy since 1830. Prince Charles is a fervent advocate, and stated to the World Health Organization that homeopathy was "rooted in ancient traditions that intuitively understood the need to maintain balance and harmony with our minds, bodies and the natural world."

I have gone into some detail about this since recent developments suggest that homeopathy may be effective, but for entirely different reasons. In 1988, Jacques Benveniste, a highly respected research scientist and senior director of the French medical research organization INSERM's Unit 200, reported in a study submitted to *Nature*, that white blood cells called basophils, which control the body's reaction to allergens, can be activated to produce an immune response by solutions of antibodies that have been diluted to such an extent that they contained none of these biomolecules. It appeared that the water molecules somehow retained a memory of the antibodies that they had previously been in contact with, so that a biological effect remained when the antibodies were no longer present. This "memory of water" study was published, but was prefaced with an editorial comment entitled "When to believe the unbelievable," which emphasized, "There is no objective explanation of these observations." and urged readers to "suspend judgement" until the results could be replicated.

Although homeopathy was not mentioned in the paper, it made international headlines, such as "Homeopathy finds scientific support," in *Newsweek*. Several teams of investigators claimed they were unable to replicate his results, the press ridiculed Benveniste and his laboratory at INSERM was shut down. He was later able to continue his research at DigiBio, a Paris-based company funded by homeopathy supporters, and proposed that biomolecules communicate by emitting low-frequency electromagnetic signals that are detected by receptors, much like radios tuned to a specific wavelength. He claimed he was able to record these signals digitally, and that by playing them back to cells in the absence of the molecules themselves he could reproduce their biochemical effect. As he later complained to me at our annual International Congress on Stress in Switzerland, others who had reproduced all of his findings were afraid to publish their results because they would be subjected to similar retribution.

Confirmation of Benveniste's results comes from Nobel Laureate Luc Montagnier, who has now shown that when a solution of a chemical compound such as a homeopathic remedy is sequentially diluted many times, electromagnetic signals of the original substance remain in the water and retain their original effects. This is not meant to be an endorsement of homeopathy, but simply to emphasize that, "High dilutions of something are not nothing. They are water structures which mimic the original molecules." He described Benveniste as a *"modern Galileo,"* as Galileo had also been persecuted and convicted of heresy for teaching that the earth revolved around the sun and was not the center of the universe. (It was not until 1992, almost 400 years later, that Galileo was officially vindicated by Pope John Paul II.) Brian Josephson, who received a Nobel Prize in Physics at age 33, agrees, noting, "Simple-minded analysis may suggest that water, being a fluid, cannot have a structure of the kind that such a picture would demand. But cases such as that of liquid crystals, which while flowing like an ordinary fluid can maintain an ordered structure over macroscopic distances, show the limitations of such ways of thinking." He went on to describe how many scientists today suffer from "pathological disbelief; that is, they maintain an unscientific attitude that is embodied by the statement 'even if it were true I wouldn't believe it.'"

Further support for the existence of structured or "biological" water with such properties, including the storage of energy, has been proposed and demonstrated by Mae-Wan Ho, Director of The Institute of Science and Society in London, in her chapter "Life is Water Electric." This is explained in much more detail by Gerald Pollack, Professor of Bioengineering at the University of Washington in Seattle in "Why Biological Water Differs from H_2O and Acts Like a Battery." Pollack has identified a fourth phase of water called exclusion zone (EZ) water, which is believed to be H_3O_2, and carries a negative charge that could explain how blood can circulate through thousands of miles of capillaries, some of which are smaller in diameter than the red blood cells that pass through them. It could also explain numerous other anomalies, such as why you sink in dry sand but can walk on wet sand near the water, or use it to build sand castles and sculptures because of its

adhesive properties. Why does water form droplets on some surfaces but not others? Why does a wave maintain its shape and gradually peter out but a tsunami wave can persist for a hundred miles or more? How can some lizards walk on water when their weight should make them sink? Gelatin desserts are mostly water, up to 99% in some cases, so why does it not leak out? Why do raindrops fall faster than they should? Why is ice usually slippery but sometimes sticky? Why does warm water freeze faster than cold water? Most things contract and become denser when they freeze. Water does the opposite, which is why ice floats on water. Yet, just prior to freezing, it expands and bursts pipes. How does water get from the roots to the top of a plant or a tall tree?

Others have long marveled at the mysteries of water. The Chinese sage Lao Tzu, called the "Father of Taoism," described it as follows in 600 BC:

> Water is fluid, soft, and yielding.
> But water will wear away rock, which is rigid and cannot yield.
> As a rule, whatever is fluid, soft, and yielding will overcome whatever is rigid and hard.
> This is another paradox: what is soft is strong.

Leonardo da Vinci wrote, "Water is the driving force of all Nature…. In rivers, the water that you touch is the last of what has passed and the first of that which comes; so with present time." Thus, the amount of water on earth and in our atmosphere, remains constant; there is never a drop more, never a drop less. All the water that will ever be is here, right now. Over four decades ago, Albert Szent-Györgyi, who received the Nobel Prize for discovering vitamin C, wrote:

> Water, the Hub of Life.
> Water is its mater and matrix, mother and medium.
> Water is the most extraordinary substance!
> Practically all its properties are anomalous, which enabled life to use it as building material for its machinery.
> Life is water dancing to the tune of solids.

This remarkable observation is now yielding some of its secrets due to the investigations of Pollack and others. With respect to homeopathy, a comprehensive update on its present status is provided in "Memory of Water and Law of Similars: Making Sense out of Homeopathy" by Shahram Shahabi, Professor, Cellular and Molecular Research Center; Urmia University of Medical Sciences, Urmia, Iran.

WHY WAS THIS EDITION'S TITLE CHANGED AND WHAT ARE SUBTLE ENERGIES?

In many respects, this volume is a tribute to Ross Adey and Jacques Benveniste, two good friends and pioneers who are no longer with us. Ross Adey was the first to show there were "biological windows" and that nonthermal energies could have significant physiological effects. Adey's chapter on "Potential Therapeutic Applications of Nonthermal Electromagnetic Fields: Ensemble Organization of Cells in Tissue as a Factor in Biological Field Sensing" for the first edition was the last paper he ever wrote and it is again the lead chapter of this one because of its importance. Benveniste's "memory of water" proposal led to a loss of funding and vicious persecution, which many believe contributed to his premature death a few months before the first edition was published. He did not live to see how he had stimulated others to confirm and extend his findings, his "A Fundamental Basis for the Effects of EMFs in Biology and Medicine: The Interface Between Matter and Function" will now be the fifth chapter. These will be followed by William Tiller's chapters "Subtle Energies and Their Roles in Bioelectromagnetic Phenomena" and "Electromagnetism versus Bioelectromagnetism" because they provide useful background information. He has contributed two new chapters updating his research on subtle energies, one of which is entitled "The Need for Quantitative Measurement Tools to Enhance Future Research Efforts on Human Intention and Human Consciousness Effects in Multidimensional Nature." If you think about that for a few seconds, as well as the chapters on acupuncture, homeopathy, and weird water, it is apparent that this volume deals with much more than bioelectromagnetic mechanisms. Some of the other new chapters that also led to changing the title to *Bioelectromagnetic and Subtle Energy Medicine*, include:

- The Energetic Heart: Biomagnetic Communication Within and Between People—Rolllin McCraty
- Science of Measuring Human Energy Fields: A Revolutionary Instrument to Reveal the Energy Fields of Humans and Nature—Konstantin Korotkov
- Subtle Electromagnetic Interactions in Living Things—Abraham Liboff
- Holistic Electromagnetic Therapy: The Seqex Approach—Adriano Gasperi et al.
- Human Brain Stimulation with Transcranial Ultrasound (TUS): Potential Applications for Mental Health—Joseph Sanguinetti et al.
- Influences of Space and Terrestrial Weather on Human Physiology and Pathology—Germaine Cornelissen et al.
- Medical Problems Arising from Solar Storms—Abraham Liboff
- The Global Coherence Initiative: Investigating the Dynamic Relationship Between People and Earth's Energetic Systems—Rollin McCraty and Annette Deyhle
- Biophysics of Earthing (Grounding) the Human Body—James L Oschman, Gaétan Chevalier, and Clinton Ober
- The Role of the Pineal in Modulating Subtle Energies—Leonard A. Wisneski
- Ion Cyclotron Resonance (Combined Magnetic Field) Applications in Medicine—Abraham R. Liboff

Tissue Resonance Interaction in the Diagnosis of Prostate and Other Tumors as well as Inflammatory Conditions—Clarbruno Vedruccio and Clara Ricci Vedruccio

MRI-Guided Focused Ultrasound: A Method for Noninvasive Surgery and Other Clinical Applications—P. Jason White and Ferenc A. Jolesz

Recent Developments in Bioelectromagnetic and Subtle Energy Medicine—James L. Oschman and Nora H. Oschman

Subtle (subtile in Old English) stems from s*ubtilis,* a Latin weaving term that is a contraction of the phrase s*ub (beneath) and téla (*the web). Subtle now generally refers to a material, remark or something that is very faint, delicate or difficult to discern. Its use in biology and medicine was popularized by Elmer Green, who founded The International Society for the Study of Subtle Energies and Energy Medicine (ISSSEEM) in 1989. A pioneer in biofeedback therapy at the prestigious Menninger Foundation, Elmer and his wife Alyce did extensive studies of yogis and healers who could perform supernatural feats. At one of our International Congresses on Stress in Switzerland in which Elmer gave his Hans Selye Award lecture, "The Detection and Measurement Of Subtle Energies," he demonstrated that a healer's energy could repeatedly produce changes of 80 volts or more in EEG tracings of an invisible subject seated 10 feet away in an enclosed and shielded booth. At another Congress, *Qigong* masters raised the temperature of water, changed the taste of scotch, and repelled anyone approaching them without any physical contact by focusing their *Qi* energy.

Conventional physics maintains that all the phenomena of the universe can be explained by four forces: the strong and weak nuclear forces, electro-magnetic and gravitational forces. William Tiller disputed this in a 1993 article titled "What Are Subtle Energies," which he defined as a "class of phenomena beyond the four fundamental energies that we already know and accept." His major objection was that the current model did not take into account mental powers, such as the remarkable *Qigong* feats described above, and remote viewing studies showing that "people can (a) perceive and accurately describe objects placed several miles away from them, (b) be given the longitude and latitude coordinates of a location on the Earth and accurately describe the terrain of that location even though it is thousands of miles away and (c) tune in to a specific individual and view a remote locality through that individual's eyes."

Another example of subtle energy was the ability of certain clairvoyants to "observe the "auric" fields around patients" and describe their state of physical and mental health. These "auric" fields appear to the clairvoyant as patterns of light of different colors extending out from the body. Some clairvoyants can perceive the patterns with their eyes closed or in total darkness and as they are not composed from physical light cannot be captured with standard photography. Much of this may sound like science fiction, but Konstantin Korotkov does appear to have demonstrated how these subtle energy or "auric" fields vary in health and disease with his gas discharge visualization (GDV) camera and electrophotonic analysis. Tiller has also shown how intentionality (the power of the mind) can influence the pH of a solution, increase ATP to speed up larval maturation, and how this mental force or energy can be transferred to a computer chip to exert the same effects at a later date and different location. Other chapters that have been updated to include advances in diagnosis and treatment include:

Repetitive Transcranial Magnetic Stimulation for Depression and Other Indications—Mark S. George et al.

The Evolution of Cranial Electrotherapy Stimulation for Anxiety, Insomnia, Depression, and Pain and Its Potential for Other Indications—Daniel L. Kirsch and Jeff Marksberry

Chronic Therapeutic Brain Stimulation: History, Current Clinical Indications, and Future Prospects—Nuprin Baxi, Ali Rezai, and Alon Y, Mogilner

Advances in Stimulation of the Vagus and Trigeminal Nerves for the Treatment of Epilepsy—Stephen C. Schachter

The Origin and Evolution of Vagal Nerve Stimulation: Implications for Understanding Brain Electrodynamics, Neuroendocrine Function, and Clinical Applications—Jacob Zabara

Clinical Application of Biophysical Stimulation on Bone in Europe—Matteo Cadossi et al.

Electroporation and Electrochemotherapy—Dietmar P. Rabussay

In addition to those chapters with a focus on subtle energies previously listed, other new contributions include:

Noninvasive Deep TMS Therapy for Diverse Neuropsychiatric Disorders—Yiftach Roth and Abraham Zangen

Electromagnetic Tissue Characterization in the Treatment of Breast Cancer—Dan Hashimony, Gil Cohen, and Iddo Geltner

Bioelectromagnetic Paradigm of Cancer Treatment: Oncothermia—Andras Szasz

Systemic Treatment of Cancer with Low and Safe Levels of Radiofrequency Electromagnetic Fields Amplitude-Modulated At Tumor-Specific Frequencies—Boris Pasche et al.

While the titles of all these chapters provide some clue as to their contents, this may not adequately convey their importance. For example, liver cancer (hepatocellular carcinoma) is the second leading cause of cancer deaths in men worldwide and has become the fastest rising tumor in the U.S., probably due the increase in Hepatitis C.

It is notoriously resistant to radiation and chemotherapy and has an average survival time of 3 to 6 months. The TheraBionic treatment described by Pasche et al. appears

to be a major breakthrough, as several patients lived 3 or 4 years, one was alive and well over 5 years later and another had a complete remission. Treatment is completely safe, has no side effects, and can be administered by patients at home for 1 h, three times a day, during which they can watch TV or read. It consists of administering radiofrequency waves that are specific for this tumor by means of a spatula like device that is held in the mouth like a lollipop. It can also be programmed for other malignancies, and one patient with breast cancer that had metastasized to the adrenal gland and bone, had a "complete response" after an 11-month treatment. A patient with stage IV thyroid cancer metastatic to the lungs has received continuous treatment for more than 7 years. The instrumentation is essentially similar to the Symtonic device for treating insomnia and anxiety I was involved with 30 years ago, as explained in the tribute to Ross Adey and was also described in the first edition. Because of this and subsequent developments, It seems likely that in the future, doctors will be prescribing frequencies, rather than pushing pills.

The operating room of the future may no longer feature surgery, which may be replaced by MRI guided focused ultrasound. As explained in this chapter, the acoustic energy of ultrasound waves is concentrated within a target area to deliver heat at a depth without affecting overlying skin and normal tissues. This scarless, bloodless, and painless procedure is effective for treating benign uterine fibroids, relieving bone pain due to metastatic disease and may be effective for patients with Parkinson's disease and other movement disorders. Focused ultrasound surgery for fibroids takes 2 or 3 h, after which patients can resume normal activities without the need for hospitalization. See www.insightec.com/ExAblate-Vision.html for a compelling video of this.

A device implanted in the brain is required to achieve the benefits of deep brain stimulation in movement disorders such as Parkinson's disease, multiple sclerosis and Tourette syndrome, as well as chronic pain, treatment resistant depression, epilepsy, and obsessive-compulsive disorder, as described in the chapter on chronic brain stimulation. (Be sure to see http://www.youtube.com/watch?v=uBh2LxTW0s0&feature=player_embedded for its amazing and life transforming effect in Parkinson's disease), However, this is a complicated operation that is generally limited to patients who have failed to respond to medication, and determining optimal electrode placement may be difficult.

It now appears that many of these benefits can be achieved by noninvasive deep TMS (dTMS) as described in the chapter by Yiftach Roth and Abraham Zanger, who developed it. It uses special H-coils to target rTMS to deep areas of the brain without damaging intervening or surrounding healthy tissues and it was approved by the FDA in 2013 for treatment resistant depression in adults. In the European Economic Area, dTMS has CE marking, and is currently prescribed for

- Alzheimer's disease
- Autism
- Bipolar disorder
- Chronic pain
- Major depressive disorder
- Parkinson's disease
- PTSD
- Smoking cessation
- Schizophrenia with auditory hallucination

Because of its versatility and safety, we may have only scratched the surface of the potential for this modality. In a study published in the March 2014 issue of the *Journal of Neuroscience*, Vanderbilt researchers reported that 20 min of dTMS resulted in an improvement in learning skills that lasted 5 h. This was accompanied by supportive EEG changes with a "success rate far better than that observed in studies of pharmaceuticals or other types of psychological therapy." Studies are planned to determine its efficacy in ADHD. This and other very recent advances that could not be included in this volume will be discussed in the concluding Afterword chapter.

The above is an attempt to explain why and how this book was assembled and why chemotherapy and other drugs, as well as surgery and radiation, may soon be replaced by prescriptions for different frequencies. In that regard, the first noninvasive pulsed EMF therapy that was approved by the FDA was in 1979 for the treatment of bone fractures that had failed to heal for over a year. As in the Preface for the first edition, I will close with this 1992 prediction by J. Andrew L. Bassett.

> In the decade to come, it is safe to predict, bioelectromagnetics will assume a therapeutic importance equal to, or greater than, that of pharmacology and surgery today. With proper interdisciplinary effort, significant inroads can be made in controlling the ravages of cancer, some forms of heart disease, arthritis, hormonal disorders, and neurological scourges such as Alzheimer's disease, spinal cord injury, and multiple sclerosis. This prediction is not pie-in-the-sky. Pilot studies and biological mechanisms already described in primordial terms, form a rational basis for such a statement.

Bassett was one of the early advocates of the use of electromagnetic fields for uniting fractures that refused to heal. Unfortunately, he died before he could see that his prophecy would come true well ahead of schedule. This book is a tribute to him, Robert Becker, Ross Adey, Carl Blackman, Abraham Liboff, and other pioneers who recognized the vast potential of bioelectromagnetic medicine, as well as Jacques Benveniste and other contributors to this volume who have striven to put subtle energies on a similar solid scientific footing.

2 A Tribute to W. Ross Adey
A Man for All Seasons

*Paul J. Rosch**

CONTENTS

There can be little doubt that William Ross Adey (1922–2004) was a child prodigy. He graduated from high school at age 14, by which time he had already built several large vacuum tube radios. He obtained a ham radio license a few years later, and by the age of 21 had received degrees in medicine (MB) and surgery (BS) from the University of Adelaide. After his first clinical position at Royal Adelaide Hospital in 1944, he served as Surgeon Lieutenant in the Royal Australian Navy for 2 years, during which he became fascinated by the new technology of radar and its clinical potential. He subsequently became involved in studying the function of limbic system structures and, because of his achievements, he was awarded a coveted Fellowship in 1950 to study at Oxford University to continue his research. The return trip from England to Adelaide included a stopover in Los Angeles, where several intriguing opportunities delayed him. In 1954, he was appointed Professor of Anatomy and Physiology at the University of California, Los Angeles and he joined their Brain Research Institute in 1961, where he worked with the Department of Defense on the CIA's super-secret Project Pandora to find ways that electromagnetic radiation could be used for mind control. In 1965, he was named Director of their new Space Biology Laboratory.

The projects his teams worked on during this period were related to brain activity of service personnel, with a focus on the effects of pulsed extremely low frequency (ELF) radiation. It included developing biotelemetry techniques that allowed electroencephalography (EEG) recordings to be done on NASA astronauts in space. In that regard, Ross made numerous contributions to all phases of EEG, from the design of surface and invasive electrodes to signal analysis. He was the first to use ordinary digital computers in EEG analysis to produce brain maps of electrical activity and assembled the first library of these maps. In the mid-1970s, he established a new laboratory at the VA Hospital in Loma Linda, CA, where, along with Suzanne Bawin, he first demonstrated the nonthermal effects of ELF-modulated radio frequency signals by showing that they caused the release of calcium ions from nerve cells. He subsequently carried out studies on the role of ELFs in the promotion of cancer and warned about the potential cancer risks from exposure to cell phone and microwave radiation.

My interest in cranioelectrical stimulation and electromagnetic therapies was kindled in 1983 when I was asked to evaluate the use of the Symtonic low energy emission therapy (LEET) device for the treatment of insomnia and anxiety that had been developed by Swiss scientists. At the time, I was a consultant to the Biotonus Clinic in Montreux Switzerland, whose Director, Claude Rossell, MD, PhD, was involved in clinical trials that appeared to confirm claims for efficacy and safety. I had been somewhat skeptical, as there was no apparent rationale or mechanism of action to support these assertions. I was invited to participate in a weeklong conference titled "Electromagnetic Fields and Neurobehavioral Function" held on August 19–23, 1984. It was conducted in a former monastery in Priorij Corsendonck, a remote and secluded area of Belgium, and as there were no nearby attractions, the speakers ate and spent all their free time at the site. That was where and how I first met and developed a lifelong and close friendship with Ross Adey, as much of our spare time was passed in discussing mutual interests and the presentations of the 20 participants.

I was aware of his prior studies of the effect of weak electromagnetic fields on behavior in animals and his conviction that this could have important clinical implications. When I asked about this, he explained that he had implanted transmitters in the brains of cats and chimpanzees that sent signals to a receiver that displayed varied electrical activity patterns. Based on this information, he could send back specific radiofrequency signals that allowed him to control the animal's behavior to conform to different patterns. He also told me about the research of Dr. Jose Delgado, a Yale neurophysiologist, who had implanted tiny wires and electrodes in different parts of the brain and then stimulated them to see what emotional or physical changes occurred. His goal was to change a patient's mood, so that those who were depressed perked up, and anxious ones were calmed down. He later developed his "stimoceiver;" quarter size chips that could be activated by remote control after being implanted in the brain. He experimented on monkeys and cats, and, after several years, found he could make them yawn, fight,

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play, mate, and sleep by remote control. He was particularly interested in managing anger and began to study Spanish bulls by implanting stimoceivers and testing his equipment by making them lift their legs, turn their heads, walk in circles, or moo 50 or more times in a row. His most famous experiment that made international headlines 20 years earlier, was stepping into a bullring in Cordova, Spain, with a ferocious charging bull named Lucero, who was notorious for his temper. He had never fought a bull and had no sword for protection, but when Lucero barreled towards him, Delgado tapped his remote control and brought the animal to a screeching halt. He tapped his remote control again, and the bull began wandering around in circles, oblivious to his presence.

I also wanted to know more about the secret Pandora project involving Delgado, Adey, and other prominent neurophysiologists. Ross explained that in 1962, the CIA discovered that the U.S. embassy in Moscow was being bombarded with electromagnetic radiation of different frequencies. This was during the height of the cold war and, according to statements from Russian scientists that were subsequently obtained, its purpose was to cause blurred vision and loss of concentration. However, the compound personnel had numerous other complaints and blood tests showed a variety of strange abnormalities and unusual chromosome changes. Ambassador Stoessel suffered from headaches and bleeding from the eyes and was later diagnosed as having a rare leukemia-like blood disease. According to one account, long-term follow-up revealed that a third of the compound's employees eventually developed some type of malignancy. It was subsequently discovered that a radio transmitter on the roof was inducing high frequency signals well above the U.S. safety standards through the phones in the political section, as well as in the lines to Stoessel's office.

The purpose of the Pandora Project, which was conducted in the late 1960s and early 1970s, was to gather data on this Russian experiment and to determine if the U.S. could develop something superior that might have applications for the military. That was all he could tell me because Pandora was still top secret. However, it was clear that Ross was selected to participate in this, as he had previously proposed that if a radio signal was made to simulate a brain wave, it could influence behavior. He was later able to demonstrate that you could make the brain wave pattern follow the modulation on the radio signal in cats. He told me that the Russians were well ahead of everyone else with respect to using radiofrequency signals as medical tools. As far back as the 1940s, researchers in Soviet Armenia had developed the prototype of an instrument for "the treatment of neuropsychic and somatic disorders, such as neuroses, psychoses, insomnia, hypertension, stammering, asthma, and asthenic and reactive disturbances." This later culminated in the LIDA device, which used pulsed light and sound waves in addition to electromagnetic radiation to treat insomnia and depression. The Russians kept it under wraps, and the only U.S. scientist who had studied it was Ross Adey, as the CIA had purchased one for him from a Canadian front.

He began testing it around 1980 and, according to press reports, said it acted like Valium, and that when he put a cat in a box and turned on the LIDA, "Within a matter of two or three minutes it is sitting there very quietly and stays almost as though it were transfixed." The Russians also pioneered the use of cranioelectrical stimulation (CES) to treat insomnia, which, when introduced into the U.S., was originally called "electrosleep." LIDA could also have this effect and there was a photo of an entire auditorium full of sleeping Russians with the LIDA on the podium. He said that a few years earlier, while he was testing the device, an electrician who was watching asked where he got the "North Korean brain washing machine." Ross told him it was a Russian medical device and the electrician explained that he had been brainwashed by a similar instrument when he was in a POW camp decades earlier. Electrodes were placed on his head and question and answers were repeatedly read to him. He said he felt like he was in a dream and when the Red Cross later came and asked questions, he replied with what had been read to him and seemed to have no control over the answers. Other prisoners had also made similar claims of having been brainwashed.

In addition, we also discussed the presentations of the other speakers, as well as our own. His dealt with the role of the cell membrane in the detection and transductive coupling of oscillating electromagnetic fields, and delineating the activation of intracellular systems responsible for amplifying these signals.[1] It seemed far removed from my assignment, the concluding talk, in which I was asked to summarize previous speakers' findings with respect to their future implications for clinical medicine. The title that I had been assigned was "Electromagnetic Waves and Neurobehavioral Function: Comments From Clinical Medicine."[2] Although I had made copious notes, I thought it would be an ideal opportunity to discuss the Symtonic device before this distinguished audience. Ross urged me to do so, as did Carl Blackman, another pioneer in ELF stimulation from the EPA, Yale's Eleanor Adair, an authority on thermoregulation and microwaves and John Monahan, head of the FDA's CDRH division.

I felt it would be best for Claude Rossell to present this in case there were technical questions I could not answer, as well as to demonstrate the device. After discussing this with the sponsors, who agreed, I called Claude and he immediately arranged to join us for the final day of the conference to report on his latest findings. His presentation was very stimulating, as he had some new supportive data and Ross was particularly intrigued with Symtonic's novel delivery system and its ease of administration and asked several stimulating and critical questions. Dr. Rossell was impressed with his extensive knowledge and experience with both the basic science and clinical aspects of extremely low frequency fields, and we both felt he would be a valuable consultant to suggest studies on other stress related disorders. Claude subsequently proposed organizing an annual International Montreux Congress on Stress under the aegis of the American Institute of Stress that would include sessions dealing with relevant advances in "electromedicine." I was given carte blanche to select the speakers and topics, and the Congress would be

conducted at the five star Grand Excelsior Hotel adjacent to the Biotonus Clinic, which funded speakers' accommodations, airfare, and honoraria.

Our First Congress was in 1988; Ross was the recipient of our annual Hans Selye Award at our 1999 Congress, and an active participant in all of them. We were constantly amazed at his wide range of knowledge, not only in his area of expertise, but also in all aspects of clinical medicine and esoteric subjects, such as *Qigong* healing and the prowess of Indian fakirs. He was equally knowledgeable about current events and social issues, such as the growing immigration problem in California, and, although always polite, could be adamant in his opinions and a formidable opponent in a debate. His presentations were eloquent and although a picture may be worth a thousand words, few could improve on his "whispering among cells" to describe the effects of nonthermal electromagnetic fields on communication between brain neurons. My wife and I spent time with him visiting Switzerland after some of our Congresses and were impressed with his knowledge of Shakespeare, which he could quote at length, as well as his humility and kindness. When he learned that we planned to visit his beloved Australia, he prepared a list of sites to visit, sent us books and articles, and arranged for his friends at various locations to escort us around.

As I noted in the *Lancet* obituary that I was asked to contribute to, of all his more than 400 publications, he will be remembered mostly for discovering what has been called the "Adey window," which "describes the confined parameters under which a very weak nonthermal electromagnetic signal has a physiological effect." Not included was my comment that Ross Adey was a true Renaissance figure in medicine, whose likes will not be seen soon again. He was "A man for all seasons." This was the expression the great German humanist Desiderius Erasmus used to describe his good friend, Sir Thomas More. Erasmus was alluding to *Corinthians* 9:22, "I become all things to all men, that I might save all" when he wrote the following in Latin, more than 500 years ago,

> More is a man of an angel's wit and singular learning. He is a man of many excellent virtues; I know not his fellow. For where is the man (in whom is so many goodly virtues) of that gentleness, lowliness, and affability, and as time requires, a man of marvelous mirth and pastimes and sometime of steadfast gravity—it would be hard to find anyone who was more truly a man for all seasons and all men. (*omnibus omnium horarum homo*).

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Section II

Chapters Reproduced from the First Edition

3 Preface from the First Edition

*Paul J. Rosch**

CONTENTS

PREFACE FROM THE FIRST EDITION

A Brief Historical Perspective

According to *The Yellow Emperor's Canon of Internal Medicine*, our oldest extant medical text, magnetic stones (lodestones) applied to acupuncture points were used to relieve pain and other complaints 40 centuries ago. The *Vedas*, religious scriptures of the Hindus also believed to be several thousand years old, similarly allude to the therapeutic powers of *ashmana* and *siktavati* (instruments of stone). The Greeks referred to these as *lapus-vivas* (live-stones) and Hippocrates purportedly used them to cure sterility. Egyptian physicians ascribed a variety of benefits to magnetic stones, as did early Buddhists. Tibetan monks still place bar magnets on the skull to improve the concentration and learning ability of novitiates in accordance with an age-old protocol.

In the early 1500s, the Swiss physician and alchemist Paracelsus became convinced that magnetism could restore the body's vitality and used magnets to promote healing and treat epilepsy, diarrhea, and certain types of hemorrhage. Lodestones were ground up to make powders that could be applied as magnetic salves or ingested to provide energy and stop bleeding. Such practices became very popular but they were debunked in 1600 by William Gilbert in *De Magnete*. By the middle 1700s, more powerful, carbon-steel magnets had become available in Europe and there was heightened interest in their curative powers. Franz Anton Mesmer quickly became famous for his miraculous cures of everything from deafness to paralysis. In his 1775 report *On the Medicinal Uses of the Magnet*, he vividly described how he had restored health to a patient with uncontrollable seizures and numerous other nervous system complaints by feeding her iron filings and applying specially shaped magnets over affected organs. He later claimed that the healing force actually resided in his own "animal magnetism" (*magnetisomum animalem*). This was hailed as a new force analogous to Newton's gravity, and people from all over Europe waited in long lines to be treated in his Paris salon. French physicians considered him a fraud and convinced Louis XVI to establish an unbiased commission consisting of Benjamin Franklin, Antoine Lavoisier, and Dr. J.I. Guillotin to investigate Mesmer's claims. They observed blindfolded patients who were exposed to very strong magnets and asked to describe their responses when fake objects were unknowingly substituted. The commission concluded in 1784 that magnetic healing was entirely due to the belief of the patient (placebo effect) and the power of suggestion (hypnosis). We still refer to hypnotism as "mesmerism."

Although Mesmer was thoroughly discredited, magnet therapy flourished in the United States and permanent magnet sales soared after the Civil War, particularly in the newly industrialized western farm belts. Magnets, magnetic salves, and liniments were dispensed by traveling magnetic healers and were readily available at food and grain stores. By the turn of the century, mail-order catalogs offered magnetic soles for boots (profitable at 18 cents a pair) as well as magnetic rings, belts, caps, girdles, and other apparel that purportedly could cure anything from menstrual cramps to baldness and impotence. The king of magnetic healers was Dr. C.J. Thacher, whose Chicago's Magnetic Company in the 1920s promised "health without the use of medicine." His mail-order pamphlet explained that the energy responsible for life comes from the magnetic force of the sun, which is conducted through the rich iron content of the blood. Disease resulted when stressful lifestyles and environmental factors interfered with these healing forces. However, "magnetism properly applied will cure every curable disease no matter what the cause." The most efficient way to expedite this alleged ability of iron in the blood to transmit healing magnetic energy was to wear magnetic clothing, and almost every conceivable garment was available. A complete costume, which promised "full and complete protection of all the vital organs of the body," contained 700 magnets!

It is not clear when electricity was first used to treat illness but electric catfish native to the Nile are portrayed in Egyptian murals several thousand years old that suggest medical applications. The Roman physician Scribonius Largus used a live torpedo fish to treat a patient with gout and wrote in 46 AD that headaches and other pains could be

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cured by standing in shallow water near these electric fish. The powerful South American electric eel was introduced to Europe in 1750, and people flocked to be treated with its "natural electricity." Around the same time, the invention of the Leyden jar had dramatically demonstrated the ability of a stored electrical charge to produce muscle contractions and shocks. The publication of Mary Shelley's *Frankenstein* in 1818 stimulated interest in electricity as the source of life. As Galvani had shown that limbs or other body parts would jump when electrical shocks were administered to animal and human cadavers, it was believed that electricity could bring the dead to life. Various "reanimation" chairs and devices were constructed, some of which may possibly have acted as pacemakers or defibrillators in the rare cases that responded. An induction coil with sponge-tipped electrodes was used in 1853 to successfully treat abnormal heart rhythms and angina. Over the next few decades, as batteries were progressively improved and electricity from generating stations became available, all sorts of "medical coils" were developed with diverse curative claims.

By the early 1900s, electrotherapeutics was viewed as a legitimate medical specialty much like the growing fields of radiology and radium therapy, and medical textbooks devoted chapters to the use of magnetism and electricity. Devices were devised to diagnose and treat anemia, hysteria, convulsions, insomnia, migraine, neuralgia, arthritis, fatigue, and all types of pain. Some were based on the proposition that each organ or individual was "tuned" to a specific electromagnetic wavelength whose application could energize or rejuvenate them. The most popular were the dynamizer and oscilloclast devised by Albert Abrams, a physician who was described by the American Medical Association in 1925 as the "dean of twentieth century charlatans." The dynamizer was said to be so sensitive it could not only diagnose a disease from a drop of blood, photograph, or handwriting sample but also pinpoint its location in the body. The oscilloclast was then simply set to the vibratory rate of the disease to be treated and the treatment was likened to shattering a wineglass with sound vibrations. A decade later, Wilhelm Reich claimed he had discovered a universal cosmic and biological energy called orgone that permeated the universe. He constructed an orgone accumulator box he claimed could collect and accumulate orgone obtained from the atmosphere. Sitting in the accumulator would not only restore and promote health and vitality but was an effective treatment for cancer. The Food and Drug Administration (FDA) sued and convicted him for fraud, and the court ordered his books and research burned and his equipment destroyed. Although Abrams died in prison in 1957, he still has fervent followers who believe in his theories and devices, judging from various websites. Other contraptions made similar extravagant but worthless claims, so it is not surprising that all bioelectromagnetic approaches came to be regarded as fraudulent. A more detailed discussion of the above is available elsewhere.[1]

Unfortunately, this dismissed legitimate research, and it is not unlikely that in some instances the baby was thrown out with the bathwater. One example may be the work of Harold Saxton Burr, whose theory of "L fields" of life showed great potential for the diagnosis of cancer and the treatment of various disorders. His research results using the comparatively crude devices available over a half century ago are now being intensively reinvestigated and confirmed with more sophisticated technology. In recent years, magnetic resonance imaging (MRI) and positive emission tomography (PET scanning) have emerged as superior diagnostic aids. Cardiac pacemakers, defibrillators, and other implantable electromedical devices have saved countless lives and eased the suffering of patients with Parkinson's disease and other debilitating disorders. The FDA has also approved specific electromagnetic devices to promote the healing of bone fractures that have failed to unite despite other interventions; this procedure has proven successful and safe in hundreds of thousands of patients over the past few decades. More recently, electromagnetic therapies for the treatment of urinary incontinence, sports injuries, and liver and kidney tumors have also been approved. Other approaches, for the treatment of osteoarthritis, pain, tinnitus, and other indications, have satisfied criteria for efficacy and safety that have led to their approval in European and other countries and that may allow them to be available in the United States under the "globalization" and "harmonization" provisions of the 1997 FDA Modernization Act.

WHY AND HOW THIS BOOK WAS WRITTEN

Permanent magnet and electromagnetic therapies are now riding the crest of a tidal wave of interest in "alternative" and "complementary" medicine. Unfortunately, charlatans, entrepreneurs, and misguided zealots with worthless devices and unfounded claims still abound. It is essential to distinguish these from authentic approaches and products. As a result, in this book we have tried to separate the wheat from the chaff by restricting contributions to evidence-based medicine supported by references in peer reviewed publications and to provide the reader with tools and skills for evaluating the legitimacy of devices and claims. In addition to a lengthy history of quackery and fraud, another criticism that has hampered wider acceptance of bioelectromagnetic approaches is the inability to identify the mechanisms of action responsible for any benefits. We have therefore attempted to identify concepts and theories that attempt to explain the mechanisms responsible for mediating the diverse benefits of bioelectromagnetic therapies and, in some instances, how they may relate to ancient concepts of subtle energies in the body that are also found in nature. How weak environmental electromagnetic energies as well as those generated internally can produce nonthermal biological effects is not clear, as the absence of detectable heat exchange would appear to violate the laws of thermodynamics.

In addition, our current concept of how communication takes place in the body is at a chemical/molecular level as we visualize small peptide and other messengers fitting into specific receptor sites on cell walls much like keys opening certain locks. Such physical structural matching that could

occur only on a random-collision basis cannot explain the myriad instantaneous and automatic reactions such as those that occur in "fight or flight" responses to severe stress. As will be seen, there is an emerging paradigm of cellular communication at a physical/atomic level that may provide some answers and also provide insights into widely acknowledged but poorly understood phenomena, such as the placebo effect, the power of prayer and a firm faith, telepathic communication, the benefits of acupuncture, homeopathy, therapeutic touch, various bodywork and massage therapies, and Kirlian and other low-level imaging procedures.

Another issue that has caused wariness about bioelectromagnetic therapies are safety concerns about possible increased risk of certain malignancies and birth defects resulting from proximity to high power lines, cell phones, microwave ovens, and electric blankets. It is not surprising that electromagnetic fields, like many other therapies, can be two-edged swords. For example, all the modalities we use to treat cancer, including radiation, chemotherapy, and hormonal interventions, can also cause cancer. Such effects may depend on dosage, duration of exposure, and genetic and other influences. It is not likely that any clear conclusion about adverse electromagnetic effects can be reached until more information has been obtained from long-term studies that focus on these factors. For this reason, we have refrained from participating in this debate other than to devote a chapter on the importance of dosimetry and to emphasize that no such adverse effects have been observed or seem likely in the therapies presented in this book. Indeed, those that have been proposed and implemented by Demetrio Sodi Pallares and Björn Nordenström, and confirmed by others have shown stunning success in treating various malignancies. Many of the chapters in this book are based on presentations at the annual International Congress on Stress over the past decade or so, and additional information on these events can be obtained at www.stress.org.

We have also attempted in this book to trace the origin and development of various therapies, such as TENS and vagal nerve stimulation, by pioneers in the field such as Norman Shealy, Donlin Long, and Jacob Zabara. Kirk Jeffrey has contributed a similar chapter on the evolution of cardiac pacemakers. We have made a concerted effort to include prominent scientists whose research may not be well known in the United States. When initially approached to serve as editor of this book, I explained that this was not my field of expertise and asked Marko Markov, a distinguished physicist, to serve as co-editor. He is also much more familiar with relevant advances in Eastern Europe and Russia, and I am grateful for his careful review of all chapters and for those he has attracted from these countries as well as his own contributions. I am also indebted to Russell Dekker for expediting this work so that the material would be current and important late-breaking advances could be included, such as radiofrequency coblation nucleoplasty for disc disease. I would also like to thank all the authors for their cooperation in responding so promptly to urgent requests for revisions necessary to adhere to this very accelerated publication schedule.

The above is a brief summary of why this book is needed and how it was assembled. I believe it is particularly appropriate to conclude with the following quotation.

> In the decade to come, it is safe to predict, bioelectromagnetics will assume a therapeutic importance equal to, or greater than, that of pharmacology and surgery today. With proper interdisciplinary effort, significant inroads can be made in controlling the ravages of cancer, some forms of heart disease, arthritis, hormonal disorders, and neurological scourges such as Alzheimer's disease, spinal cord injury, and multiple sclerosis. This prediction is not pie-in-the-sky. Pilot studies and biological mechanisms already described in primordial terms, form a rational basis for such a statement.
>
> **J. Andrew L. Bassett**
> *1992*

Andy Bassett was one of the early advocates of the use of electromagnetic fields for uniting fractures that refused to heal. Unfortunately, he died before he could see that his prophecy would come true well ahead of schedule. In many respects, this book is a tribute to him and other pioneers such as Bob Becker, Abe Liboff, Björn Nordenström, and Ross Adey who recognized the vast potential of bioelectromagnetic medicine and have helped to put it on a solid scientific footing. I am particularly delighted that we were able to obtain contributions from most of these trailblazers.

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4 Potential Therapeutic Applications of Nonthermal Electromagnetic Fields

*Ensemble Organization of Cells in Tissue as a Factor in Biological Field Sensing**

W. Ross Adey†

CONTENTS

There are major unanswered questions about possible health risks that may arise from human exposures to various man-made electromagnetic fields where these exposures are intermittent, recurrent, and may extend overa significant portion of the lifetime of the individual. Current equilibrium thermodynamic models fail to explain an impressive spectrum of observed electromagnetic bioeffects at nonthermal exposure levels. Much of this signaling within and between cells may be mediated by free radicals of the oxygen and nitrogen species.

INTRODUCTION

In our solar system, the natural electromagnetic environment varies greatly from planet to planet. In the case of planet Earth, a semiliquid ferromagnetic core generates a major and slowly migrating *static* geomagnetic field. Concurrently, there are much weaker natural *oscillating* low frequency electromagnetic fields that arise from two major sources: in thunderstorm activity in equatorial zones of Central Africa and the Amazon basin and in lesser degree from solar magnetic storms in years of high activity in the 11-year solar sunspot cycle.

* Portions of this chapter were first published in D. Clements-Croome, ed. *Electromagnetic Environments and Safety in Buildings*. London: Spon Press; 2002.

† Deceased.

Comparison of Natural and Man-Made Electromagnetic Environments

All life on earth has evolved in these fields. Defining them in physical terms permits direct comparison with far stronger man-made fields that have come to dominate all civilized environments in the past century. Energy in the *oscillating* natural fields is almost entirely in the extremely low frequency (ELF) spectrum, with peaks at frequencies between 8 and 32 Hz, the Schumann resonances.[1] Their electric components are around 0.01 V/m, with magnetic fields of 1–10 nT. These natural oscillations are ducted worldwide between the earth's surface and the ionosphere at an approximate height of 250 km. With a circumference of 41,000 km, the earth may act as a cavity resonator for this ducted propagation (at the velocity of light, 300,000 km/s), behaving resonantly at a frequency around 8 Hz. Neither solar nor terrestrial sources contribute significant amounts of radiofrequency or microwave energy to the earth's biosphere, and we may contrast these weak ELF fields with the earth's much larger static geomagnetic field around 50 μT (0.5 gauss).

The earth's *static* magnetic field at 50 μT is 5000 times larger than the natural oscillations but still substantially less than a wide range of daily human exposures to static and oscillating fields in domestic and occupational environments.

Generation and distribution of electric power has spawned a vast and ever growing vista of new electronic devices and systems. They overwhelm the natural electromagnetic environment with more intense fields. They include oscillations far into the microwave spectrum, many octaves higher than the Schumann resonances. This growth of radio frequency (RF) and/or microwave fields is further complicated by the advent of digital communication techniques. In many applications, these microwave fields, oscillating billions of times per second, are systematically interrupted (pulsed) at low frequencies. This has raised important biological and biomedical questions, still incompletely answered, about possible tissue mechanisms in detection of amplitude- and pulse-modulation of RF and/or microwave fields.[2]

Historical Evidence on Possible Health Effects of Man-Made Environmental Fields

There are major unanswered questions about possible health risks that may arise from human exposures to various man-made electromagnetic fields where these exposures are intermittent, recurrent, and may extend over a significant portion of the lifetime of the individual. Historical correlations have been reported between growth of rural electrification in the United States and the United Kingdom and an increased incidence of childhood leukemia. A peak in childhood leukemia at ages 2 through 4 emerged *de novo* in the 1920s. Using U.S. census data for 1930, 1940, and 1950, Milham and Osslander[3] concluded that the peak in the common childhood acute lymphoblastic leukemia (ALL) may be attributable to electrification.

Design of modern office buildings has led to their electrification through one or more large distribution transformers that may be located in basement vaults, or in some cases, located on each floor of the building. Milham[4] has examined cancer incidence in such a building over a 15-year period and found evidence for *cumulative risks.* An analysis of linear trend in cancer incidence, using average years employed as an exposure score, was positive ($p = 0.00337$), with an odds ratio of 15.1 in workers employed longer than 5 years.

In large modern offices, the electromagnetic environment has been further complicated by introduction of local area networks (LANs) for local telephonic (voice) and data transmission. Workers may be continuously exposed to fields from a plethora of sources located on each computer and on local network controllers. Their power output is typically in the low milliwatt to microwatt range—so low that significant heating of workers' tissues is improbable. Any bioeffects attributable to their operation strongly suggest *nonthermal* mechanisms of interaction, and raise further important questions about mechanisms mediating a cumulative dose from repeated, intermittent exposures, possibly over months and years. None of these studies supports tissue heating as an adequate model for bioeffects seen in a wide spectrum of laboratory experiments (see below) or in reported epidemiological findings.

The American National Standards Institute (1992) first recognized a tissue dose of 4.0 W/kg as a *thermal* (heating) tissue threshold possibly associated with adverse health effects and proposed an exposure limit in controlled environments (occupational) at 0.4 W/kg, thus creating a supposed "safety margin" of 10. For uncontrolled environments (civilian), a larger safety margin was set with a permissible exposure limit (PEL) 50 times lower at 0.08 W/kg. As actual measurement of tissue specific absorption rates under environmental conditions is not a practical technique, PELs are typically expressed as a function of *incident field power density,* the amount of energy falling on a surface per unit area, and expressed in mW/cm^2.

More recently, the U.S. government Interagency Radio Frequency Working Group (1999) has emphasized the need for revisions recognizing nonthermal tissue microwave sensitivities:

> Studies continue to be published describing biological responses to nonthermal ELF-modulated RF radiation exposures that are not produced by CW (unmodulated) radiation. These studies have resulted in concern that exposure guidelines based on thermal effects, and using information and concepts (time-averaged dosimetry, uncertainty factors) that mask any differences between intensity-modulated RF radiation exposure and CW exposure, do not directly address public exposures, and therefore may not adequately protect the public.

INITIAL TRANSDUCTION OF IMPOSED MICROWAVE FIELDS AT NONTHERMAL ENERGY LEVELS *t*

Tissue components of environmental RF and microwave fields are consistent with two basic models. Sources close to the body surface produce *near-field exposures,* as with users

of mobile phones. The emitted field is magnetically coupled directly from the antenna into the tissues. At increasing distances from the source, the human body progressively takes on properties of a radio antenna, with absorption of radiated energy determined by physical dimensions of the trunk and limbs. This is a *far-field exposure,* defined as fully developed at ten or more wavelengths from the source and based on interactions with the electric component of the radiated field. Permissible exposure limits (PELs) have rested on measurement of microwave field energy absorbed as heat, expressed as the *specific absorption rate* (SAR) in W/kg.

There is an initial dichotomy in possible modes of interaction of cells in tissue with environmental microwave fields. It is principally determined by the separation of responses attributed to tissue heating from those elicited by certain fields at levels where frank heating is not the basis of an observed interaction. Their interpretation and possible significance has required caution in both biological and biophysical perspectives. Many of these biological sensitivities run counter to accepted models of physiological thresholds based in equilibrium thermodynamics of *kT* thermal collision energies. In a physical perspective, the search also continues for biological systems compatible with a first transductive step in a range of functionally effective vibrational and electromagnetic stimuli that are orders of magnitude weaker than *kT*. Aspects of these findings are reviewed in the section "The Role of Cellular Ensembles in Setting Tissue Thresholds for Intrinsic and Environmental Stimuli." Their occurrence invites hypotheses on directions of future research.[5]

Cell Membranes as the Site of Initial Field Transductive Coupling

Collective evidence points to cell membrane receptors as the probable site of first tissue interactions with both ELF and microwave fields for many neurotransmitters,[6] hormones,[7,8] growth-regulating enzyme expression,[9–12] and cancer-promoting chemicals.[13] In none of these studies does tissue heating appear involved causally in the responses.[2] Physicists and engineers have continued to offer microthermal, rather than athermal, models for these phenomena[14,15] with views that exclude consideration of cooperative organization and coherent charge states. However, it is difficult to reconcile experimental evidence for factors such as modulation frequency dependence and required duration of an amplitude-modulated signal to elicit a response (*coherence time*)[11] with models based on the equilibrium dynamics of tissue heating.

Evidence for the Role of Free Radicals in Electromagnetic Field Bioeffects

Examination of vibration modes in biomolecules, or portions of these molecules,[16] has suggested that resonant microwave interactions with these molecules, or with portions of their structure, is unlikely at frequencies below higher gigahertz spectral regions. This has been confirmed in studies showing collision-broadened spectra, typical of a heating stimulus, as the first discernible response of many of these molecules in aqueous solutions to microwave exposures at frequencies below 10 GHz.

However, there is an important option for biomolecular interactions with static and oscillating magnetic fields through the medium of *free radicals*[17,18]. Chemical bonds are magnetic bonds, formed between adjacent atoms through paired electrons having opposite spins, and thus, magnetically attracted. Breaking of chemical bonds is an essential step in virtually all chemical reactions, each atomic partner reclaiming its electron, and moving away as a free radical to seek another partner with an opposite electron spin. The brief lifetime of a free radical is about a nanosecond or less, before once again forming a *singlet pair* with a partner having an opposite spin or for electrons with similar spins, having options to unite in three ways, forming *triplet pairs* (reviewed in Reference 2).

During this brief lifetime, imposed magnetic fields may delay the return to the singlet pair condition, thus influencing the *rate* and the *amount of product* of an ongoing chemical reaction.[19] McLauchlan points out that this model predicts a potentially enormous effect on chemical reactions for static fields in the low mT range. For oscillating fields, the evidence is less clear on their possible role as direct mediators in detection of ELF frequency-dependent bioeffects. *Spin-mixing* of orbital electrons and nuclear spins in adjacent nuclei is a possible mechanism for biosensitivities at extremely low magnetic field levels, but these interactions are multiple, complex, and incompletely understood.[20] The highest level of free radical sensitivity may reside in hyperfine-dependent singlet–triplet state mixing in radical pairs with a small number of hyperfine states that describe their coupling to nearby nuclei.[21,22] Although sensitivities to magnetic fields in such a system might theoretically extend down to zero magnetic field levels, singlet–triplet interconversion would need to be sufficiently fast to occur before diffusion reduced the probability of radical re-encounter to negligible levels.

Lander[23] has emphasized that we are at an early stage of understanding free radical signal transduction. "Future work may place free radical signaling beside classical intra- and intercellular messengers and uncover a woven fabric of communication that has evolved to yield exquisite specificity." A broadening perspective on actions of free radicals in all living systems emphasizes a dual role: first, as messengers and mediators in many key processes that regulate cell functions throughout life and second, in the pathophysiology of *oxidative stress diseases.*

At cell membranes, free radicals may play an essential role in regulation of receptor specificity, but not necessarily through a lock-and-key mechanism. As an example, Lander cites the location of cysteine molecules on the surface of P21-*ras* proteins at cell membranes. They may act as selective targets for nitrogen and oxygen free radicals, thereby inducing covalent modifications, and thus, setting the *redox potential* of this target protein molecule as the critical determinant for its highly specific interactions with antibodies,

hormones, etc. Magnetochemistry studies have suggested a form of cooperative behavior in populations of free radicals that remain *spin-correlated* after initial separation of a singlet pair.[24] Magnetic fields at 1 and 60 Hz destabilize rhythmic oscillations in brain hippocampal slices at 56 μT (0.35 to 3.5 nV mm^{-1}) via, as yet unidentified, nitric oxide mechanisms involving free radicals.[23,25] In a general biological context, these are some of the unanswered questions that limit free radical models as general descriptors of threshold events.

SENSITIVITIES TO NONTHERMAL STIMULI: TISSUE STRUCTURAL AND FUNCTIONAL IMPLICATIONS

Conductance Pathways in Multicellular Tissues

In its earliest forms, life on earth may have existed in the absence of cells, simply as a "soup" of unconstrained biomolecules at the surface of primitive oceans. It is a reasonable assumption that the first living organisms existed as single cells floating or swimming in these primordial seas. Concepts of a cell emphasize the role of a bounding membrane, surrounding an organized interior that participates in the chemistry of processes essential for all terrestrial life. This enclosing membrane is the organism's window on the world around it.

For unicellular organisms that swim through large fluid volumes, the cell membrane is both a sensor and an effector. As a sensor, it detects altered chemistry in the surrounding fluid and provides a pathway for inward signals generated on its surface by a wide variety of stimulating ions and molecules, including hormones, antibodies, and neurotransmitters. These most elemental inward signals are susceptible to manipulation by a wide variety of natural or imposed electromagnetic fields that may also pervade the pericellular field. As effectors, cell membranes may also transmit a variety of electrical and chemical signals across intervening intercellular fluid to neighboring cells, thus creating a domain or ensemble of cells, often able to "whisper together" in a faint and private language. Experimental evidence suggests that these outward effector signals may also be sensitive to intrinsic and imposed electromagnetic fields.

Rather than being separated in a virtually limitless ocean, cellular aggregates that form tissues of higher animals are separated by narrow fluid channels that take on special importance in signaling from cell to cell. Biomolecules travel in these tiny "gutters," typically not more than 150 Å wide, to reach binding sites on cell membrane receptors. These gutters form the *intercellular space* (ICS). It is a preferred pathway for induced currents of intrinsic and environmental electromagnetic fields. Although it occupies only ~10% of the tissue cross section, it carries at least 90% of any imposed or intrinsic current, directing it along cell membrane surfaces. Whereas the ICS may have a typical impedance of ~4–50 ohm cm^{-1}, transmembrane impedances are ~10^4–10^6 ohm cm^{-2}.

Structural and Functional Organization of the Extracellular Space

The organization of cell membrane surfaces and intercellular gutters in detection of these tissue components of extrinsic and intrinsic electromagnetic fields enters the realm of *nonequilibrium* thermodynamics,[26,27] characterized by *cooperative processes,* mediated by *coherent states* of electric charges on cell membrane surface molecular systems.

Spaces in the ICS are not simple saline filled channels. Numerous stranded protein molecules protrude into these spaces from the cell interior and form a *glycocalyx* with specialized receptor sites that sense chemical and electrical stimuli in surrounding fluid. Their amino sugar tips are highly negatively charged (*polyanionic*) and attract a *polycationic* atmosphere, principally of calcium and hydrogen ions. This Debye layer has an extremely high virtual dielectric constant at low frequencies ($D_k > 10^6$ at frequencies <1 kHz).[28] Biological cooperative processes occur in systems where at least one energetic parameter in that system (e.g., temperature, electric charge) has been moved far from equilibrium by the addition of external energy. This added energy may induce a population of substrate elements, all at the same higher energy level—a *coherent* energetic state. In such a system, a weak external trigger may elicit a *cooperative* process, with an energy release far greater than in the initial trigger. Capping and patching on the lymphocyte cell surface[29] offers a striking example of such a cooperative response, based on intracellular metabolic energy.

The proteins of the glycocalyx offer an anatomical substrate for the first detection of weak electrochemical oscillations in pericellular fluid, including field potentials arising in activity of adjoining cells, or as tissue components of environmental fields. Research in molecular biology has increasingly emphasized essentially direct communication between cells due to their mutual proximity. Bands of *connexin* proteins form *gap junctions* directly uniting adjoining cell membranes. Experimental evidence supports their role in intercellular signaling.

Tissue Detection of Low Frequency Fields and RF/Microwave Fields Amplitude-Modulated at Low Frequencies: Structural and Functional Options

Differential bioeffects, to be discussed below, have been reported between certain nonthermal RF or microwave fields with low-frequency amplitude or pulse modulation when compared to exposures to unmodulated continuous wave (CW) fields at similar power levels. The findings suggest, but do not yet establish unequivocally, that this frequency dependence may be a system property in a sequence of molecular hierarchies beyond the first transductive step. If the concept of modulation frequency-dependence continues to gain support in further research, answers must be sought as to the manner of its detection.

For ELF fields, models based on joint static-oscillating magnetic fields have been hypothesized. They include ion

cyclotron resonance,[30] where mono- and divalent cations, such as potassium and calcium (abundant in the cellular environment), may exhibit cyclotron resonance at ELF frequencies in the presence of ambient static fields of less than 100 μT, such as the geomagnetic field. Other models describing ELF frequency dependence have considered phase transitions[31] and ion parametric resonance,[32] but interpretation of this frequency dependence based on ion parametric resonance remains unclear.[33]

For amplitude- or pulse-modulated RF and/or microwave fields, there is the implication that some form of *envelope demodulation* occurs in tissue recognition of ELF modulation components, but the tissue may remain essentially transparent to the same signal presented as an unmodulated carrier wave.[2,34] However, crucial questions remain unanswered. It is not known whether biological low frequency dependence is established at the transductive step in the first tissue detection of the field, or whether it resides at some higher level in a hierarchical sequence of signal coupling to the biological detection system.[35] For ELF magnetic fields, experimental evidence points to a slow time scale in inhibition of tamoxifen's antiproliferative action in human breast cancer cells.[36]

It is a principle of radio physics that extraction of ELF modulation information from an amplitude-modulated signal requires a *nonlinear element* in the detection system. This required nonlinearity may involve a spatial component, such as differential conduction in certain directions along the signal path, or the path itself may exhibit nonlinearities with respect to such factors as spatial distribution of electric charges at fixed molecular sites (so-called fixed charges), or conduction itself may involve a nonlinear quantum process, as in electron tunneling across the transverse dimensions of the cell membrane.

These constraints impose a further essential condition for demodulation to occur in the multicellular tissues of living organisms. There must be a *site for demodulation* to occur. Evidence supports a role for cell membranes to act in this way, based not only on their intrinsic structure, but also on their proximity to neighboring cells in the typical organization of tissues of the body. Typical tissue organization meets the three criteria outlined above but, as a cautionary note, does not allow calculation of possible detection efficiency. Direct neighbor–neighbor cellular interactions will invite our further consideration of properties of cellular ensembles or domains in determining tissue threshold sensitivities.

Directional Differences in Tissue Signal Paths

As already noted, the narrow gutters of the intercellular spaces offer preferred conduction pathways, with conductivity 10^2–10^4 higher through extracellular spaces than through cell membranes.[37] Thus, the intercellular spaces become preferred pathways for *conduction along (parallel to) cell membrane surfaces* and will reflect the changing directions and cross sections of a myriad channels. Although predominantly an ionic (resistive) conduction pathway, it may also exhibit reactive components, due to the presence of protein molecules in solution.

Nonlinearities in Extracellular Spaces Related to Electric Charge Distribution

A suggested basis for envelope demodulation at cell surfaces may reside in the intensely anionic charge distribution on strands of glycoprotein that protrude from the cell interior, forming the glycocalyx.[2,38] As already noted, they provide the structural basis for specific receptor sites, and they attract a surrounding cationic atmosphere composed largely of calcium and hydrogen ions. This charge separation creates a Debye layer. In models and experimental data from resin particles, Einolf and Carstensen[28] concluded that this physical separation creates a large virtual surface capacitance, with dielectric constants as high as 10^6 at frequencies below 1 kHz. Displacement currents induced in this region by ELF modulation of an RF field may then result in demodulation.

Electron Tunneling in Transmembrane Conduction: Nonlinearities in Space and Time

Experimental studies of transmembrane charge tunneling by DeVault and Chance[39] and their more recent theoretical development by Moser et al.[40] offer an example of extreme functional nonlinearity within the cell membrane. Chance described temperature-independent millisecond electron transfer over a temperature range from 120 K to 4 K. Considering a cell membrane transverse dimension of 40 Å, Moser et al. noted that a variation of 20 Å in the distance between donors and acceptors in a protein changes the electron transfer rate by 10^{12}-fold. Concurrently in the time domain, the electron transfer rate is pushed from seconds to days, or a 10-fold change in rate for a 1.7 Å change in distance.

Issues of Comparability between Bioeffects of ELF Fields, ELF-Modulated RF Fields, and Unmodulated (CW) RF Fields

From the beginning of these studies in the 1970s, it was noted that there were similarities in responses of tissues and cultured cells to environmental fields that were either in the ELF spectrum or were RF and/or microwave fields modulated at ELF frequencies. Available evidence has indicated similarities between certain cell ionic and biochemical responses to ELF fields and to RF and/or microwave fields amplitude modulated at these same ELF frequencies, suggesting that tissue demodulation of RF and/or microwave fields may be a critical determinant in ensuing biological responses.

These findings have been reviewed in detail elsewhere.[2,18] They are briefly summarized here in experiments at progressively more complex levels in the hierarchies of cellular organization. Early studies described calcium efflux from brain tissue in response to ELF exposures,[38,41] and to ELF-modulated RF fields.[38,41–43] Calcium efflux from isolated brain subcellular particles (synaptosomes) with dimensions under 1.0 μm also exhibit an ELF modulation frequency dependence in calcium efflux, responding to 16-Hz sinusoidal modulation, but not to 50 Hz modulation, nor to an unmodulated RF carrier.[44] In the same and different cell

culture lines, the growth regulating and stress responsive enzyme ornithine decarboxylase (ODC) responds to ELF fields[11,45] and to ELF-modulated RF fields.[9,11,12]

In more recent studies also related to cellular stress responses, Goodman and Blank and their colleagues have reported rapid, transitory induction of heat shock proteins by micro-tesla-level 60-Hz magnetic fields.[46] In human HL60 promyelocytic cells, these exposures at normal growth temperatures activated heat shock factor 1 and heat shock element binding, a sequence of events that mediates stress-induced transcription of the stress gene HSP70 and increased synthesis of the stress response protein hsp70kd. Thus, the events mediating the field-stimulated response appeared similar to those reported for other physiological stressors (hyperthermia, heavy metals, oxidative stress), suggesting to the authors a general mechanism of electromagnetic field interaction with cells. Their further studies have identified endogenous levels of c-*myc* protein as a contributor to the induction of HSP70 in response to magnetic field stimulation,[47] with the hypothesis that magnetic fields may interact directly with moving electrons in DNA.[48–50]

Immune responses of lymphocytes targeted against human lymphoma tumor cells (allogeneic cytotoxicity) are sensitive to both ELF exposures[51] and to ELF-modulated fields, but not to unmodulated fields.[52]

Communication between brain cells is mediated by a spectrum of chemical substances that both excite and inhibit transaction and transmission of information between them. Cerebral amino acid neurotransmitter mechanisms (glutamate, gamma-aminobutyric acid [GABA], and taurine) are influenced by ELF fields,[25,53] and also by ELF-modulated microwave fields, but not by unmodulated fields. Kolomytkin et al.[6] examined specific receptor binding of three neurotransmitters to rat brain synaptosomes exposed to either 880- or 915-MHz fields at maximum densities of 1.5 mW cm^{-2}. Binding to inhibitory GABA receptors decreased 30% at 16 pulses/s, but it was not significantly altered at higher or lower pulse frequencies. Conversely, 16 pulses/s modulation significantly increased excitatory glutamate receptor binding. Binding to excitatory acetyl choline receptors increased 25% at 16 pulses/s, with similar trends at higher and lower frequencies. Sensitivities of GABA and glutamate receptors persisted at field densities as low as 50 μW cm^{-2}.

A selective absence of responses to unmodulated (CW) RF and/or microwave fields reported in many of these earlier studies has focused attention on establishment of threshold sensitivities to CW field exposures. De Pomerai et al.[54] have reported cellular stress responses in a nematode worm as a biosensor of prolonged CW microwave exposures at athermal levels. Tattersall et al.[55] exposed slices of rat hippocampal cerebral tissue to 700-MHz CW fields for 5–15 min at extremely low SARs in the range 0.0016 – 0.0044 W kg^{-1}. No detectable temperature changes (±0.1°C) were noted during 15-min exposures. At low field intensities, a 20% potentiation of electrically evoked population potentials occurred, but higher field intensities evoked either increased or decreased responses. The exposures reduced or abolished chemically induced spontaneous epileptiform activity. Bawin et al.[25] also tested the rat hippocampal slice, using ELF magnetic fields. At 56 μT (0.35–3.5 nV mm^{-1}), magnetic fields destabilized rhythmic electrical oscillations via as yet unidentified nitric oxide mechanisms involving free radicals.

The Roles of Field Intermittency and Exposure Duration in Seeking Optimal Therapeutic Responses: Possible "Time Windows" in Trans-Membrane Signaling Paths

It has been apparent from the earliest clinical applications of pulsed magnetic fields to such problems as delayed fracture healing that continuous exposure is not an optimal technique. For example, initial tests with FDA-approved 76-Hz magnetic field generators and cultured bone samples or osteoblast cell lines revealed a range of hormonal and enzymatic responses that occurred only at the onset or immediately after termination of field exposures. In turn, similar clinical testing of various exposure schedules in bone healing led to adoption of intermittent exposure regimes.[56] In B-lineage lymphoid cells exposed to 60-Hz magnetic fields, Uckun et al.[57] reported an initial stimulation of tyrosine protein kinases (PTKs) Lyn and Syk. Activation of these Src proto-oncogene PTKs is a proximal and mandatory step in the later activation of protein kinase C. They play "myriad roles" in signal cascades affecting proliferation and survival of B lymphoid cells.

How does a cell distinguish between transient and sustained signaling? Murphy et al.[58] have shown that in 3T3 fibroblasts, the immediate early gene *c-Fos* functions as a sensor for duration of activation of *extracellular-signal-regulated kinases* (ERK-1 and ERK-2). When ERK activation is transient (30–45 min), its activity declines before the *c-Fos* protein accumulates, and under these conditions *c-Fos* is unstable. However, when ERK signaling is sustained beyond 60 min, *c-Fos* is phosphorylated by still active ERK and by RSK (90 K-ribosomal S6 kinase), thus exposing a docking site for ERK (the DEF domain). Together, these data identify a time-dependent general mechanism by which cells can interpret differences in ERK activation kinetics, including control of cell cycle progression towards either differentiation or proliferation.

Rudiger et al.[59] have reported an optimal timing sequence of 5 min ON, 10 min OFF in induction of DNA single and double strand breaks in human diploid fibroblasts and blood lymphocytes. The response to 50-Hz sinusoidal magnetic fields was dose dependent with a threshold at 70 μT. Also using cultured fibroblasts, Litovitz et al.[11] determined the minimal duration that a single low frequency modulation frequency must be sustained (*coherence time*) in order to elicit activity in the enzyme ornithine decarboxylase (ODC). Using a 915-MHz field, switching modulation frequencies from 55 to 65-Hz at coherence times of 1 s or less abolished enhancement of ODC responses, while coherence times of 10 s or longer produced full enhancement.

It is abundantly clear that such a patchwork of observations fails to provide a database that would allow selection of

optimal temporal stimulus patterns in specific clinical situations. Nevertheless, they may be considered the first pointers to crucial stimulus parameters, essential in the foundations of all magnetotherapy. They emphasize the importance of further research in that direction to define both the physical characteristics of an optimal stimulus pattern, and more importantly, the cell and molecular biology in underlying tissue substrates.

THE ROLE OF CELLULAR ENSEMBLES IN SETTING TISSUE THRESHOLDS FOR INTRINSIC AND ENVIRONMENTAL STIMULI

Our pursuit of mechanisms mediating tissue electromagnetic sensitivities at nonthermal levels raises questions about the relevance of observed thresholds in the sensory physiology of other modalities. By extrapolation, do these data suggest the need to explore collective properties of populations of cells in setting thresholds by forms of intercellular communication? Do cooperative processes yield one or more faint and private languages that allow ensembles of cells to whisper together in one or more faint and private languages? Do observed tissue-sensory thresholds differ significantly from thresholds measured in single cells in isolation from their neighbors?

Evidence for Domain Functions as a General Biological Property in Tissues

Research in sensory physiology supports this concept, that is, that some threshold properties may reside in highly cooperative properties of populations of elements rather than in a single detector.[60] Seminal observations in the human auditory system point to a receptor vibrational displacement of 10^{-11} m, or approximately the diameter of a single hydrogen atom.[61,62] Human olfactory thresholds for musk occur at 10^{-13} M, with odorant molecules distributed over 240 mm^2,[2,63] and human detection of single photons of bluegreen light occurs at energies of 2.5 eV.[64] In another context, pathogenic bacteria, long thought to operate independently, exhibit ensemble properties by communication through a system recognizing colony numbers as an essential step preceding release of toxins. These *quorum sensing* systems may control expression of virulence factors in the lungs of patients with cystic fibrosis.[65]

Domain Properties in Systems of Excitable Cells

Bialek addressed the problem of the auditory receptor in quantum mechanical terms. He evaluated two distinct classes of quantum effects: a *macroquantum effect,* typified by the ability of the sensory system to detect signals near the quantum limits to measurement, and a *microquantum effect,* in which "the dynamics of individual biological macromolecules depart from predictions of a semiclassical theory." Bialek concluded that quantum-limited sensitivity occurs in several biological systems, including displacements of sensory hair cells of the inner ear. Remarkably, quantum limits to detection are reached in the ear in spite of seemingly insurmountable levels of thermal noise.

To reach this quantum limit, these receptor cells must possess amplifiers with noise performance approaching limits set by the uncertainty principle. It is equally impressive that suppression of intrinsic thermal noise allows the ear to function as though close to 0 K. Again, this suggests system properties inherent in the detection sequence. These "perfect" amplifiers could not be described by any chemical kinetic model nor by any quantum mechanical theory in which the random phase approximation is valid. The molecular dynamics of amplifiers in Bialek's models would require preservation of quantum mechanical coherence for times comparable to integration times of the detector. It is not known whether comparable mechanisms may determine electromagnetic sensitivities as a more general tissue property at cellular and subcellular levels.

Behavioral electrosensitivity in sharks and rays may be as low as 0.5 nV mm^{-1} for tissue components of electrical fields in the surrounding ocean.[66] These marine vertebrates sense these fields through specialized jelly-filled tubular receptors (ampullae of Lorenzini) up to 10 cm in length, located near the snout and opening on the skin surface through minute pores. Sensing nerve cells lie in the wall of this ampullary tube. In support of a cooperative model of organization of these neurons, behavioral electrosensitivity in sharks and rays is 100 times below measurable thresholds of individual electroreceptor neurons.[67]

Domain Properties in Systems of Nonexcitable Cells: Culture Dimensions and "Bystander" Effects

Jessup et al.[68] have pioneered studies on the role of gravitational fields in determining trends towards either apoptosis (programmed cell death) or towards cell proliferation. Concurrently, they tested the physical configuration of cell cultures in their influence on these same trends. Based on a colorectal cancer cell line, they compared cells cultured in adherent monolayers with three-dimensional (3D) cultures.

Biochemical measures of apoptosis and cell proliferation were tested (i) in static cultures, (ii) in cultures subjected to slow rotation, and (iii) in cultures exposed to the microgravity of low-earth-orbital space flight. Over the course of 6 days on earth, static 3D cultures displayed the highest rates of proliferation and lowest apoptosis. Rotation appeared to increase apoptosis and decrease proliferation, whereas static 3D cultures in either unit gravity or microgravity had less apoptosis. Expression of the carcinoembryonic antigen as a marker of cell differentiation was increased in microgravity.

For ionizing radiation, the U.S. National Council on Radiation Protection (NCRP) has recommended that estimates of cancer risk be extrapolated from higher doses by using a linear, no-threshold model. This recommendation is based on the dogma that the DNA of the nucleus is the main target of radiation-induced genotoxicity and, as fewer cells are directly damaged, the deleterious effects of ionizing radiation proportionally decline. Experimental evidence seriously challenges this concept.[69] They used a precision microbeam of α particles to target an exact fraction (either

100% or ≤20%) of the cells in a confluent cell population and irradiated their nuclei with exactly one α particle each. The findings were consistent with nonhit cells, contributing significantly to the response, designated *the bystander effect*. Indeed, irradiation of 10% of a confluent mammalian cell population with a single α particle resulted in a mutant yield similar to that observed when all the cells in the population were irradiated. Importantly, this effect was eliminated in cells pretreated with 1 mM octanol, which inhibits intercellular communication mediated by gap-junction proteins. "The data imply that the relevant target for ionizing radiation mutagenesis is larger than an individual cell."

CONCLUSIONS

Epidemiological studies have evaluated ELF and RF fields as possible risk factors for human health, with historical evidence relating rising risks of such factors as progressive rural electrification and, more recently, methods of electric power distribution and utilization in commercial buildings. Appropriate models describing these bioeffects are based in nonequilibrium thermodynamics, with nonlinear electrodynamics as an integral feature. Heating models, based in equilibrium thermodynamics, fail to explain an impressive spectrum of observed electromagnetic bioeffects at nonthermal exposure levels. We face a new frontier of much greater significance.

In little more than a century, our biological vista has moved from organs to tissues, to cells, and, most recently, to the molecules that form the exquisite fabric of living systems. We discern a biological organization based in physical processes at the atomic level, beyond the realm of chemical reactions between biomolecules. Much of this signaling within, and between, cells may be mediated by free radicals of the oxygen and nitrogen species. In their brief lifetimes, free radicals are sensitive to imposed magnetic fields, including microwave fields. Free radicals are involved in normal regulatory mechanisms in many tissues. Disordered free radical regulation is associated with oxidative stress diseases, including Parkinson's and Alzheimer's diseases, coronary heart disease, and cancer.

Although incompletely understood, tissue free radical interactions with magnetic fields may extend to zero field levels. Emergent concepts of tissue thresholds to imposed and intrinsic magnetic fields address ensemble or domain functions of populations of cells, cooperatively whispering together in intercellular communication and organized hierarchically at atomic and molecular levels.

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5 A Fundamental Basis for the Effects of EMFs in Biology and Medicine

The Interface between Matter and Function

*Jacques Benveniste**

CONTENTS

Our current key–keyhole concept of random collision communication in the body cannot explain the myriad biochemical and physiologic reactions that can occur instantaneously and automatically. A new paradigm of electromagnetic signaling may explain these and other well-accepted but poorly understood observations.

INTRODUCTION

Why should any fields that are nonmaterial by essence act on biological constructions, which, as everybody knows since the beginning of modern biological research, are exclusively made of matter? I remember attending a presentation at a Federation of American Societies for Experimental Biology (FASEB) meeting in the United States about 10 years ago on the effect of electromagnetic fields (EMF) on living matter. At the end of the talk, the presenter was quite apologetic: "It is clear that EMF act on living matter but we don't know really why since this effect does not fit into classical molecular biology." Another interesting comment is from Tian Yow Tsong[1]:

> A prominent biochemist, in a recent conversation with the author, even labeled study of this type of cell-to-cell communication as "astrology" and maintained that signals could only be carried by "the substance of chemistry," such as molecules or ions. Although any activity of a cell or an organism must ultimately be accountable or linked to reactions of molecules, these reactions can be and most likely are driven by physical forces. Here we will consider how communications through space by force fields (electrical, magnetic, pressure, etc., i.e., the substance of physics) may also accomplish similar tasks and are universally used by cells and organisms.

What is striking in these quotations is the neglect by classical biology of the existence of physical interactions between cells and molecules. T. Y. Tsong himself seems to consider that there are two ways of communication, one, which is supposed to be strictly molecular, and one that is physical.

THE MOLECULAR SIGNAL: FROM PTOLEMEUS TO NEWTON

An interesting aspect of this near blindness of current biology is the universal use of the words *molecular signal* or *signaling.* These words, along with *molecular genetics,* are certainly the most used nowadays by biologists at large. Readers of these pages may be willing to experience personally the reality of this biological black hole. It would be surprising if in any nearby university there were not one conference a month dealing directly or indirectly with molecular signaling. The experiment that I have myself practiced quite often is the following: attend the conference. At the end, ask the following question: I am not a specialist in molecular signaling, but I heard repeatedly the word *signal, signal, signal…* would you please tell me what is the physical nature of the molecular signal?

The result is rather funny, most lecturers and participants reaching near catalepsy. In fact, they do not understand the question. Most of the time an answer will come such as "the molecule is the signal." It is clear that biologists confuse the origin of the signal with the signal itself (everybody knows that if a man waves a red flag to stop a train, the signal is the red flag, not the man) and that they are reluctant to envision the role of physical forces in the generation and transmission of the signal. It took me several years to realize with

* Deceased.

astonishment that the cornerstone of biology, that is, the communication between molecules, relies on a Ptolemean concept, which postulates that the exchange of information takes place following a mere physical contact between coalescent molecules. The Newtonian principle of action between two distant bodies without any material connection has not yet penetrated biology.

FROM THE "MEMORY OF WATER" TO DIGITAL (ELECTROMAGNETIC) BIOLOGY

Starting from the surprising result (surprising, to say the least, for the "normal" biologist that I was at that time) that water could convey and keep for quite a long time the specific molecular message, I reached, through several experimental steps, the conclusion that molecular signal could be mimicked by electromagnetic signals in the sound range. The well-known emissions of frequency spectra by molecules, which is the basis of molecular spectroscopy, appear not only to be a physical characteristics but seems to be generating the specific molecular signal that is instrumental in the exchange of information between molecules, probably via the phenomenon of coresonance.

The history of my involvement with "high dilutions" is summarized in Table 5.1.

SIX BIOLOGICAL SYSTEMS

Meanwhile, we have developed several biological systems that allow us to extend the concept of high dilutions being capable of mimicking the effect of the original molecule. Besides the basophil degranulation (1984–1986), we have completed hundreds, if not thousands, of experiments on isolated perfused guinea-pig heart according to Langendorff (1990–1998), and in the same time period, activation of human neutrophils by electronically transmitted phorbol-myristate acetate. Then, in 1997–1998, we worked on a skin test (guinea pig or rabbit) and on an antigen-antibody precipitation system, which allows us to remotely detect any antigen or groups of antigens. The latter has been our main supporting procedure for research along with the effect of digitally recorded heparin and heparin like substances on plasma or fibrinogen clotting, developed in 1999. More recently, we have constructed an automatic analyzer which performs the digital technique without any human intervention.

We do not have enough space in this short review to show experimental results on all these systems. We have presented these results at many FASEB meetings along these years and recently succeeded, in spite of open censorship from main scientific journals, to publish one full article.[2] A complete bibliography can be found at http://www.digibio.com/cgi-bin/node.pl?lg=us&nd=n4_7.

TABLE 5.1
History of High Dilution (Dubbed the "Memory of Water")

1984	Fortuitous discovery of basophil degranulation triggered by high dilution of anti-IgE antiserum
1988	Publication in *Nature*, followed by an "inquiry"
1991	Erasing of high dilution activities by an oscillating magnetic field (series of blind experiments in collaboration with a CNRS team)
1992	Electronic transfer (via an amplifier) of biological information to a tube of water
1995	Digitization: recording then replay of the biological signal using a computer
1998	Activation by agitation of a solution at very low concentration (down to 10^{-14}M)

THE FLYING MOLECULES

One of our most spectacular experiments was performed in 1996 between Northwerstern University, Chicago, USA, and our laboratory in Clamart-Paris, France. Molecular solutions of ovalbumin, acetylcholine, and, as control, dextran or water were recorded in Chicago using a purpose-designed transducer and a computer equipped with a sound card. The recordings were sent coded to us either on diskettes or by E-mail. Results on 25 files are summarized as follows. The variation in coronary flow of ovalbumin-sensitized guinea-pig isolated hearts induced by digitally recorded ovalbumin was (in percent ±1 standard deviation) 24.0 ± 1.4 (number of measures = 30), whereas that induced by digitally recorded water was 4.4 ± 0.3 ($n = 58$); $p = 4.5\ e - 17$. The effect of naive water was 4.9 ± 0.3 ns ($n = 41$) compared to d water, and that of molecular ovalbumin was 0.1 μM 28.9 ± 3.7 ns ($n = 19$) compared to digital ovalbumin. Specificity of the system was absolute: no effect was seen when the ovalbumin signal was applied to hearts from nonsensitized animals. Similarly, atropine but not antihistamine inhibited the acetylcholine digital signal as well as the real molecule.

This experiment, I believe, unequivocally demonstrates that the specific molecular signal can be recorded, transmitted at long distance, and then reapplied to the relevant biological system, where it induces the same effect as the original molecule. It is for this experiment that I was awarded a second Ig-Nobel prize. The problem is that no scientific criticism was voiced by the distinguished jury, composed of self-appointed guardians of the scientific purity. Here it is worth noting that our high-dilution experiments have been replicated by six independent laboratories, one doing it twice. How many replications are required for a work to be considered as replicated?

TWO WORKHORSES

Our present main experimental systems are[1] the inhibition of fibrinogen coagulation by digital anticoagulant (see www.digibio/video);[2] the precipitation of antigen-antibody complexes following exposure to the signal of the specific antigen or antibody. The latter method could allow us to remotely detect the presence of microbes (bacteria, viruses, parasites, fungi).

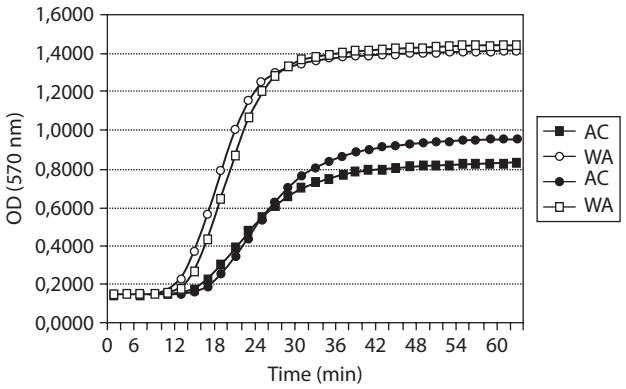

FIGURE 5.1 Thrombin-induced fibrinogen coagulation after exposure to anticoagulant (AC) or water (WA) signals. Blind experiment performed by an automatic analyzer (July 5, 2002).

Figure 5.1 is a representative example of inhibition of coagulation by the signal of an anticoagulant. We have performed hundreds of such experiments.

CONCLUSIONS

This set of results provides an answer for our initial question: EMF act on living matter because the mode of communication between molecules, which is essential to life, is electromagnetic in nature. Molecules communicate like a radio set that receives waveforms carrying specific information from the station to which it is tuned to coresonate and to none other. This communication takes place through water molecules surrounding all biological molecules. Water may have an amplifying role. Some of our data indicate that the signal is indeed emitted by the molecules but is finally conveyed by water, similar to the strings of a violin, which do not create music unless affixed to the resonating wooden box. In addition, we have clear evidence of an influence of some humans on our experiments. This may apply to classical biology too.

These results represent a small theoretical step forward. That molecules emit specific frequencies has been known for decades. We claim, and we believe we have shown, that they use these frequency spectra as their major means of communication. The heretofore physically undefined molecular signal appears to be composed of hertzian waves

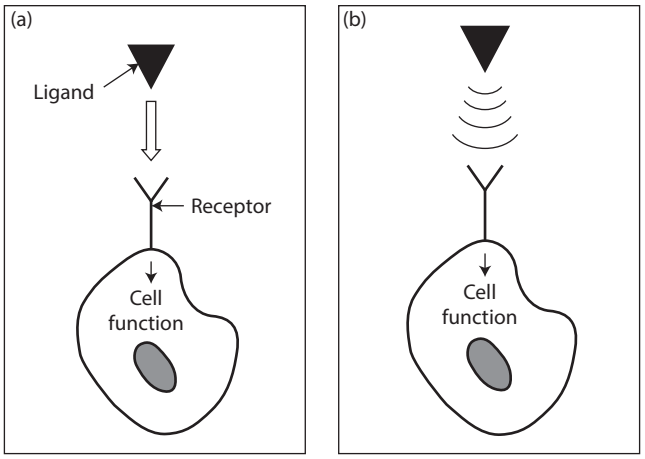

FIGURE 5.2 Molecular signaling. Chemical/molecular versus Physical/atomic communication. (a) 20th century communication structural contact, (b) 21st century communication structural contact.

at least in the sound range. This is not a scientific revolution, as stated by conservative scientists who accused us of "negating the existence of molecules, hence two centuries of research." We simply replace the arrow that is supposed to represent the interaction of two ligands with a symbol representing the waveforms that support this interaction (Figure 5.2).

As a vast array of technological devices are now at our disposal to record, transmit, analyze, modify, and digitize these types of signals, this advance could profoundly change our views and our experimental approaches to biology and medicine. The now obvious failure of classical structural biology to explain the complex mechanisms supporting life and provide solutions to its disorders shows that it is about time that biology makes, at long last, its Newtonian revolution, that is, going from matter to energy.

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6 Subtle Energies and Their Roles in Bioelectromagnetic Phenomena

*William A. Tiller**

CONTENTS

Various studies are presented to illustrate how human consciousness and intentionality can generate subtle energy fields that are translated into electromagnetic fields having significant biochemical and physiologic effects. Such subtle energies can also be stored in an electrical device and utilized to change the pH of a solution, increase the *in vitro* thermodynamic activity of enzymes and increase the *in vivo* ratio of ATP to ADP in developing fruit fly larvae to significantly reduce the maturation time to adult flies.

INTRODUCTION

The existing formalism for the quantum mechanical (QM) paradigm of physics is perhaps the greatest stumbling block that we have in trying to understand the essential differences that exist between bioelectromagnetism (bio-EM) and conventional electromagnetism (EM). Most scientists and engineers tend to think that bio-EM is just conventional electricity and magnetism applied to biological systems—it is not! In this chapter and the next, we show why it is not and how to begin revealing the differences.

To help the reader understand these differences, the next section deals briefly with key concepts and definitions that need to be comprehended in order to grasp the viewpoint of this chapter. In the section "Some General, Background Psychoenergetic Data," some general psychoenergetic experimental data will be utilized to illustrate how human bio-EM can be very different from conventional EM. In this section, one particular example will be utilized to show how human consciousness can generate subtle energy fields that, in turn, translate into experimentally measurable EM-fields. In the section "Some Robust Effects of Human Intention on Space Conditioning," recent experimental studies by the author and his colleagues regarding some very robust effects of human intention on "conditioning" the experimental space to a higher EM gauge symmetry state will be presented. In turn, this higher symmetry level strongly influences physical reality via altered material properties manifesting in experimental measurements. In the next chapter, this work is extended to show why humans, and probably all vertebrates, contain a higher EM gauge symmetry state system functioning in their bodies and this system *strongly* influences their bio-EM. Here, we will see how subtle information-energy fields convert, in part, to measurable E and H fields, and how conscious intent can act as a true thermodynamic variable to influence the magnitude of E and H, the only fields we can instrumentally quantify at the moment. There, we finally get to discuss some quantitative differences between bio-EM and standard EM. A multidimensional theoretical model is presented that

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both rationalizes the aforementioned experimental observations and provides a meaningful quantitative basis for expanding our QM paradigm. Finally, the next chapter closes by returning to day-to-day expectations for one area of near-future applications of bio-EM and subtle energies in the area of medical therapeutics.

SOME CONCEPTS AND DEFINITIONS

De Broglie's Particle–Pilot Wave Concept

Classical mechanics dealt only with particles, whereas this concept, which became one of the cornerstones of QM, is perhaps best illustrated by Figure 6.1.[1,2] De Broglie proposed that every particle had a pilot wave envelope enclosing it and moving at the particle's velocity. This concept required that, as this pilot wave envelope moved along, some new wave components moved into the envelope while some old wave components moved out. Calling the particle wave velocity v_p and an individual wave component velocity v_w, relativity theory requires that the following relationship holds:[3]

$$v_p v_w = c^2 \tag{6.1}$$

where c is the velocity of light. Since $v_p < c$ always, $v_w > c$ always, these waves were dubbed "information" waves in order to not make trouble for relativity theory (see Chapter 18, Figure 40.1).

Although in QM, de Broglie's concept (proven experimentally) became known as wave-particle *duality,* this author proposes that nature expresses itself simultaneously via its particle aspect and its information wave aspect. This means that the quantitative magnitude of *any* physical measurement is comprised of two parts: (i) the coarse particulate part and (ii) the fine information wave part. Here, it is important for us to realize that all the waves of our cognitive experience are merely modulations of particle fluxes or particle densities in space-time. All the continuum type EM waves, drawn in electrical engineering textbooks, are actually de Broglie's information waves traveling through the vacuum level of substance.

The Vacuum Level of Substance

The fundamental particles making up our atoms and molecules are so tiny that they occupy only a miniscule amount of the total space. The remainder of that space (99.999 + %) is the vacuum level of substance. This particular vacuum, like that between the planets, *is not empty.* For QM and relativity theory to be internally self-consistent, others have calculated that it must contain an energy density, in mass units, of 10^{94} g/cm^3. This is a huge number. What it means in more practical terms is that provided we can assume our universe to be flat (and current day astronomers say that we can), there is a trillion times more latent energy stored in the volume of a single hydrogen atom's vacuum level than in all the mass of all the planets and all the stars in our universe out to a radius of 20 billion light-years. Thus, the vacuum level of substance is what we must look to for our scientific and technological future.

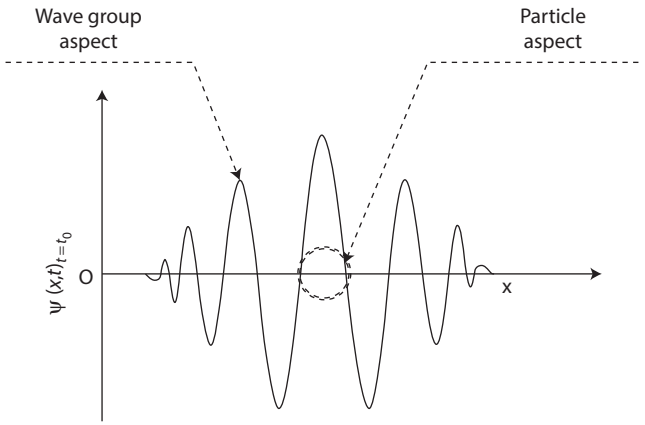

FIGURE 6.1 A group of pilot waves for a physical particle located somewhere in the group.

Gauge Symmetry

In current physics, one of the key discussions that connects the *Gauge* condition to important concepts and hypotheses is that associated with the big bang concept. Here, one encounters a description of energy and eventually matter undergoing evolutionary changes of state, from states of higher fundamental symmetry to states of lower fundamental symmetry.[4] At amazingly short times in this proposed process, gauge transformations occurred from very high symmetry states and progressively drop to the lower state of the SU(2) EM gauge and then on down to the U(1) EM gauge symmetry level—our present cognitive domain.

Symmetry changes for matter still occur at the U(1) gauge level but these all involve collective interactions described as changes of state of the plasma → gas → liquid → solid kind as the temperature continues to fall. Further lowering of temperature leads to magnetic dipole ordering in some materials, electron pairing in others and phonon–photon coherence development in still others. All of this is a manifestation of the lowering of the Gibb's free energy for the system.

We are all familiar with the simple symmetry rule of rotational invariance, examples being 60° for the snowflake, 90° for the cube and 120° for the triangle. For the U(1) EM gauge symmetry state, it is a little more complex with the major requirements being (i) the coexistence of electric monopoles and magnetic dipoles, (ii) Maxwellian equations for EM, (iii) Abelian algebra applies ($XY - YX = 0$, where X and Y are unique fields), and (iv) a completely disordered vacuum level. On the other hand, for the SU(2) EM gauge symmetry state (a higher Gibb's free energy state than the U(1) state), the situation is still more complex in some ways. Here, the major requirements for this chapter are (i) the coexistence of both electric and magnetic monopoles, (ii) non-Maxwellian EM,[5] (iii) nonabelian algebra ($XY - YX \neq 0$), and (iv) the existence of domains of order in the vacuum.[6]

What one notes regarding the big bang process is that, *unimpeded by consciousness inputs,* thermodynamics will drive the system towards a lower and lower Gibb's free energy state.

The Conditioning of Space

This involves the sustained use of human intention at a particular spatial location. This raises the EM Gauge symmetry condition, metastably at first and then, eventually, to a sufficiently high state that a symmetry phase transition can be nucleated at the vacuum level of that location. This stabilizes the higher symmetry state for an extended period of time (years), but perhaps can be destabilized by the reverse intention.

Our Particular Biconformal Base-Space Frame of Reference (FR)

The current reference frame for QM is distance-time, (x, y, z, t), and this is fine provided no mathematical singularities are present.[1,2] However, QM abounds in singularities and relativity theory has a major one at $v = c$. Based on Equation 6.1, Figure 6.2 illustrates this latter singularity. When mathematical singularities are present in the domain of interest, it is well known that the expansion of any mathematical function about a point in the domain requires the use of Laurent's procedure rather than Taylor's procedure, which is usually used. As an example, for the Gibb's free energy function G, we must use

$$G(z) = \underbrace{\underbrace{G(z_0) + \sum_{n=1}^{\infty} a_n (z - z_0)^n}_{\text{Taylor}} + \sum_{n=1}^{\infty} b_n (z - z_0)^{-n}}_{\text{Laurent}} \tag{6.2a}$$

where z_0 is the point about which we are expanding. In the thermodynamics of homogeneous systems, only the first ordered terms are considered. Typically, one either lets z represent the thermodynamic intensive variables of P, T, n_j, etc.

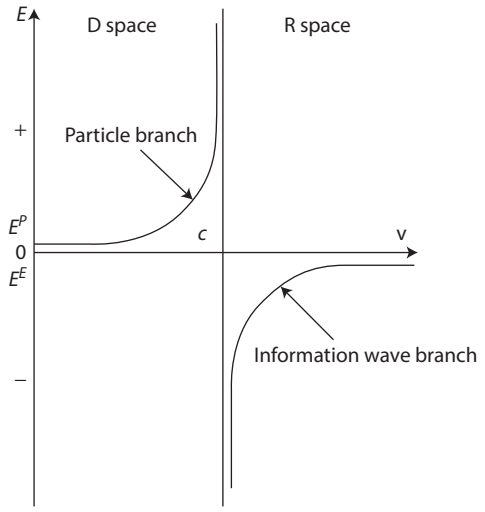

FIGURE 6.2 Energy–velocity diagram for a D-space particle ($v < c$ branch) and its R-space pilot wave conjugate ($v > c$ branch).

(P = pressure, T = temperature, n = number of moles of chemical species j, etc.) or the distance-time coordinates, (x, y, z, t).[2,7] For our interest here, it is the first-order expansion terms in distance-time that are important, therefore, Equation 6.2a shows us that we have terms involving (x, y, z, t) plus terms involving (x^{-1}, y^{-1}, z^{-1}, t^{-1}). If we define $b_1' = b_1/2\pi$, $k_j = 2\pi/(z_j - z_{j_0})$ and $z_j = (x, y, z, t)$, then we can begin to see our biconformal base-space reference frame developing out of Equation 6.2a. It is two, four-dimensional subspaces, (x, y, z, t) and its reciprocal (x^{-1}, y^{-1}, z^{-1}, t^{-1}) or (k_x, k_y, k_z, k_t). The reciprocal coordinates are all frequencies, x^{-1} = number per unit distance = a spatial frequency and t^{-1} = number per unit time or a temporal frequency. Thus, Equation 6.2a, in its first-order form but with all coordinates represented, becomes

$$\begin{aligned} G - G_0 \approx\ & a_x(x - x_0) + a_y(y - y_0) + a_z(z - z_0) + a_t(t - t_0) \\ & + b_x'k_x + b_y'k_y + b_z'k_z + b_t'k_t \\ =\ & \text{D-space } (x, y, z, t) \text{ terms} \\ & + \text{R-space } (k_x, k_y, k_z, k_t) \text{ terms} \end{aligned} \tag{6.2b}$$

Here D space refers to direct space, while R space refers to its reciprocal space. Together, they form a unique 8 space.

One of the beautiful things about this particular biconformal base-space RF is that it naturally separates into particle space (D space) and information wave space (R space). Another is that the D-space contribution allows only local forces while the R-space contribution allows nonlocal forces. This is because things that are far away and far apart in D space (like planets and stars) are very close together in the low-frequency domain of R space. A third important outcome of choosing this particular RF is that, for such reciprocal 4 spaces, mathematics *requires* that any substance quality in D space can be quantitatively related to its conjugate equilibrium quality in R space by a *Fourier transform* type of relationship and vice versa. This latter outcome means that, for *any* physical measurement Q_M, we must have

$$Q_M = Q_D + Q_R. \tag{6.3}$$

And we have a quantitative pathway connecting Q_R to Q_D (the modified Fourier transform). Thus, we must begin to look at physical reality as consisting of two layers: (i) the coarse, particulate layer that we all cognitively access; and (ii) the fine information wave layer, which most of us do not presently cognitively access because it functions at the vacuum level of nature.

Deltron Coupling

As we will see later in the Section "Some Robust Effects of Human Intention on Space Conditioning," a strong DC magnetic field polarity effect occurs on the pH of water when the water is in a conditioned space[2] but not when it is in an unconditioned space (the U(1) EM Gauge symmetry state). The fact that such a polarity effect can arise would seem to suggest that magnetic monopoles are somehow being accessed. This

implies that the information wave aspect of substance may be "written" by the magnetic monopoles. If this is so, then the actual existence of any form of EM requires a meaningful although not direct interaction between electric monopole substance traveling at $v < c$ and magnetic monopole substance traveling at $v > c$ (see Equation 6.1). Let us invent a higher dimensional coupling substance that is *outside* the constraints of relativity theory and can travel at both $v < c$ to interact with D-space substances *and* at $v > c$ to interact with R-space substances. I label this coupling substance "deltrons" from the next higher dimension (9 space), which I have elsewhere[1] designated as the domain of emotion.

Subtle Energies

We are all familiar with the four fundamental forces of gravitation, electromagnetism, the long-range nuclear force, the short-range nuclear force, and the energies that they give rise to. Subtle energies are none of these! Subtle energies need not be weak, but they are elusive because we do not presently have direct detection probes for them. At this point in time, it is thought that all subtle energies reside at *the vacuum level* of nature (see Figure 6.3). At present, only the information wave substance and the deltron substance have been articulated and discriminated by this author. However, acupuncture energies, homeopathy energies, remote viewing energies, etc., are all thought to fall into the R-space category.

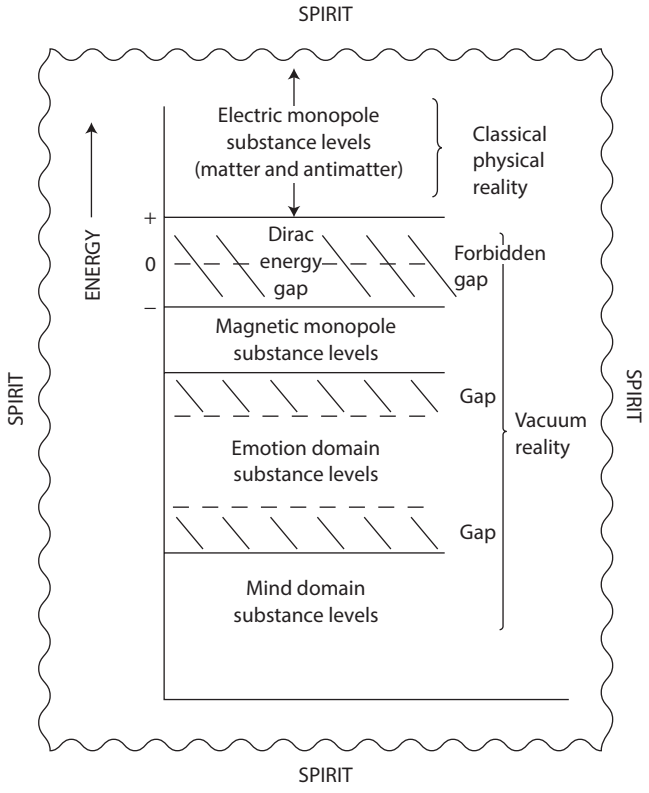

FIGURE 6.3 An energy level diagram embracing both classical physical substance and "unseen" vacuum substances.

Equilibrium Cluster Populations

Many scientists hold the naive view that all liquids, and particularly pure water, are completely homogeneous down to the atomic or molecular level and exhibit structural characteristics in complete accord with the random network model proposed over a half-century ago for glasses.[8] However, nothing could be further from the truth and even the nanoscale heterogeneous perspective of water's structure has grown greatly in the last few decades and is available in some fine reviews.[9] This topic is considered here because it is so relevant to medical therapeutics.

From a theoretical perspective,[10] one naturally expects pure water to contain a wide spectrum of thermodynamically distinguishable species because the configurational entropy contribution of each unique species lowers the bulk free energy of water. The equilibrium population, N_i^*, of each unique species *i,* is given by $N_i^* = N_0 \exp(-\Delta G_{F_i}/kT)$, where N_0 is the monomer H_2O concentration available for forming these new species, kT is the thermal energy and ΔG_{F_i} is the free energy of formation of the *i* species from this multispecies "soup." These species range from H^+, OH^- and monometric H_2O in the H-bonded network to clusters, differentiated by both polymorphic structure and size, and to microvoids of varying size and internal gas content. Although the statistical ensemble of these associated entities exhibits a stable equilibrium population distribution at any particular temperature and pressure, a particular cluster may dissociate and another re-form at a high frequency to stabilize the total ensemble on time average. Whenever N_i falls below or exceeds N_i^*, a thermodynamic driving force exists to change N_i toward N_i^* at the fastest rate allowed by the local reaction kinetics. It is also important to note that a specific solute, *j,* added to water also has a specific equilibrium population, N_j^*, given by the above formula with ΔG_{F_i} equal to the free energy of solution for *j.* However, the concentration of this species can only be changed by dilution with pure water or by the addition of more solute. As all of these various N_i^* and N_j^* species are enfolded into the bulk water host via surrounding envelopes of H bonds that join the general H bond network of the water and, as overall free energy minimization of the total system may be constrained by the availability of such H bonds, solute agglomeration might be an anticipated result below some specific degree of dilution.[11] If H bond availability can be a thermodynamic and perhaps a kinetic rate-limiting constraint in water, this suggests that a large fraction of the H_2O molecules present in bulk water are associated with unique complexes of the types delineated above. From the foregoing, one must expect great heterogeneity in the fluid aspect of human cells.

External Field Effects

General electric *E* and magnetic *H* field effects on the thermodynamic properties of a homogeneous liquid can be inferred from References 2 and 10. However, the nanoscale heterogeneity of water discussed above introduces several new and important factors that need to be addressed here. This arises

from the fact that our standard environment contains a DC magnetic field, AC electromagnetic fields of a wide range of frequencies plus atmospheric ion-generated DC electric fields. For either DC or AC fields, the clusters and microbubbles have different electric and magnetic susceptibilities relative to bulk water. Thus, both electric and magnetic dipoles are induced at these interfaces[12] and, for nonuniform fields, will migrate towards the high field regions under the influence of dielectrophoresis and diamagnetophoresis[13] forces. These quasiparticles will migrate towards the high-field regions of the bulk water sample where many will annihilate ($N_i > N_i^*$) while new cluster/nanobubble creation events must occur in the low field regions ($N_i < N_i^*$) adding to the overall dynamism of change. It has been shown recently that magnetically shielded water stays for a remarkably long time in metastable states without actively moving towards equilibrium and that miniscule H fields greatly enhance the rate of pH and ORP progression towards some stationary state with the rate of progression increasing strongly with the magnitude of H.[14] Abundant experimental data exists to confirm many strange effects associated with electromagnetic field effects and water.[15] Surprisingly, when the water is first degassed before EMF exposure, these strange effects are absent.[16] Direct electron microscope evidence also exists for magnetic field alteration of the Helmholtz layer thickness at solid–water interfaces.[17]

Perhaps a simple example from medical therapeutics will best illustrate the complexity of the issues here. Suppose we have a device placed around a human's knee that creates a macroscopically uniform AC electromagnetic field intensity (E^2 and H^2) outside the knee. One might quickly assume that nothing will happen inside the knee because this imposed field is macroscopically uniform. However, inside the knee, the structure is polyphase (bone, cartilage, tendons, fluid, "colloids," ions, etc.) and thus heterogeneous with respect to electric and magnetic susceptibilities. This means that, *inside* the knee, the E and H fields are macroscopically nonuniform and it is these internal environment fields that drive "colloids" and small dipoles to drift towards the local high field regions. Further, with the passage of time, these "colloids" and small dipoles concentrate in certain regions and now create *DC fields* that, in turn, initiate local ion movements (electrophoresis) to neutralize such induced DC fields.

The main point to be communicated by this final section is that the presence of any structural heterogeneities in water leads to local heterogeneities in electric permittivity and magnetic permeability and these, in turn, respond directly or indirectly to ambient E and H fields so as to cause drift movement of such moieties in the solution. Such long-range movement upsets the homeostasis of the solution with a variety of interesting consequences.

SOME GENERAL, BACKGROUND PSYCHOENERGETIC DATA

In a recent book, Radin[18] has provided clear and incontrovertible evidence to support the existence of extra sensory perception (ESP) capabilities in humans. Although the effect size is small for the average population, it is clearly nonzero. This field also has its superstars, like a Michael Jordan or a Tiger Woods, where the effect size can be very large. Ingo Swann[19] and Edgar Cayce[20] are two names that come readily to mind. For today's medicine, this type of data sheds strong light on the so-called placebo effect. The prevailing medical view is that nothing real has occurred and that any improvement is delusional. In Benson's work[21] among patients receiving a variety of treatments they believed in, but for which medicine finds no physiological basis, treatments were effective 70%–90% of the time. However, when the physicians doubted whether these treatments actually worked, their effectiveness dropped to 30%–40%.

Similar belief-related success was observed in Stewart Wolf's work[22] with women who experienced persistent nausea and vomiting during pregnancy. First, sensors were positioned in their stomachs so that contractions could be recorded. Next, they were given a drug that they were told would cure their nausea. In fact, they were given Ipecac. However, because of their belief, the women reversed the laboratory-proven action of the drug and their measured stomach contractions damped down to negligible values. Further, Enserink[23] has pointed out that "when companies started testing drugs for obsessive-compulsive disorder back in the mid-1980s, the placebo response rate was almost zero. As time went on, this response rate began to creep upward, up to a point when one could reasonably conclude that some clinical trials failed because of high placebo response rates." A recent meta-analysis of 19 antidepressant drug trials revealed that the placebo effect on average accounted for 75% of the effect of *real* drugs. Although many feel that this data represents a kind of soft underbelly that both academic and industry researchers are more comfortable leaving out of sight, others are fascinated by the power of the placebo effect viewing it not as a problem but as a source of insight into mental health. Going even further, what is it saying about the *actual* laws of nature, as distinct from our metaphysical assumptions about them, and *why* has the magnitude of the placebo effect increased so remarkably in the last 20 years?

Another major psychoenergy experiment involves the conscious cognition of objects, terrain, atmospheric conditions, and so forth located hundreds to thousands of miles away, given only the coordinates of the location. This experiment, originally conceived, conducted and developed by Ingo Swann and given the name *remote viewing,* was refined and perfected by him in association with Puthoff and Targ[24] at Stanford Research International. For government service remote viewers, successful completion of a training program required a minimum of 85% accuracy with respect to the coordinates of 20 blind targets. In some cases time coordinates, past or future, were also involved.

A more familiar mode of remote viewing involves one's ability to "tune in" to a specific individual and view a specific remote locality through that individual's eyes. This mode of remote viewing ability is more easily acquired and has been replicated in many laboratories around the world.[24]

Dossey,[25] Targ and Katra[26] plus many others have clearly shown that humans are not only capable of highly accurate long-range cognition of local details plus events but they are also capable of eliciting human health transitions at such distant locations. From Dossey's three eras of medicine model, Era III-Medicine is defined by *nonlocal* approaches to healing.[25] It views the mind as unbounded and unconfined to points in space and time so that this category of healing events may bridge persons who are widely separated from each other. This category of medicine goes well beyond today's view of physics so that mind, not matter, is ultimately considered as being primary. Expanding on nonlocal force and influence effects, a great deal of data[27] is now available to show that both *Qigong* masters and adepts can significantly influence materials and processes both locally and nonlocally located. For example, Yan Xin emitted his *Qi* into samples of tap water both from a local arrangement and via a nonlocal arrangement (~7 km away) and any change in the water's Raman spectrum was investigated.[28] There are two peaks in the Raman spectrum of normal water: one very large peak is at 3430 cm^{-1}, corresponding to the stretching vibrational mode of OH, and one weak at 1635 cm^{-1}, corresponding to the bending vibration mode for HOH. Before Yan Xin's *Qi* emission, this is what was observed for all samples. However, after *Qi* emission, there was a huge peak (~18 times higher than the normal peak at 3430 cm^{-1}) ranging from 1000 cm^{-1} to 3000 cm^{-1} observed in the Raman spectrum for the water samples. This huge peak decayed by ~2/3 within the first 1.5 h and it had completely disappeared after ~2 h from *Qi* emission, leaving a Raman spectrum that was essentially identical to that of the untreated water.

All of the aforementioned works are examples of subtle energies producing substantial effects on physical reality! Now, let me provide a few examples from this author's own work.[1,29]

In the 1970s, I carried out a series of experiments with a man whose bio-EM field was such that he had a unique ability with cameras and its photographic film. Whenever he took a picture while he was experiencing a particular familiar feeling in his seventh cervical and fourth thoracic vertebrae, some striking anomaly would appear in the photograph. His held intention during the picture-taking process was, he said, "to reveal God's universe."

My experiments with him used two cameras, one of them sensitized by keeping it close to his body for several days and the other unsensitized. Both cameras were mounted on the same tripod and tripped with a single shutter release. Ordinary colored film was used in both cameras and was processed by its manufacturer, and the subject was never allowed to touch the film. Often, though not always, pictures taken with the sensitized camera showed one or more people as if they were partially transparent, or translucent, so that objects located behind them could be seen "through" them[29,30] The pictures from the unsensitized camera appeared normal. On other occasions, clear pictures were taken via the sensitized camera with the lens cap firmly in place on the camera.[30]

My interpretation of this phenomenon is that

1. Some radiations exist in nature that can travel through materials that are opaque to visible light.
2. Because of some presently unknown quality inherent in the subject's biofield, these radiations can be detected by film in the sensitized camera.
3. Some time is required for the camera placed in this special human energy field to acquire its anomalous capacity.
4. The anomalous capacity leaks away in about an hour or so unless continuously pumped by the energy field of the subject.

In a second set of studies,[29,30] an AC voltage at 450 Hz was applied to dielectric-coated electrodes that bounded a 2 mm layer of gas in a sandwichlike gas discharge device (see Figure 6.4). The applied voltage peak to the device was kept 10%–15% below the breakdown voltage for the layer of gas, and electron "microavalanches" passing through the gas were monitored by a pulse counter that could be set to count any pulse over a predetermined size.

Typically, the pulse counter was set to just miss the largest avalanches traveling across the gas. Thus, the system was poised but yielding a zero count for many hours until a human subject attempted to influence it. Almost a thousand or so experimental runs involved a person holding their hands about 6 in. from the device and *intending* to increase the count rate. Over a 5-min/period of such intending, the number of recorded pulses often went from zero to the 50,000 range.

If the subject's hands were not held near the device but the intention was still to increase the count rate, total counts could still be increased from zero to a range of 10,000–20,000 counts within 5 min. If, during the same type of experiment, the subject's intention was directed *away* from the device by being focused on a different mental task, no change in the count rate occurred, and the total counts was still zero at the end of 5 min even though the subject's hands were straddling the device.

From these results, I deduced that

1. People manifest a heretofore undetected energy that has the property of increasing both electron microavalanche size and number in a nearby gas discharge system.
2. A person can direct the flow of this energy in a chosen direction by their mind.
3. The mind–electron interaction can be effective over appreciable distances.

Elmer Green and his associates at the Menninger Clinic devised a simulated healing experiment involving an accomplished healer in a specially designed environment in a larger room[29,30] (see Figure 6.5). The healer, wired to a variety of electrophysiological measurement instruments, stood or sat on an electrically insulated framework placed within four

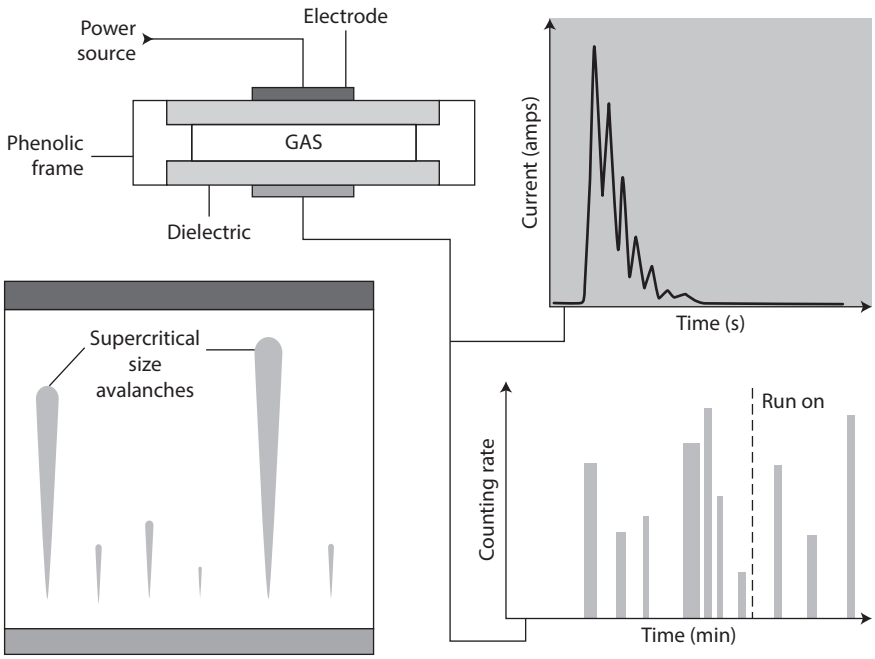

FIGURE 6.4 The gas-discharge experimental setup comprised a high fidelity, high-voltage power source, the gas discharge device, and a monitoring system. This schematic illustration shows electron avalanches passing through the gas, a typical oscilloscope tracing of total electron avalanche current versus time and a plot of the count rate as a function of time during an experimental run.

large, square copper walls (one in front, one behind, one above, and one below). Electrically insulated electrometers simultaneously recorded the voltages of these four walls plus that from an electrode placed on the healer's earlobe.

Instead of the 10- or 15-mV baseline reading with 1-mV ripples that are typical of the human body, it was observed that the healer's body voltage often plunged by 30–300 V and then returned to baseline within 0.5–10 s. This astoundingly large voltage pulse is about 100,000 times normal. Correlated pulses of 1–5 V appeared on each of the four copper walls. In a 30-min simulated healing session, the healer manifested 15 of these anomalously large pulses.

From this experiment, I generated a theoretical model[30] of a nondirectly observable subtle energy pulse emitted from some locations in the healer's body that was transduced through a series of stages and manifested as an electric dipole pulse at a specific location in the healer's body (see Figure 6.6). With this model and the experimental data, I was able to make a quantitative analysis from the 15 pulses.[30]

In 13 of the 15 pulses, the place of origin in the healer was the lower abdomen. The dipole was predicted to extend from the ear (negative charge end) to the feet (positive charge end), and it required quite small current flows for a very short time to achieve the result (~5 nA flowing for ~1 s). Such a current flow is much less than that typically observed when two different acupuncture points on the body are connected.

For the other two anomalous pulses, it was necessary to propose the formation of two simultaneous electric dipole pulses to account for the different type of data observed. From this data, the location of the second dipole was predicted to be in the head.[30]

What I deduced from this study was that (i) the healer's intention to heal can manifest, ultimately, as large, observable electric voltage pulses in physical reality, (ii) some medium exists that couples the nondirectly observable subtle energy to an observable physical energy, and (iii) a precise mathematical analysis can be generated to concretize this elusive concept.

From what is to come later, a hypothesized subtle energy field, χ, is pulsed in time. This is transduced to a magnetic vector potential, A, profile in time of a gaussianlike shape. From our conventional U(1) EM gauge symmetry equations, this leads to the type of E-field pulse illustrated in Figure 6.6c which, in turn, causes ion movement in the electrolyte of the body to create a charge dipole of the type needed to rationalize the experimental data.

SOME ROBUST EFFECTS OF HUMAN INTENTION ON SPACE CONDITIONING

For the past several years, my colleagues and I have been conducting specific target experiments on the use of intention imprinted electrical devices (IIEDs) to influence both inanimate and animate materials with respect to some of their properties.[2] For each target experiment, one starts with two identical simple electronic devices housed in 17.8 cm × 7.6 cm × 2.5 cm black plastic boxes. One isolates them from each other by first wrapping them in aluminum foil and then storing them in separate electrically grounded Faraday cages (FCs). One is left as is and is designated as the "control." The other is taken out of its FC, unwrapped, and "charged" with the specific intention or the particular target

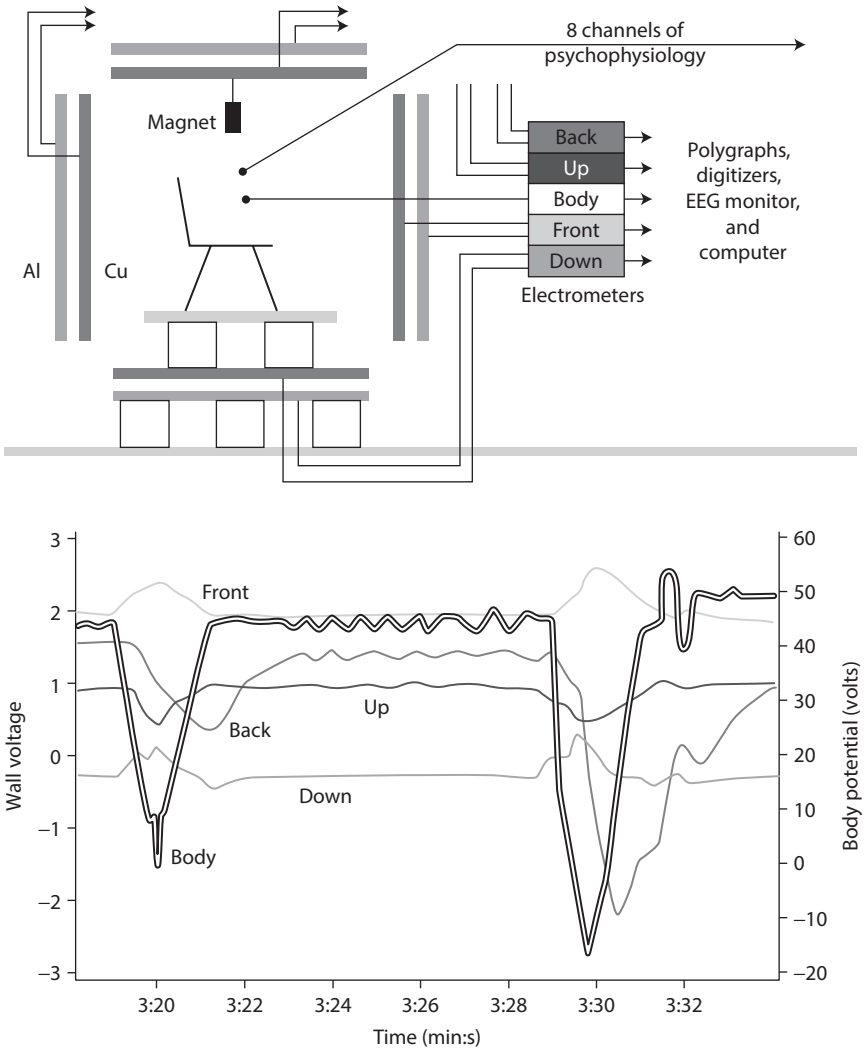

FIGURE 6.5 In the copper-walled meditation room, four pairs of insulated copper and aluminum panels float in electrical space around a research chair, which also floats electrically, insulated from the "down" panel by glass construction blocks. Signals from the subject's body and from the four copper walls are fed into electrometers, and data from all channels are forwarded to polygraphs, digitizers, and a computer. The graph shows an example of simultaneous body and wall potentials.

experiment under consideration. It is then rewrapped in Al foil and returned to its FC.

This charging process involved the services of four highly qualified meditators to "imprint" the device with the specific intention following a specific protocol (see the appendix of section IA in Reference 2). Then, on separate days, the control device and the imprinted device were shipped via Federal Express about 3000 km to a laboratory where the actual target experiments were conducted by others.

When not in use, the devices were always wrapped in Al foil and stored in individual FCs. This was found to be necessary because without it, even if the devices were separated by 100 m and in the off-state, the control device gradually became imprinted with that specific intention and we eventually lost our "control." Following this isolation procedure, we could maintain the imprint charge in the active device for ~4 months before reimprinting was felt to be needed.

Target Experiment 1

Here, the specific intention was to either increase or decrease the pH of aqueous solutions and purified water (ASTM type 1) by one full pH unit. Separate IIEDs were needed for $\Delta pH = +1$ and $\Delta pH = -1$. Thus, considering both, a swing of hydrogen ion concentration by a factor of 10^2 was attempted without any intentional chemical additions except those entering via contact with the local air atmosphere. The experimental setup used is shown in Figure 6.7 where a modern, high-quality pH meter (accuracy of ±0.01 pH-unit, resolution of 0.001 pH-unit) and a high-quality temperature probe (accuracy of ±0.012°C, resolution of 0.001°C) were utilized. The device was merely placed ~15.25 cm (6 in.) from the water and turned on (total radiated electromagnetic energy $<10^{-6}$ W).

Figure 6.8 demonstrates an obvious difference in the coherence state for one of the aqueous solutions, exposed for

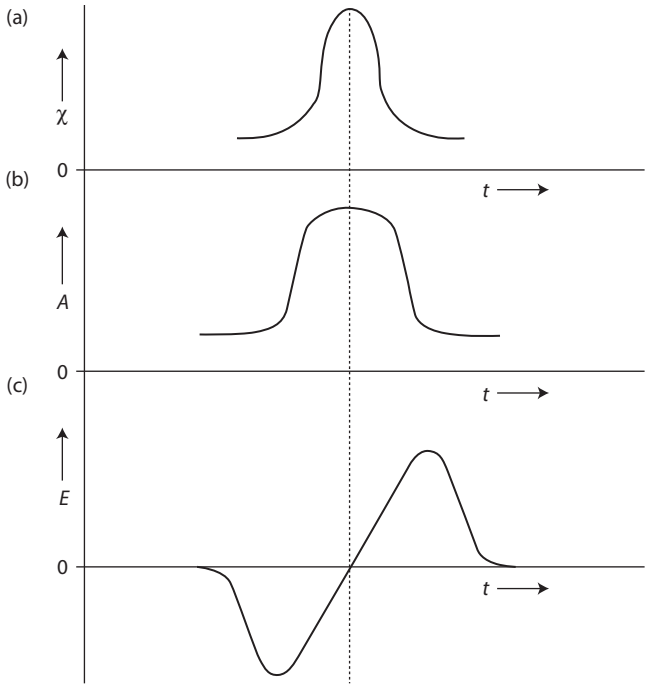

FIGURE 6.6 Schematic illustration of a subtle energy pulse χ, which generates the magnetic vector potential pulse *A* shown in (b), which, in turn, generates the electric field *E* shown in (c) at some specific origin in the healer's physical body.

2 h to either an unimprinted device (Figure 6.8a) or to an imprinted device (Figure 6.8b) and then monitored for several subsequent days.[2] For the unimprinted device, the subsequent pH readings are erratic while, for the imprinted device, the pH readings monotonically vary over time and step in an orderly fashion from day to day. The readings were taken from ~9:00 AM to 11:00 AM every day and at the start of each day with the buffer calibration. Later, in a separate experiment, the pH electrode was placed in the test solution, which initially drives the pH downward to equilibrate with the solution (initial transient deleted).

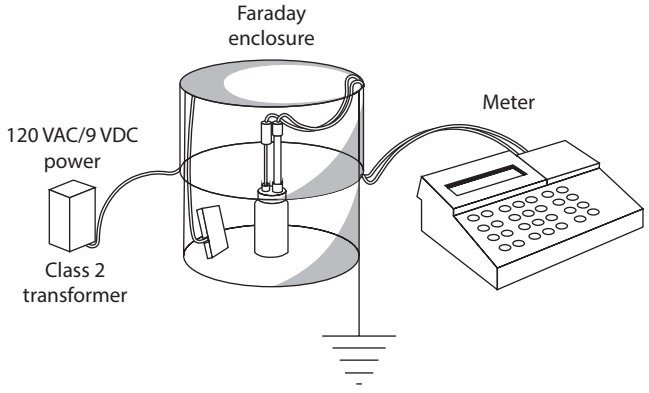

FIGURE 6.7 Schematic drawing of experimental setup used in simultaneous exposure to a device and pH plus temperature measurements.

Figure 6.9 demonstrates results with two different IIEDs, one with the intention to *decrease* the pH by one full unit (Figure 6.9a) and the other with the intention to *increase* the pH by one full pH unit (Figure 6.9b). The tests were made using different solutions so the equilibrium pH ranges were quite different. The purified water was ASTM type 1 (resistivity ≥18.2 MΩ cm, TOC < 5 ppb) water, while the Castle Rock water is a naturally occurring spring water with total dissolved solids (TDS) of about 95 mg/L and $[Ca^{2+}]/[Mg^{2+}] = 2.0$. In these particular experiments, the pH change over ~5 days (7200 min) was ~ −0.5 pH units for the pH-decreasing IIED and ~+1 pH units for the pH-increasing IIED, relative to the equilibrium pH range at 20–25°C for each experiment. When one uses a control device (unimprinted) instead of an IIED, the pH tends to stay in the equilibrium range or very close to it.

Target Experiments 2 and 3

To show the scope of this new potential technology, I briefly demonstrate its application in the area of biological materials (both inert and living) as well. Details, only of interest to biologists, are provided in Reference 2.

For target experiment 2, the specific IIED intention was to increase the *in vitro* thermodynamic activity of a specific liver enzyme, alkaline phosphatase (ALP). Four simultaneous, side-by-side variants were conducted on the same shelf in an incubator (held at 4°C) as shown in Figure 6.10. Comparisons could then be readily made between the control ALP solution (*C*) and

1. ALP solution placed in a small but otherwise empty grounded FC (*F*)
2. The same as (1) but with an activated *imprinted* device (*d*, *j*) present
3. The same as (1) but with an activated *unimprinted* device (*d*, *o*) present

The first comparison, (*C*) with (*F*), allows one to assess the effect of the broad band ambient EMFs in the incubator on the ALP activity. The second comparison, (*F*) with (*d*, *o*), allows one to assess the effect of low power (less than 1 μW) and specific frequency (three frequencies in the 1–10-MHz range) EMFs on ALP activity. The third comparison, (*d, j*) with (*d*, *o*), allows one to assess the effect of imprinted human intention, at constant EMF output, on ALP activity. In addition, simultaneous correlations between any and all of these different experimental states are available.

The results of this experiment, in terms of means with their standard deviations, are provided in Figure 6.11. The data were assessed via the ANOVA statistical procedure, and based on this, pairwise comparison with Tukey post hoc tests were examined. Visual inspection of Figure 6.11 and the ANOVA indicated that both the treatment and the dilution significantly modified ALP activity. The treatment rankings

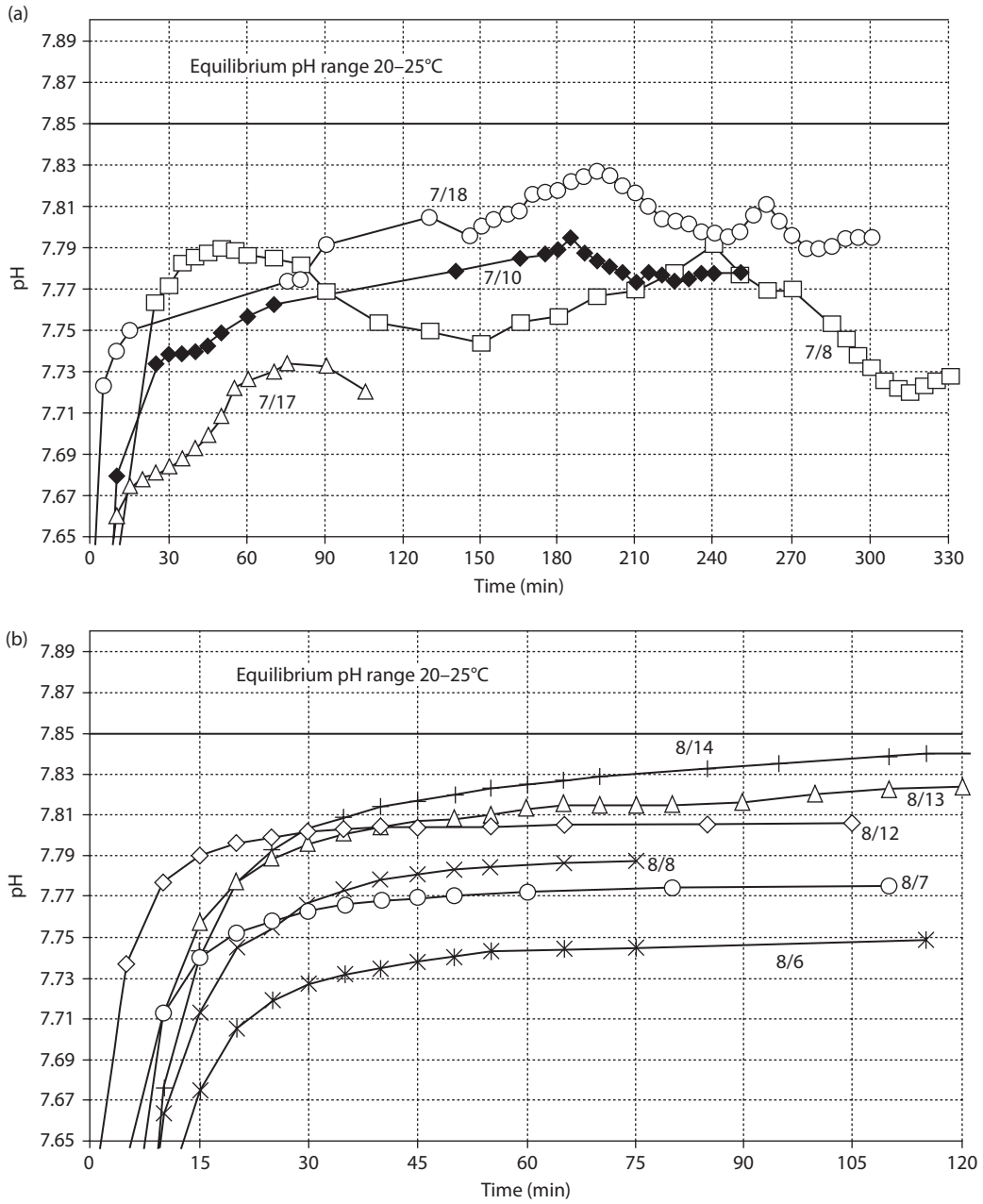

FIGURE 6.8 pH versus time for 50/50 dilution of Castle Rock Water with purified H_2O. (a) Measurements were made on a solution that had been exposed to an *unimprinted* three-oscillator device on July 7, 1997. Note irregular pH behavior and oscillation of pH in the days following exposure. (b) Measurements were made on a solution that had been exposed to the *imprinted* three-oscillator device on August 5, 1997. Note monotonically increasing pH behavior and steady increase in pH in the days following exposure.

for both dilutions were $(d, j) > (F) > (C) > (d, o)$ and the Tukey post hoc comparisons between treatments indicated that

1. (d, j) was significantly ($p < 0.001$) greater than (d, o) and also significantly ($p < 0.005$) greater than (C)
2. (F) was significantly ($p < 0.011$) greater than (C)

For target experiment 3, the specific IIED intention was to increase the *in vivo* ratio of ATP to ADP in developing fruit fly (*Drosophila melanogaster*) larvae to significantly reduce their development time to the adult fly stage. Once again, we incorporated four simultaneous experimental variants in a side-by-side positioning on a laboratory bench top (at 18°C and 55% relative humidity) as indicated in Figure 6.12. The four treatments investigated were as follows:

1. (C): The control culture of 30 larvae (0–4 h old) transferred to a single vial containing nonstressful food
2. (F): A similar culture inside an otherwise empty Faraday cage

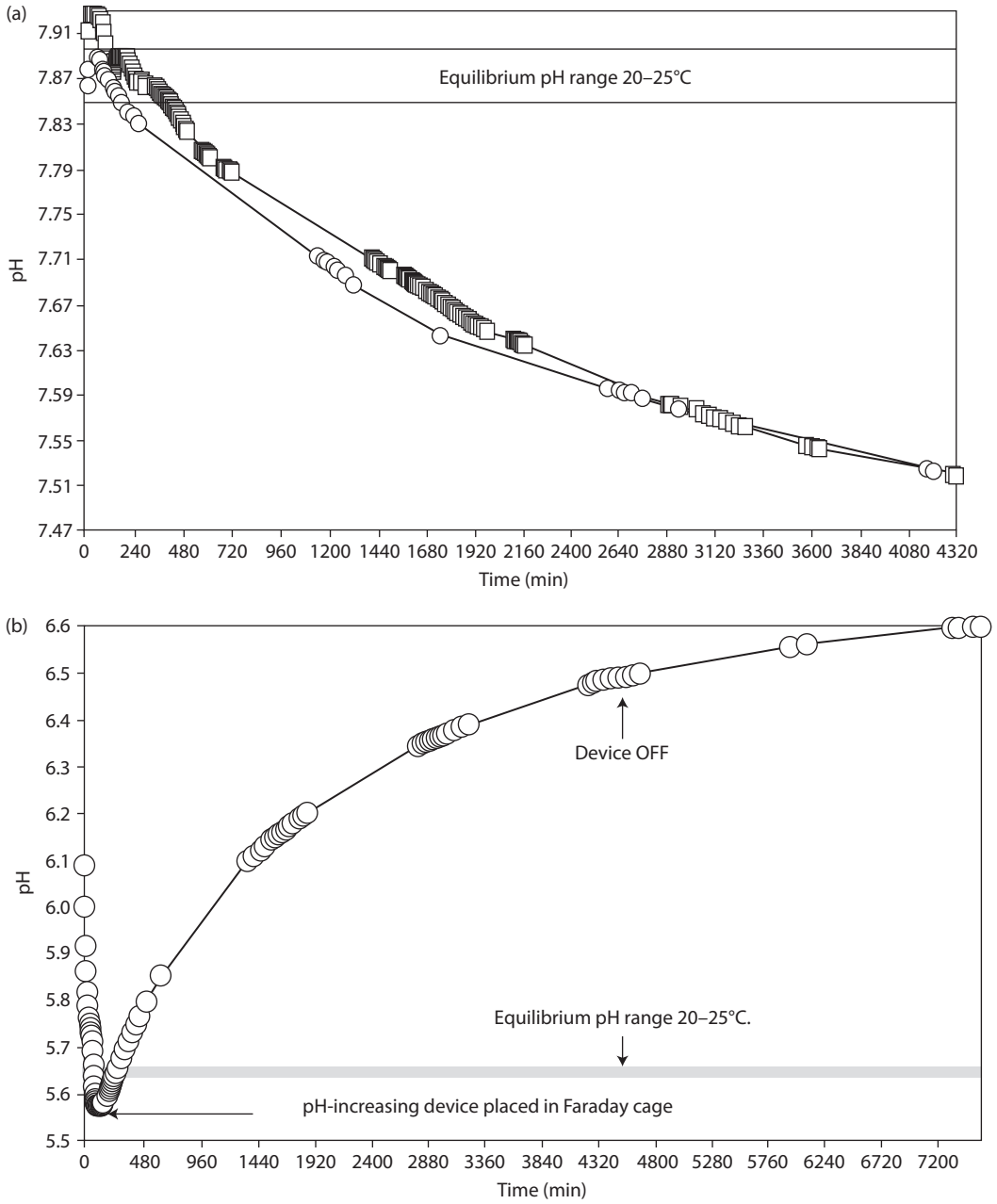

FIGURE 6.9 (a) pH versus time for 50/50 dilution of Castle Rock Water with purified H_2O. Measurement of pH was done simultaneously with exposure to the imprinted *pH-lowering* device for the data points depicted by square but only after exposure for the data points depicted by circles. (b) pH versus time of pure water in equilibrium with laboratory air during exposure to *pH-increasing* IIED.

3. (*d*, *o*): Culture as in (2) but containing an *unimprinted* device in the "on" state
4. (*d*, *j*): Culture as in (2) but containing an *imprinted* device in the "on" state

Our larval assay used high-performance liquid chromatography (HPLC) to measure changes in levels of ATP, ADP, and AMP present in larval homogenate samples. From this, the [ATP]/[ADP] ratio was readily determined. Larval development time (LDT) is defined as the time taken for half of the surviving adults to emerge. We assessed LDT and [ATP]/[ADP] ratio in a total study involving approximately 10,000 larvae and 7000 adult flies over an 8-month period.[2] For the [ATP]/[ADP] ratio assessment, we utilized a specific added amount of either nicotinamide adenine dinucleotide (NAD) or purified water to the larval homogenate samples for a set time period.

The experimental data is presented in Figure 6.13 as means with standard deviations arising from ANOVA statistical procedures and Tukey post hoc tests. For both results, the ANOVA gives $p < 0.001$ overall. In terms of our basic hypothesis concerning the influence of intention-augmented EMFs on larval fitness, this data provides robust support from LDT with $(d, j) < (d, o)$ at the $p < 0.001$ level of statistical significance.

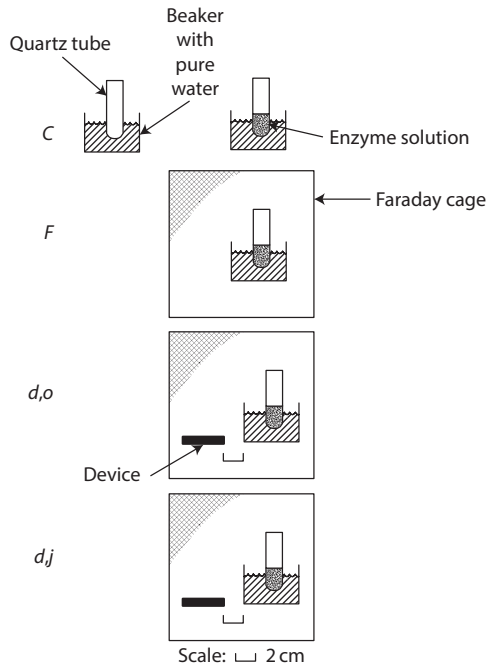

FIGURE 6.10 Schematic drawing of the side-by-side experimental configuration for the four simultaneous ALP treatments.

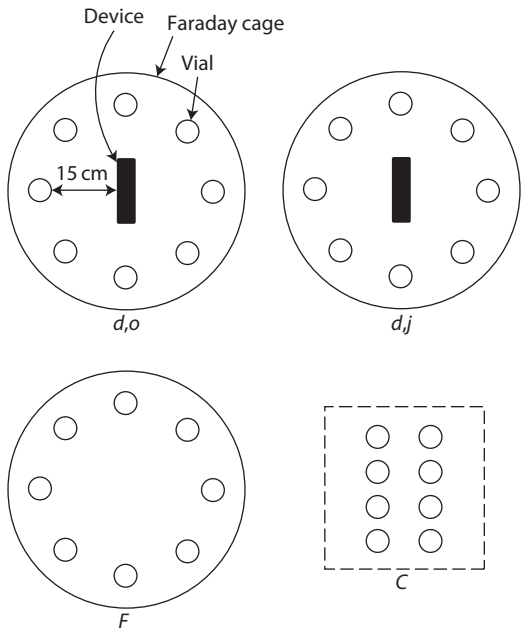

FIGURE 6.12 Experimental configuration for the simultaneous, four-treatment, side-by-side, *in vivo* larval development study.

The unexpected findings that $(F) < (C)$ at $p < 0.001$ and that $(F) << (d, o)$ at $p < 0.0001$ illustrates that both random ambient EMFs and specific high-frequency EMFs (even at quite low power levels) are significant stressors for *D. melanogaster.* The finding that the [ATP]/[ADP] ratio practically mirrors the LDT data for the added NAD case, at a high Pearson correlation value, strongly supports the connection between energy availability to the cells and organism fitness as well as the profound importance of NAD to overall metabolic activity. Finally, it is important to note that, even for the added pure water case, the different treatments gave an overall statistically significant effect ($p < 0.001$).

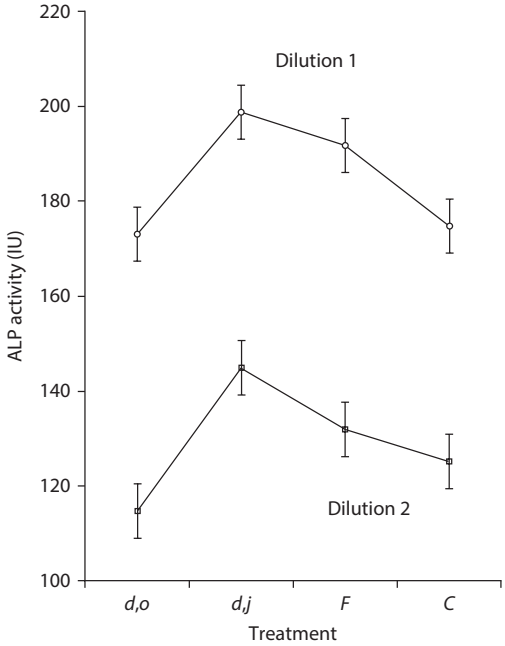

FIGURE 6.11 Statistical means data on ALP activity for the four simultaneous treatments (dilution 1 is 100 mL ALP solution plus 150 mL purified water; dilution 2 is 100 mL ALP solution plus 200 mL purified water).

Target Experiment 4

During the course of the preceding experiments, it began to be apparent that some type of "conditioning" process was going on in the particular locale associated with continued use of the IIEDs in that locale. In the purified water experiments locale, after some incubation period, we began to observe oscillations[2] in air temperature, water temperature, water pH, and water electrical conductivity whose amplitude often exceeded 10^2 times the sensitivity of our detection systems (see Figure 6.14). In other nearby locales (~6–15 m away), where no previous IIED studies had taken place, no such oscillations were observed.

In Figure 6.14a, one sees the presence of both highly periodic short period (<2 h) and long period (>20 h) oscillations in both pH and temperature. Figure 6.14b is an expanded scale view of one oscillation train from Figure 6.14a (near the end) to illustrate the "lawful" nature of the pH waveform. These oscillations are among the largest amplitude pH oscillations we recorded. Figure 6.14c provides the amplitude spectrum for a pH-oscillation wavetrain from Figure 6.14a that demonstrates how periodic even the lowest amplitude pH oscillations can be.

To probe the nature of this conditioning, we conducted a DC magnetic field polarity experiment using the experimental

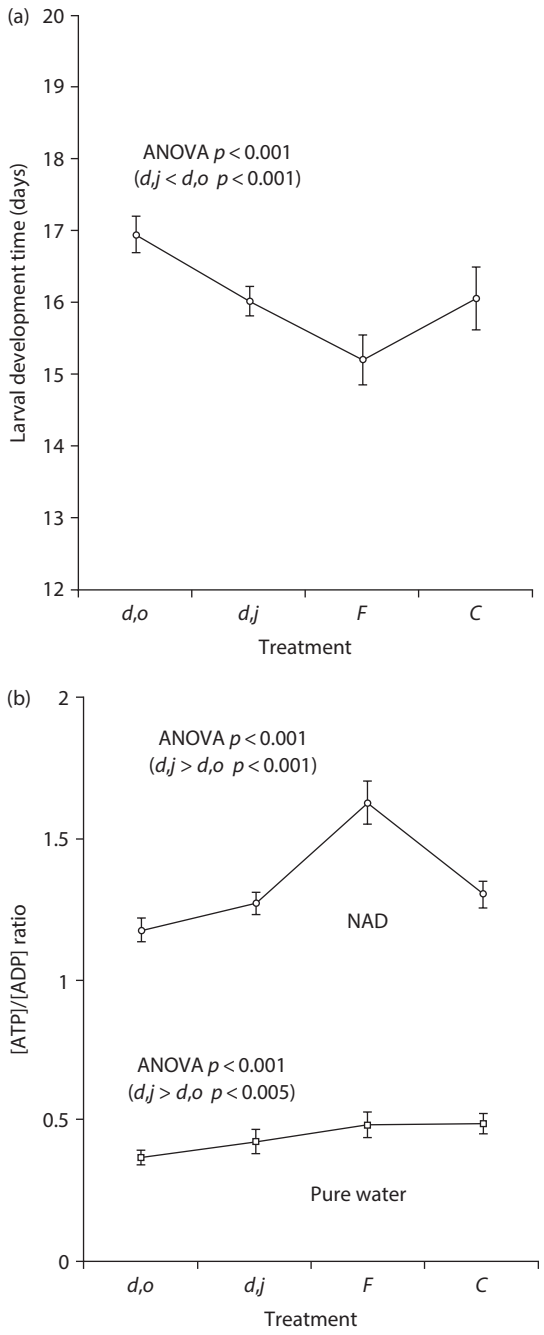

FIGURE 6.13 (a) Means for larval development time versus treatment and (b) [ATP]/[ADP] ratio for the larvae versus treatment (means).

setup shown in Figure 6.15. With this configuration, one can readily measure any water pH changes associated with the north pole versus the south pole pointing upwards without altering the basic cylindrical symmetry of the field. When one conducts this pH measurement experiment in a typical laboratory environment were no conditioning has occurred, one observes two things:

1. There is no measurable difference between the N-pole up case and the S-pole up case.
2. There is no measurable pH change in the water for either field polarity (for field strengths ≤500 G).

On the other hand, when one makes such measurements in a "conditioned" locale, the results are remarkably different. There, one generally finds a marked difference for $\Delta pH = pH(S) - pH(N)$. Figure 6.17 demonstrates an example wherein ΔpH grows in magnitude with the passage of time to attain a maximum value of ~0.60 pH units.

To demonstrate both simultaneous water and air temperature (T) oscillations plus the correlation between them, a Faraday cage with a central water vessel was set up in one conditioned space (purified water plus 1 gm of fine-grained $ZnCO_3$ powder, surface area = 21.4 m^2/g, was added to 250 mL of ASTM-type 1 purified water in a polypropylene bottle). High-resolution digital thermometers were located with the local geometry shown in Figure 6.16. Figure 6.18a shows the air T oscillations at the 15.25 cm (6″) location outside the cage plus the water T and water pH in the vessel located inside the cage. Figure 6.18b is an expanded view of the data collected just before that shown in Figure 6.18a while Figure 6.18c shows the amplitude spectrum for a portion of this data (from hour 9 to hour 17.5 in Figure 6.18b). These air T oscillations are huge (~230 times our best measurement accuracy and ~3500 times the resolution), and all have the same waveform. Figure 6.18d illustrates the comparative amplitude spectra data for simultaneous T and pH oscillations taken in this vessel of water 2 days earlier (oscillation data shown in inset). Again, the same wave shape (revealed by the nesting of the amplitude spectra) is exhibited for these two very different material properties.

To illustrate that the Figure 6.18 results were not generated by some type of natural convection phenomenon, a mechanical fan experiment was conducted in a strongly conditioned space. The focus of this experiment was to see if the air T oscillations would be strongly influenced by the forced convection from a mechanical fan. The furniture arrangement in the conditioned room, including both the location of the water vessel inside its Faraday cage (similar to Figure 6.16 configuration) adjacent to a monitoring computer and the two fan locations, X (one on the floor) and Y (on a desktop) is shown in Figure 6.19. Temperature measurements outside of the Faraday cage occurred at 15.25 cm (6 in.) intervals out to 3.35 m (11 ft). High-resolution digital thermometers (resolution = 0.001°C) were used in the water and at 30.5 cm (1 ft) outside the cage. Lower resolution, digital thermometers (resolution = 0.1°C) were used in the air inside the cage and at all other locations outside the cage. All measurements were computer monitored.

Earlier measurements had shown that the major floor–ceiling temperature gradients occurred between the floor and ~1 m (3–4 ft) above the floor; thus, we started with the fan at position X (on the floor) and operated it for 55 h. Later, the fan was moved to position Y and operated for 42 h. For comparison purposes, a 24-h period, real-time record of the T oscillations for the three cases of (i) no fan, (ii) fan at X, and (iii) fan at Y are given in Figure 6.20. From Figure 6.20, it seems clear

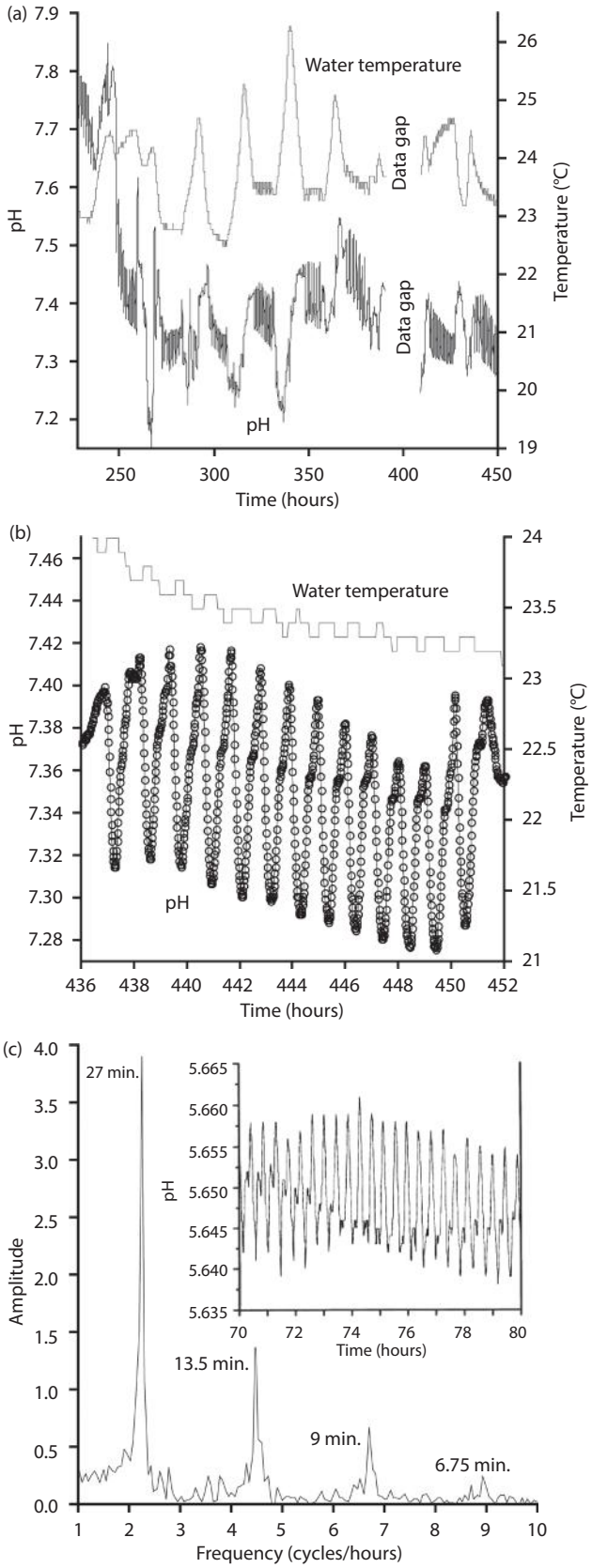

FIGURE 6.14 (a) pH and temperature changed with time for pure water containing fine-grained $ZnCO_3$ particulates. The plots reveal both long t_L and short t_s periods of undulations. (b) An expanded short interval from (a) illustrating the regularity of the t_s oscillations. Note the inverse correlation between pH oscillations and temperature fluctuations. (c) Amplitude spectra data via Fourier transform for part of the real-time data set (shown in inset) depicted in the lowest plot in Figure 6.14.

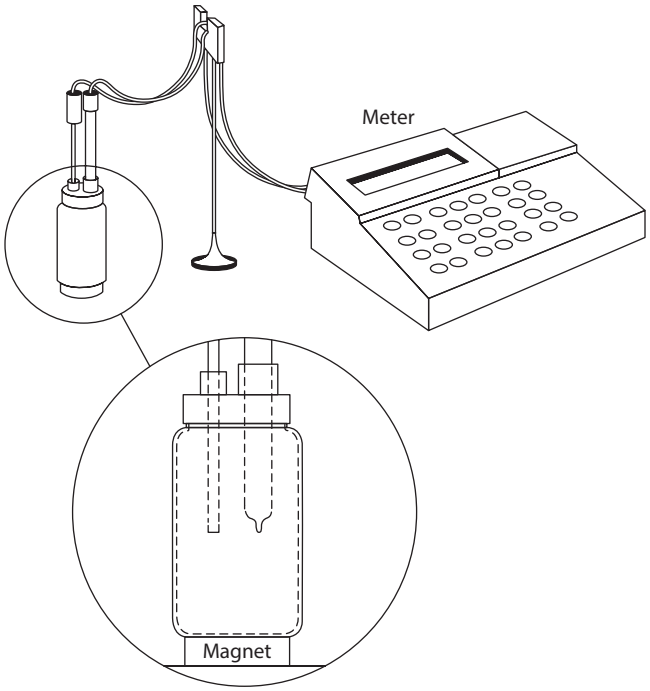

FIGURE 6.15 Conditioned locale pH changes with time for purified water with either the north pole or south pole of a DC magnetic field aligned vertically upwards (at 100 and 500 G). (Adapted from Tiller WA, Dibble WE Jr, Kohane MJ. *Conscious Acts of Creation: The Emergence of a New Physics*. Walnut Creek: Pavior Publishing; 2001.)

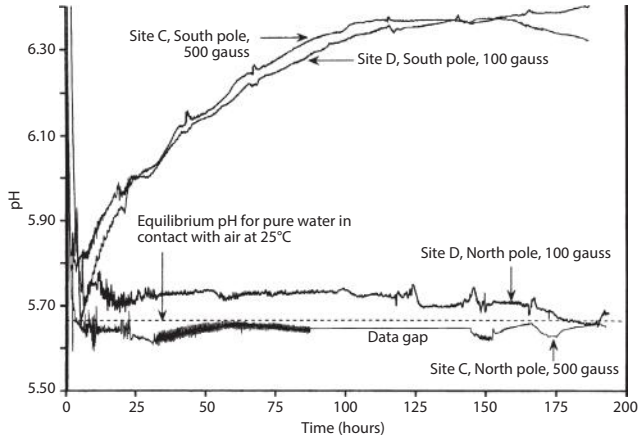

FIGURE 6.16 Experimental setup for testing changes due to a DC magnet placed under the water vessel with either the N pole or the S pole aligned upwards.

that these T oscillations neither cease nor change in a significant way due to the operation of the fan. It is also clear that the total oscillation ΔT excursion is a large percentage (sometimes 100%) of the total diurnal temperature variation in this room.

As the 3 m (10 ft) measuring point was in the hallway outside the office depicted in Figure 6.19, it was possible to close the office door and compare the T oscillations both inside the Faraday cage with those outside in the hallway. It was apparent that the air T-oscillation amplitudes did

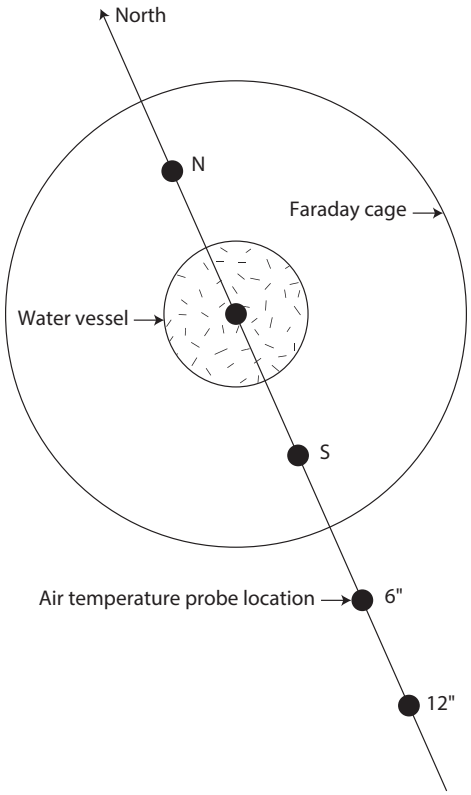

FIGURE 6.17 Schematic illustration of air and water temperature probe locations relative to a centrally located water vessel in an electrically grounded Faraday cage.

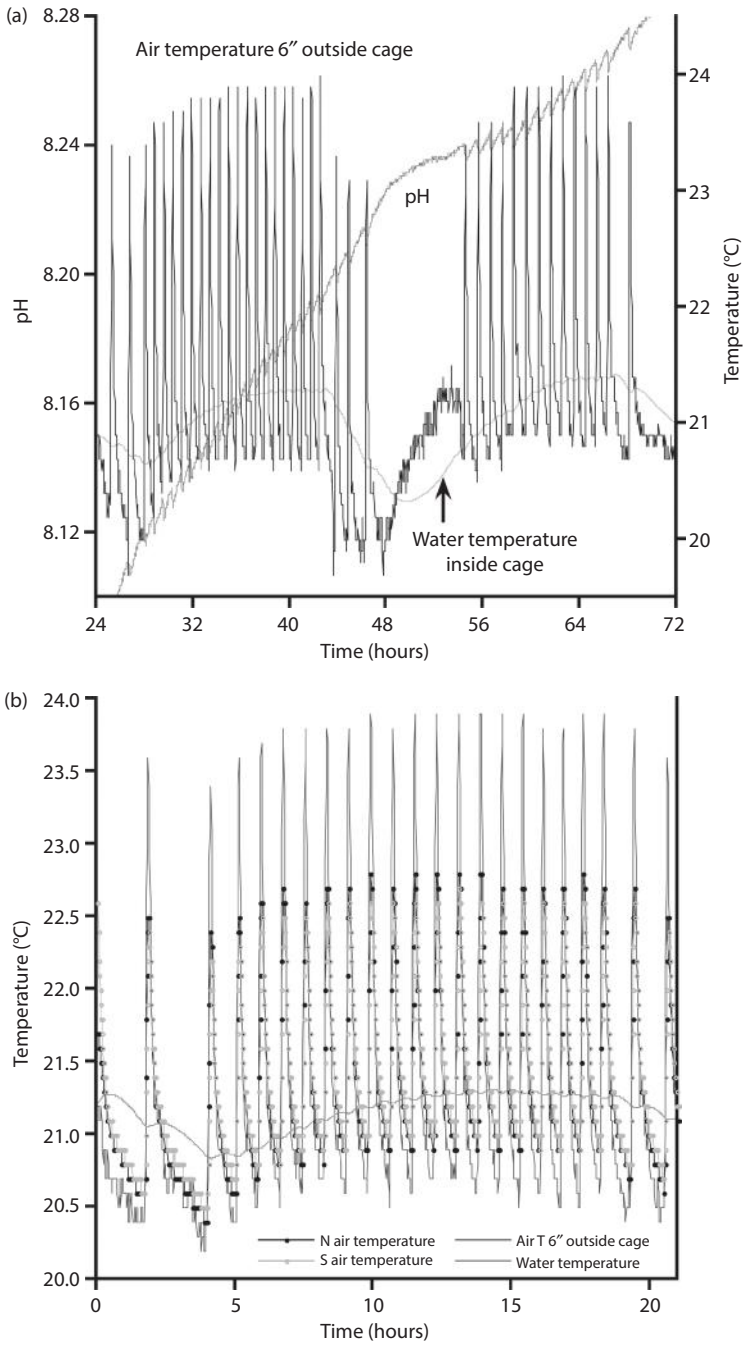

FIGURE 6.18 (a) Pure water with zinc carbonate particulates in vessel in Faraday cage. Simultaneous measurement of air and water temperature plus pH in the Figure 6.16 configuration on May 12, 1999 to May 13, 1999. Note the precise frequency correlation for the three variables. (b) Four real-time temperature versus time plots for simultaneous air temperature measurements made at the N, S, and 6-in. positions of Figure 6.16 plus the water temperature inside the vessel (May 11, 1999). (c) Fourier transformed amplitude spectra data for an 8.5 h interval of (b) (between hour 9 and 17.5). The fundamental period is 46.5 min and five harmonics can be observed. (d) Fourier transform comparison of both water T-oscillation and pH-oscillation data in the water vessel of Figure 6.16 on May 10, 1999. Real-time oscillation data shown in inset. The fundamental period is 36.6 min and three harmonics can be discerned.

decline significantly with distance from the FC. However, they were still measurable more than 3 m away. The inset in Figure 6.21 shows the simultaneous, real-time data at these two locations. The Fourier analysis for these two oscillation data sets reveals that they share the same basic wave harmonics, despite the fact that they were separated by a 3 m (10 ft) distance, a closed door, and a Faraday cage. Clearly, it is predominantly something other than standard air that is being monitored here (perhaps the vacuum phase within the air molecules?)!

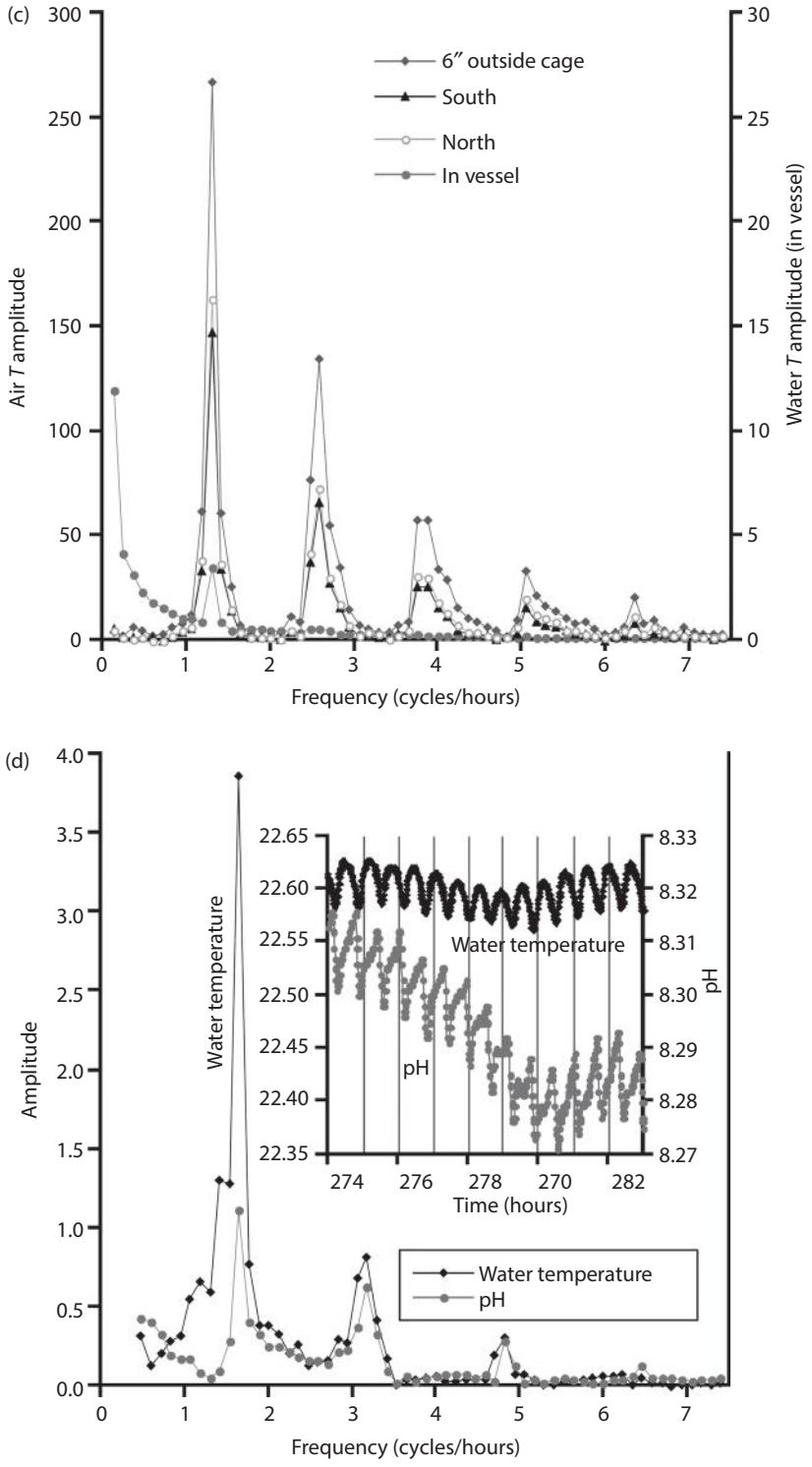

FIGURE 6.18 (Continued) (a) Pure water with zinc carbonate particulates in vessel in Faraday cage. Simultaneous measurement of air and water temperature plus pH in the Figure 6.16 configuration on May 12, 1999 to May 13, 1999. Note the precise frequency correlation for the three variables. (b) Four real-time temperature versus time plots for simultaneous air temperature measurements made at the N, S, and 6-in. positions of Figure 6.16 plus the water temperature inside the vessel (May 11, 1999). (c) Fourier transformed amplitude spectra data for an 8.5 h interval of (b) (between hour 9 and 17.5). The fundamental period is 46.5 min and five harmonics can be observed. (d) Fourier transform comparison of both water *T*-oscillation and pH-oscillation data in the water vessel of Figure 6.16 on May 10, 1999. Real-time oscillation data shown in inset. The fundamental period is 36.6 min and three harmonics can be discerned.

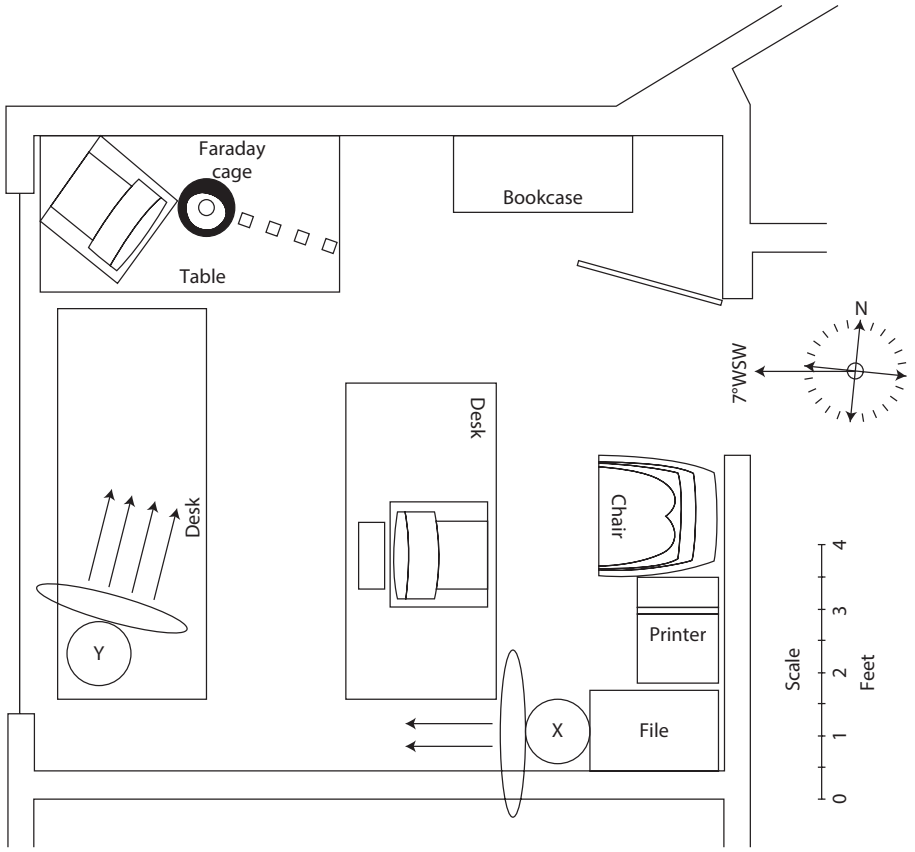

FIGURE 6.19 Forced convection experiment using a mechanical fan to perturb the air around a series of aligned temperature measurement probes. Fan location positions (X is on the floor, Y is on a desk) relative to the water vessel in a Faraday cage on upper left table top and a line of temperature probes (small boxes) 6 in. (15.24 cm) apart.

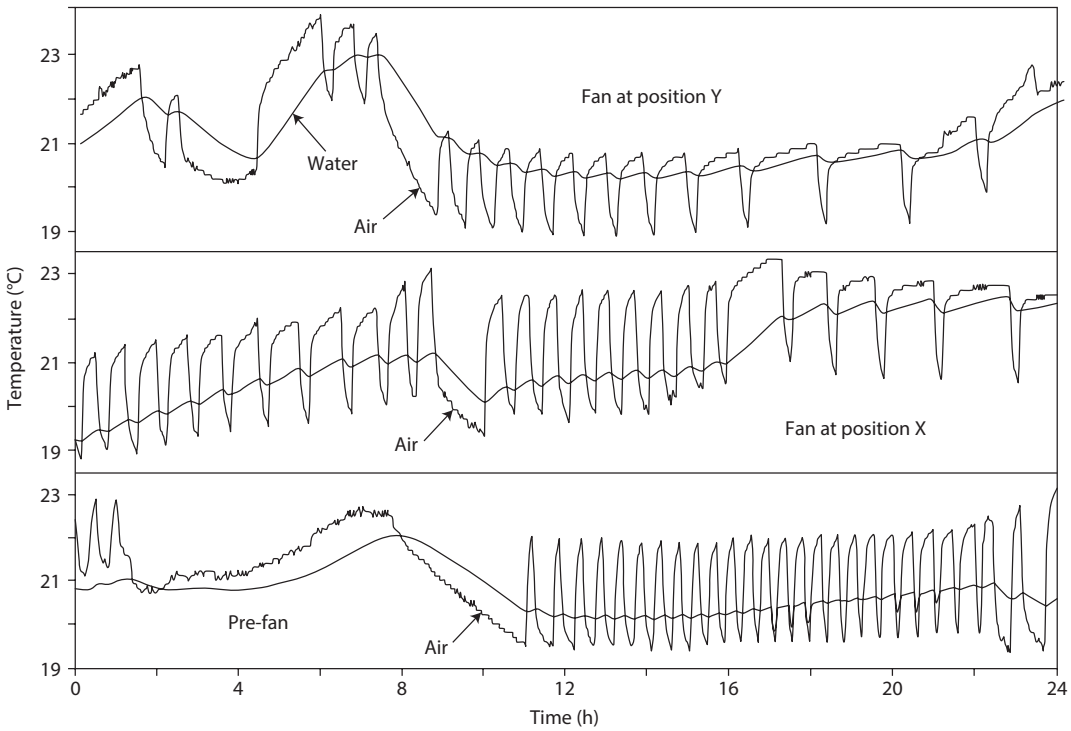

FIGURE 6.20 Temperature oscillation in air (1 ft [30.5 cm] outside FC) and water (inside FC), with and without the fan operating.

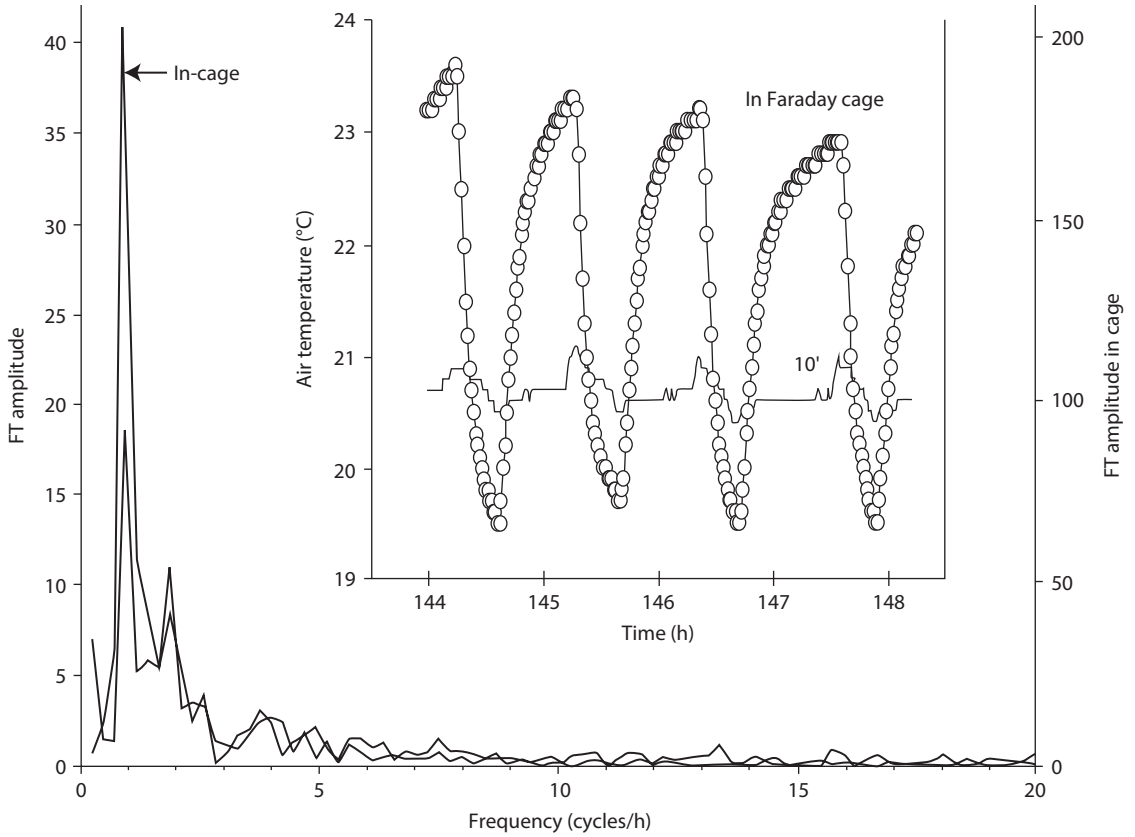

FIGURE 6.21 Amplitude spectra from Fourier analysis of air, *T*-oscillation real-time data (see inset) both in the FC and 10 ft (3.05 m) away outside the closed door of Figure 6.19. Note the high correlation between the oscillations measured at locations separated by 10 ft (3.05 m), a closed door and a FC.

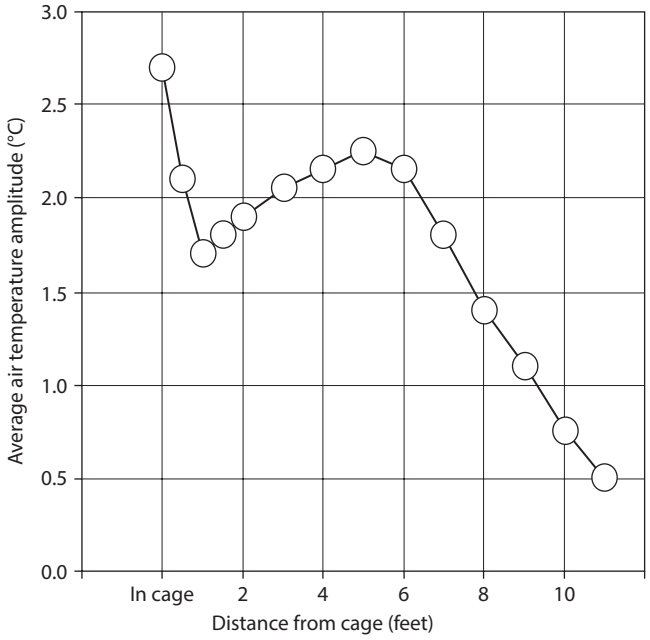

FIGURE 6.22 Composite amplitude versus distance plot for air, *T* oscillations in the Figure 6.16 geometry (between August and September 1999).

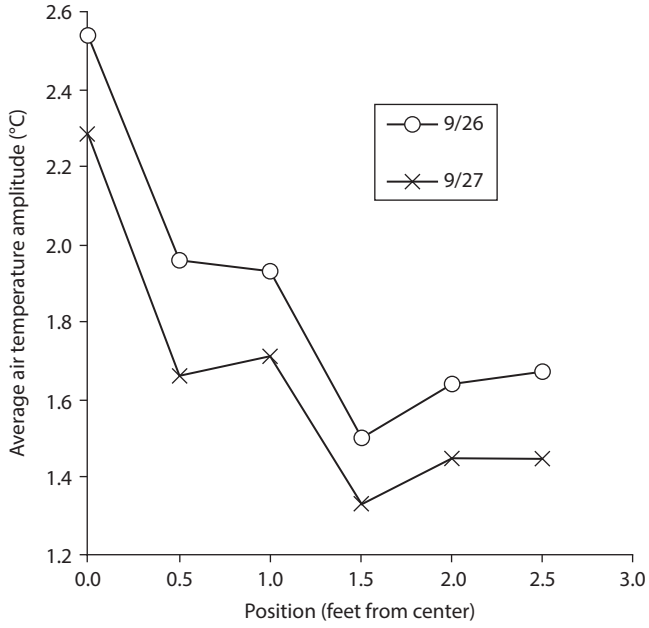

FIGURE 6.23 Average air, *T*-oscillation amplitude versus. distance plot for Figure 6.16 geometry 1 and 2 days after removal of the FC and water vessel (the former FC edge was located at 0.5 ft).

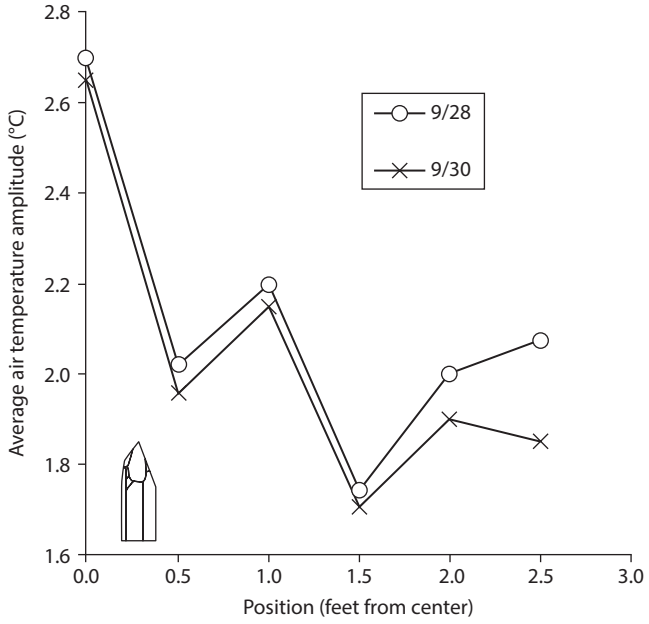

FIGURE 6.24 Average air, *T*-oscillation amplitude versus distance plot on the phantom profile immediately after placing a natural quartz crystal (*c* axis up) between position 0.0 and 0.5 ft as shown.

The variation of *T*-oscillation amplitude from inside the FC to a point out in the hall ~11 ft away is shown in Figure 6.22. This is certainly a very anomalous profile with the secondary maximum being prominently present. This profile certainly establishes the water vessel and its surrounding FC as a type of "source" for the temperature oscillations. After removal of this D-space "conditioning center," the air *T*-oscillation amplitude profile remained and only decayed over a period of weeks to months. Figure 6.23 displays the "phantom" profile, a very anomalous result indeed.[2] When a natural quartz crystal (6 in. long in the *c*-axis direction and 3 in. in diameter) was placed near the now absent "source" center with the *c* axis upwards, a sharpened definition and small increase of the phantom *T*-oscillation amplitude profile occurred (see Figure 6.24), with no meaningful change in the shape of the *T*-oscillation waveform. However, when the crystal was rotated to lay with a prism face flat on the table and its *c* axis aligned with the row of thermometers and its apex pointing away from the center position, *immediately* the *T*-oscillation amplitude waveform changed dramatically (see Figure 6.25). The oscillation amplitude decreased by about a factor of 4–5, the oscillation frequency increased by a factor of 2–3 and the oscillation wave shape became inverted.

This very anomalous behavior led us to propose strongly that we were *not* dealing with properties of D-space coarse particulate substance here but rather with the R-space fine information wave substance from the coarsest level of the vacuum.

ACKNOWLEDGMENTS

I wish to thank Ditron LLC and The Samueli Institute for partial support of this work.

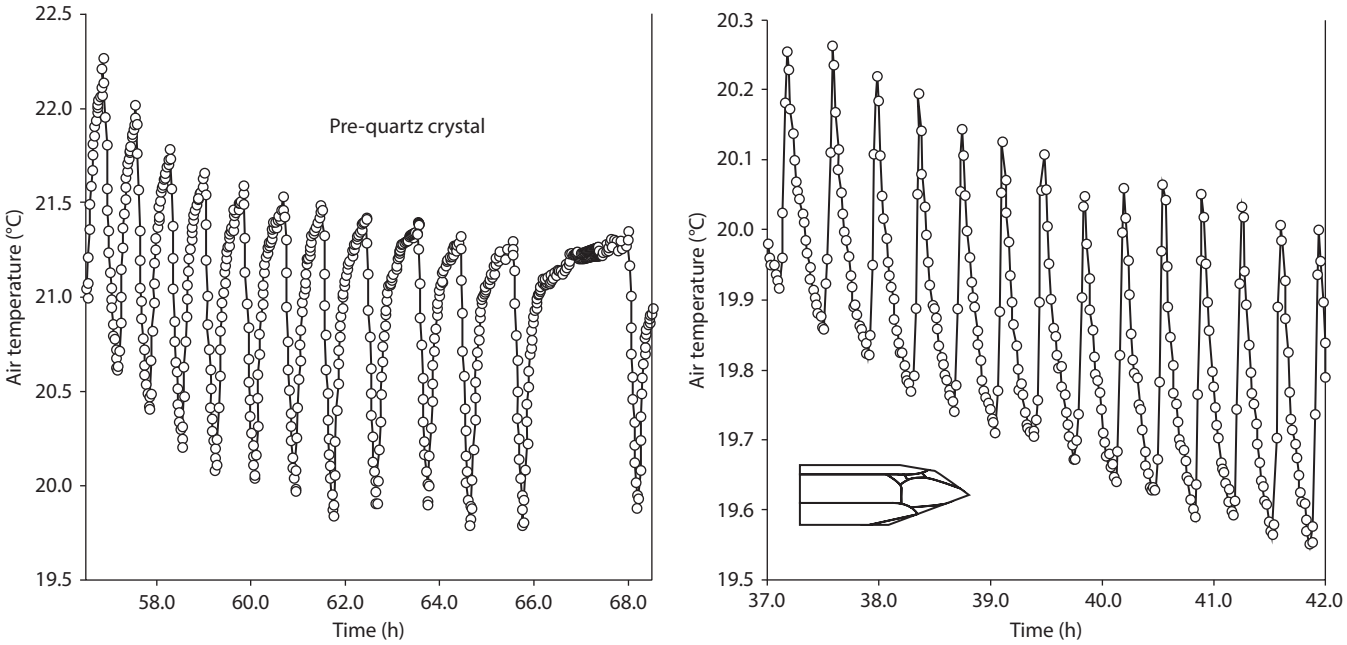

FIGURE 6.25 Comparison of air, *T*-oscillation amplitude, frequency, and waveform between the pre-quartz crystal condition and the condition immediately after changing the orientation of the quartz crystal to the *c*-axis horizontal position.

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7 Electromagnetism versus Bioelectromagnetism

*William A. Tiller**

CONTENTS

Most scientists and engineers mistakenly believe that bioelectromagnetic phenomena can be comprehended in terms of conventional electrical and magnetic forces acting on biological systems. Eletromagnetic gauge symmetry physics concepts and definitions explain why this is not true by demonstrating the differences between electromagnetism and bioelectromagnetism.

INTRODUCTION

As indicated in the previous chapter, a higher electromagnetism (EM) gauge symmetry state than the U(1) state has a higher thermodynamic free energy than the U(1) state (see Figure 7.1). This means that useful work can be pumped from any of these states X, Y, SU(2), Z, etc., to the U(1) gauge symmetry world. Thus, if a single organ or system of the human body was elevated to one of these higher symmetry states at birth and the rest of the body was not, seemingly all functions of the body could be driven via this energy source to exhibit what we call life. That is, the heart would pump blood, nerve synapses would switch on and off, electric currents would flow, the brain would be activated to direct various body processes, etc. Interestingly, experimental data shows us that there is at least one important body system that is at one of these higher EM gauge symmetry states!

It is a fairly common experience in advanced kinesiology studies that a practitioner can slide a small circular DC magnet (with a central hole) onto the tip of their finger and, bringing this finger-magnet into the biofield of a particular muscle group of a patient, can either strengthen or weaken this muscle group depending upon which pole points towards the muscle group. The S pole facing the group strengthens the muscle's response while the N pole facing the group weakens the muscle's response. Thus, it is the acupuncture meridian system (in the R-space layer of the human biobodysuit) that is at a higher EM gauge symmetry state (probably the SU(2) gauge symmetry state).[1] What the Asian culture has called *Qi* (or chi) for millennia is what flows in this meridian-chakra system driven by this EM gauge symmetry "pump." This pump drives everything else in the physical body and is what we call the *life force*.

The general picture that I would like to leave with the reader as I close this introduction relates to how we operate in life with respect to another; whether we be a minister, a healer, a medical doctor, an acupuncturist, or just a spouse and parent. This picture is illustrated via Figure 7.2 for the practitioner–client interaction. Usually, all five components are intimately involved in the interaction even though the practitioner, using some device, may only acknowledge that they and the client are involved. It is the practitioner's love, compassion, devotion to service, and intent that can elicit the unseen assistance of the universe to co-raise the EM gauge symmetry of the intervening space, allowing the intention to be more empowered. Even saturating the device with activated deltrons is an important factor in the overall effectiveness of the process. It is via being fully appreciative of this entire operating system in all the processes of our lives that we can collectively lift the gauge symmetry state throughout our entire world and move us forward into the next phase of our great human adventure.

This seems remarkably like the general human experience wherein a group of well-intended individuals come into a room to meditate together, pray together, meaningfully commune from a "spiritual" perspective together, etc. Then, an elevated and tangible "field of consciousness" seems to fill the room and one does not want to leave this room. When the group eventually leaves, a residue of the experience remains in the room and slowly disperses. If this gathering meets daily in the same room for the same purpose then, after years to decades of such processing, the room takes on a seemingly permanent "conditioning" that can be tangibly felt by most individuals when walking singly into the room. Some of these sites become what we currently call *sacred spaces*.

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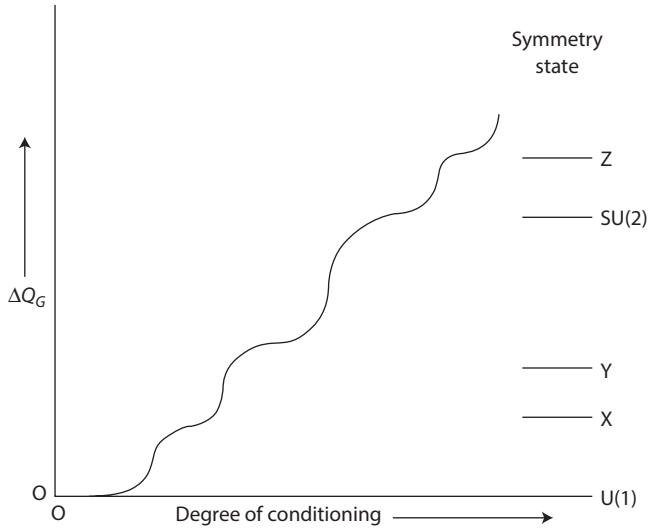

FIGURE 7.1 Schematic illustration of free-energy change ΔQ_G from the ground symmetry state, U(1), as the degree of locale conditioning increases.

On a more technical and theoretical level, our working hypothesis concerning nature's structural element involved in the laboratory conditioning process is that we are changing the degree of order in the physical vacuum state of the room. This vacuum fills the spaces between all the atoms and molecules of the room as well as most of the space within all the atoms and molecules of the room. This vacuum is thought to contain unseen substances that today's science has not explored in any detail. However, its normal state is postulated to be highly energetic, chaotic, and completely random (disordered). Our intention imprinted electrical device work suggests that human consciousness, specifically human intention, can interact with this vacuum stuff and alter its degree of order in a seemingly permanent way. As material properties are EM gauge symmetry specific, changing the local EM gauge symmetry state via our focused intention, the Qi-Prana pump changes the material properties of that local space to some degree.

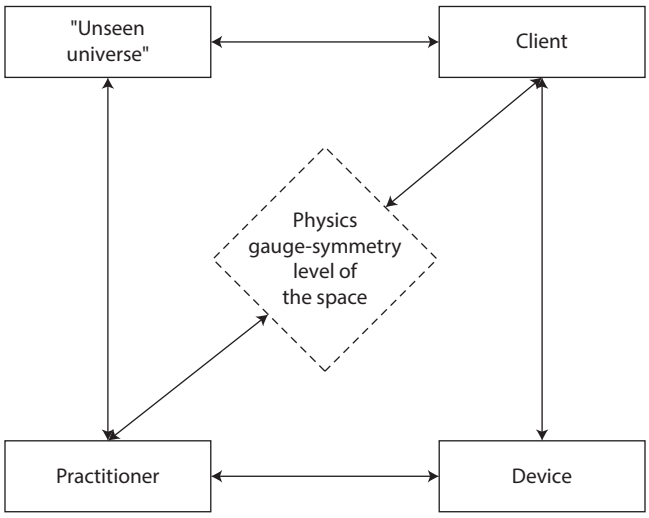

FIGURE 7.2 Illustration of the five key ingredients involved in every human action and every human interaction.

ELECTROMAGNETISM VERSUS BIOELECTROMAGNETISM

From a macroscopic and U(1) EM gauge viewpoint, the interaction of matter with an electric field occurs in two ways: (i) as a conduction of mobile charge carriers through the material (called *conduction* current) and (ii) as a polarization or electric dipole formation in the material (called *displacement* current). The former is always in phase with the electric field E, leading to a conductivity σ', while the latter is always out of phase with E leading to a conductivity σ''. The total electrical conductivity of the material is thus σ, given by

$$\sigma = \sigma' + i\sigma'' \tag{7.1}$$

where $i = \sqrt{-1}$ and means a counterclockwise rotation by 90°. Alternatively, and equivalently, these two material response effects may be considered as the out-of-phase and in-phase electrical permittivities, ε'' and ε', respectively, of the material. Once again, these may be lumped together as a complex permittivity, ε, given by

$$\varepsilon = \varepsilon' - i\varepsilon'' \tag{7.2}$$

the conversion relations between Equations 7.1 and 7.2 are

$$\sigma = i\omega\varepsilon \quad \sigma' = \omega\varepsilon'' \quad \sigma'' = \omega\varepsilon' \tag{7.3}$$

where ω is the angular frequency of the applied voltage source to the material ($V = V_0 \exp i\omega t$).

Our sample material can be thought of as a "leaky" capacitor of capacitance C ($C = \varepsilon' A/d$, where A is the cross-sectional area and d is the length of our material). The charge built up along this capacitor is Q, and the charging current I_C is given by

$$I_C = \frac{dQ}{dt} = \frac{d(CV)}{dt} = i\omega CV \tag{7.4a}$$

and I_C is said to lead V by 90°. Simultaneously, the conduction current, $I_{\sigma'}$ (called a *loss* current, here) is given by

$$I_{\sigma'} = GV = \frac{A\sigma' V}{d} \tag{7.4b}$$

where G is the conductance of the material. The total current I is thus

$$I = I_C + I_{\sigma'} = i\omega CV + GV = (i\omega\varepsilon' + \sigma')C_0 \frac{V}{\varepsilon_0} \tag{7.4c}$$

where $C = C_0(\varepsilon'/\varepsilon_0)$ and C_0 is the capacitance when our material is replaced by normal vacuum having electric permittivity ε_0. Using Equations 7.1 through 7.3, we have

$$I = i\omega\varepsilon V\frac{C_0}{\varepsilon_0} = \sigma V\frac{C_0}{\varepsilon_0} \tag{7.4d}$$

in terms of either the complex permittivity or the complex conductivity description, respectively.

From an electric circuit viewpoint, the foregoing simultaneous conduction and displacement processes are seen as a resistor and capacitor in parallel as illustrated in Figure 7.3a, where the resistance is $R = d/A\sigma'$. The time constant τ for charging up this circuit is $\tau = RC = \varepsilon/\sigma$ and its impedance Z is $Z = R/(1 + i\omega\tau)$ with $I = V/Z$.

The bottom line point of the foregoing discussion is that from an electrical response viewpoint, the material medium is considered to contain both electric monopoles and electric dipoles that respond to the driving electric potential.

Going a little further, from Ampere's law, we learn that current flow induces a clockwise circulating magnetic field, H, in the plane perpendicular to the direction of the current flow. The quantitative expression of this law is that the line integral of H around a closed path is equal to the current I enclosed $\left(\oint H \cdot d\ell = I\right)$. The spatial distribution of this magnetic field in the medium around our material sample is given by

$$H = \frac{I}{2\pi r} \tag{7.5}$$

for a long straight sample, where r is the radial distance from the wire. The magnetic flux density B at any location r is just given by

$$B = \mu H \tag{7.6}$$

where μ is the magnetic permeability of this surrounding medium in units Henrys per meter (Hm^{-1}). Thus, as analysis shows us that energy $\tilde{E} = \frac{1}{2}\mu H^2$ per unit volume is stored in this field, our circuit diagram for this overall process must change from that of Figure 7.3a to that of Figure 7.3b to incorporate this effect.

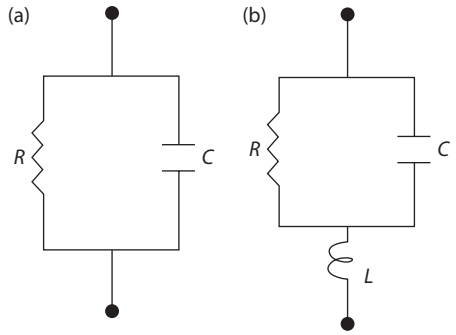

FIGURE 7.3 Electrical equivalent circuits for a material displaying both conduction current flow (due to R) and displacement current flow (due to C) for the two cases, (a) where magnetic field energy storage is neglected and (b) where it is not (L is the inductance).

From Faraday's law, one also learns that there is an EMF induced in a closed electrical circuit due to any change in the magnetic flux linking it (a kind of magnetic displacement current). Expanding this type of discussion, Maxwell's general equations for electromagnetism in materials can be simplified into four mathematical expressions: one derived from Ampere's law, one from Faraday's law, and two from Gauss' law. These are shown in Figure 7.4 and indicate that the U(1) EM gauge state is "source" free with respect to magnetic charge (Equation 1 of Figure 7.4).

One last perspective addition to the foregoing discussion of conventional electro-magnetism is to note that, just as the electrostatic potential (or voltage) V is given by Equation 7.7a.

$$V = \frac{1}{4\pi\in}\int_v \frac{\rho_e\, dv}{r} \tag{7.7a}$$

where ρ_e is the electric charge density and the integration is over the entire volume of electric charge, we can also define a magnetic potential, A_e, which is given by Equation 7.7b and is a vector:

$$A_e = \frac{\mu}{4\pi}\int_v \frac{J_e}{r}\, dv \tag{7.7b}$$

$$\nabla \cdot \underline{B} = 0 \tag{1}$$

$$\nabla \cdot \underline{E} + \frac{\partial \underline{B}}{\partial t} = 0 \tag{2}$$

$$\nabla \cdot \underline{D} = \rho \tag{3}$$

$$\nabla \times \underline{H} - \left(\underline{J} + \frac{\partial \underline{D}}{\partial t}\right) = 0 \tag{4}$$

with

$$\underline{D} = \varepsilon\underline{E} = \varepsilon_0(\underline{E} + \underline{P}); \qquad \underline{B} = \mu\underline{H} = \mu_0(\underline{H} + \underline{M})$$

and in S. I. units, $\varepsilon_0 = 8.854 \times 10^{-12}(J^{-1}C^{-2}m^{-1})$,

$$\mu_0 = 4\pi \times 10^{-7}(Js^2C^{-2}m^{-1}).$$

$\underline{\mathbf{B}}$ is the magnetic flux density, $\underline{\mathbf{H}}$ is the magnetic field strength, $\underline{\mathbf{E}}$ is the electric field strength, $\underline{\mathbf{D}}$ is the electric displacement, ρ is the electric charge density, $\underline{\mathbf{J}}$ is the electric current density, $\underline{\mathbf{P}}$ is the electric polarization, $\underline{\mathbf{M}}$ is the magnetization, ε is the electric permittivity, (ε_0 is the vacuum value), and μ is the magnetic permeability (μ_0 is the vacuum value).

FIGURE 7.4 The classical Maxwell equations.

where J_e is the electric current density. Now, from the two potentials V and A_e, both the electric field E and the magnetic field H in the U(1) EM gauge symmetry state are readily given by

$$E = -\nabla V - \frac{\delta A_e}{\delta t} \tag{7.8a}$$

and

$$H = \frac{1}{\mu}\nabla X A_e \tag{7.8b}$$

Here, t is time, ∇ represents the gradient operation, while ∇X represents the curl operation. From Equation 7.7b, one sees that A_e is collinear with the electric current so ∇X in Equation 7.8b just represents a clockwise screw operation along the locus of this electric current. To completely define A_e, standard electromagnetic practice is to set $\nabla \cdot A_e = 0$ (which is the same as saying that A_e is a constant spatially). This may be acceptable for the U(1) EM gauge symmetry state, but it is unlikely to hold true for the higher EM gauge symmetry states of Figure 7.1.

As a bridge to our consideration of higher EM gauge symmetry states, we must also incorporate separate response characteristics of the vacuum level of substance (fine information wave level) into the foregoing description. A simple initial procedure for this is illustrated by the parallel circuit diagram of Figure 7.5a. An important refinement of this approach is illustrated in Figure 7.5b.

In Figure 7.5a, Z_{cp} is the electrical impedance of the coarse particulate level with the electrical equivalent circuit of Figure 7.3b and Z_v is the impedance of the vacuum level. In Figure 7.5b, the subscripts R, δ, and D stand for R space, deltron, and D space, respectively. For the U(1) EM gauge state, we have

$$\frac{1}{z} = \frac{1}{z_V} + \frac{1}{z_{CP}} \approx \frac{1}{z_{CP}} \tag{7.9a}$$

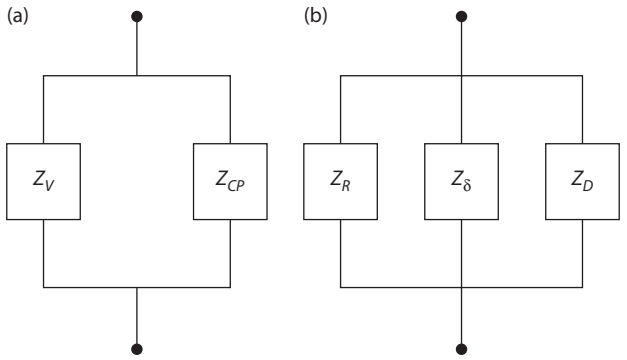

FIGURE 7.5 Two equivalent electromagnetic circuit illustrations for total physical reality; that is, both the coarse particulate level (subscript *CP*) and the fine information wave level (subscript *V* in (a)) for the two cases, (a) neglecting separation of deltrons and (b) discriminating D-space, R-space, and deltron levels.

or

$$\frac{1}{z} = \frac{1}{z_R} + \frac{1}{z_\delta} + \frac{1}{z_D} \approx \frac{1}{z_D} \tag{7.9b}$$

since z_V and $(1/z_R + 1/z_\delta)^{-1} \sim 0$ for this state. Thus, the experimentally measured impedance, z is $\approx Z_{CP} = Z_D$. However, for higher EM gauge symmetry states, we must consider that magnetic charge ρ_{mj} is present and that the vacuum permeability/permittivity has changed to $\mu'_{0j}/\in'_{0j}$ (due to the possibility of both magnetic and electric dipoles manifesting in the vacuum), where j refers to the particular higher EM gauge symmetry state (X, Y, SU(2), or Z, in Figure 7.1) under consideration.

Now, returning to our simple material example of Figure 7.3b, A_e from Equation 7.7b is expected to act on the magnetic charge ρ_{mj} to produce a magnetic conduction current J_{mc_j} and a magnetic displacement current J_{md_j} along the same vector direction (the same as J_e). This new axial total magnetic current, $J_m = J_{mc} + J_{md}$, will give rise to a circulatory E field and associated electric current in the perpendicular plane. Likewise, the magnetic polarization due to J_{md} creates a B field (like a magnetic capacitor) in this axial direction. Thus, overall, a material in one of these higher gauge symmetry states will exhibit both axial and circulatory fields in the perpendicular plane for both E and B. One also sees that

$$A_j = A_{e_j} + A_{mj} = \frac{\mu}{4\pi}\int_v \frac{J_e}{r}dv + \frac{1}{4\pi\mu'_{0j}}\int_v \frac{\tilde{\rho}_{mi}}{r}dv \tag{7.10a}$$

and

$$V_j = V_{e_j} + V_{m_j} = \frac{1}{4\pi \in}\int_v \frac{\rho_e}{r}dv - \frac{\in'_{0j}}{\sigma_m 4\pi}\int_v \frac{(\delta \tilde{J}_{mj}/\delta t)}{r}dv \tag{7.10b}$$

The tilde over ρ_{mj} and J_{mj} indicates that we do not know the nature of these quantities; however, it is perhaps reasonable to think of them as tensors of some unknown rank. The right-hand term in Equation 7.10b comes from the application of Faraday's law to the magnetic current, and because of this tensorial nature, it is also not clear that this term has the mathematically correct formulation.

Applying this conceptualization to humans, whose body's fine information wave level of substance is most probably in the SU(2) EM gauge symmetry state, one sees that their bioelectromagnetism is significantly different that conventional electromagnetism. Following Barrett's lead,[2] Figure 7.6 shows us how SU(2) EM gauge symmetry equations of electromagnetism differ from those of the U(1) gauge symmetry state. The actual experimentally measured manifestation of higher gauge symmetry electromagnetism will be somewhat different than that provided by Equation 7.9a because these are based on the Figure 7.5a approximation. However, in reality, one must take into account the deltron coupling between the D-space and R-space aspects of substance. Thus, the

$$\nabla \cdot \underline{B} = \rho_m \quad (1)$$

$$\nabla \times \underline{E} + \frac{\partial \underline{B}}{\partial t} + g_m = 0 \quad (2)$$

$$\nabla \cdot \underline{E} = \rho_e \quad (3)$$

$$\nabla \times \underline{H} - \left(g_e + \frac{\partial \underline{D}}{\partial t} \right) = 0 \quad (4)$$

$$g_e = \sigma \underline{E}; \quad g_m = s\underline{H} \quad (5)$$

U(1) Symmetry	SU(2) Symmetry
$\rho_e = \dot{J}_0$	$\rho_e = \dot{J}_0 - iq(\underline{A} \cdot \underline{E} - \underline{E} \cdot \underline{A})$
$\rho_m = 0$	$\rho_m = -iq(\underline{A} \cdot \underline{B} - \underline{B} \cdot \underline{A})$
$g_e = \underline{J}$	$g_e = iq[\underline{A}_0, \underline{E}] - iq(\underline{A} \times \underline{B} - \underline{B} \times \underline{A}) + \underline{J}$
$g_m = 0$	$g_m = iq[\underline{A}_0, \underline{B}] + iq(\underline{A} \times \underline{E} - \underline{E} \times \underline{A})$
$\sigma = \underline{J}/\underline{E}$	$\sigma = (iq[\underline{A}_0, \underline{E}] - iq(\underline{A} \times \underline{B} - \underline{B} \times \underline{A}) + \underline{J})/\underline{E}$
$s = 0$	$s = (iq[\underline{A}_0, \underline{B}] + iq(\underline{A} \times \underline{E} - \underline{E} \times \underline{A}))/\underline{H}$

Here, g_e, g_m, ρ_e, ρ_m, σ, s and $\underline{A}$ stand, respectively, for electric current density, magnetic current density, electric charge density, magnetic charge density, electric conductivity, magnetic conductivity, and magnetic vector potential, respectively.

FIGURE 7.6 Amended Maxwell's equations with symmetry parameters.

Figure 7.5b approximation is required for the proper mathematical formulation. It will require careful experimentation in conditioned spaces to sort this out.

A MULTIDIMENSIONAL THEORETICAL MODEL

The key elements of this model are[3,4]

1. A network of nodal points that act as transponders and/or transducers for consciousness-wave-energy–wave conversion. The nodal point network functions on three size scales with the two larger grids being superlattice-like grids for the primary grid at the smallest size scale.
2. Spirit activates the driving consciousness-wave pattern for its specific intention and the nodal points in the grid convert these consciousness-wave patterns into various kinds of energy-wave patterns. These energy-wave patterns communicate with the various types of particles and agglomerations of particles within the interstices of the appropriate nodal point network.
3. Because these three nodal networks, when perfectly ordered, form reciprocal hexagonal lattices to each other, any quality of substance in the space of one network is related to the complementary quality in another network via a modulated Fourier transform relationship.

To use the Big Bang concept for illustrative purposes, this model proposes that at the inception of our universe, the mind and emotion domain substructures of the vacuum pre-existed (see Figure 7.7). Thus, directed intention from the domain of spirit has a ready mechanism for creating the Big Bang process. As alluded to above, the key structural element of the mind domain is a 10-dimensional network of active nodal points in a close-packed arrangement with a lattice spacing of $\lambda_M \approx 10^{-27}$ m (so this network forms an extremely fine grid closely related to the fundamental Planck length and Planck time). These nodal points are undetectable by the tools of today's physics.

During the condensation phases of the Big Bang, both the substances and the nodal networks of R space and D space are formed. The latter via a type of self-induced coherence of superposed consciousness waves broadcast from the mind domain nodal points. We will label these three nodal networks (NN) as NN_M, NN_R, and NN_D, where the subscripts are used to distinguish the particular level of the model. Thus, this primary lattice of mind nodal points contains within itself two potential superlattices of nodal points that are reciprocals to each other (see Figure 7.8). The first sublattice, NN_R, is also a reciprocal of the primary mind lattice, NN_M. The use of the word *potential* here is meant to imply that these particular nodal points must first form (via some process of organization) and then they must organize themselves into an array, which originally will be a relatively random array. This then proceeds through

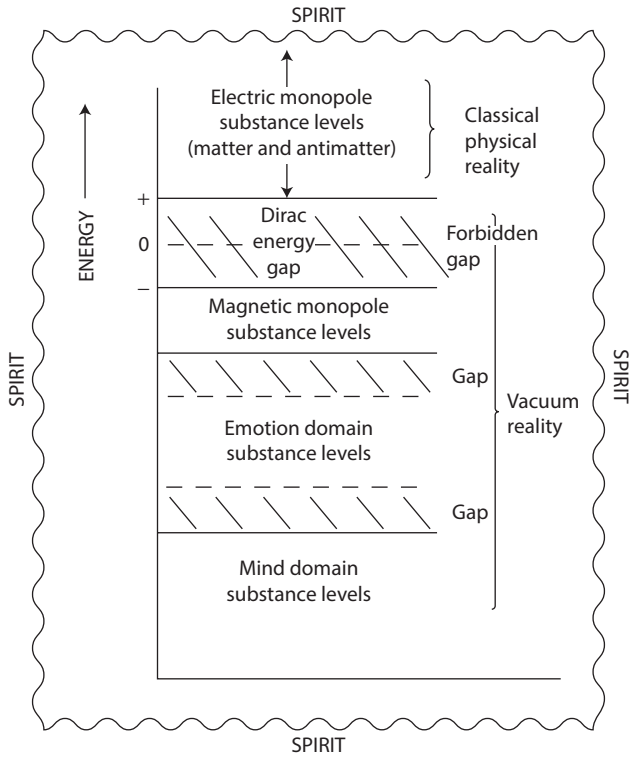

FIGURE 7.7 An energy level diagram embracing both classical physical substance and "unseen" vacuum substances.

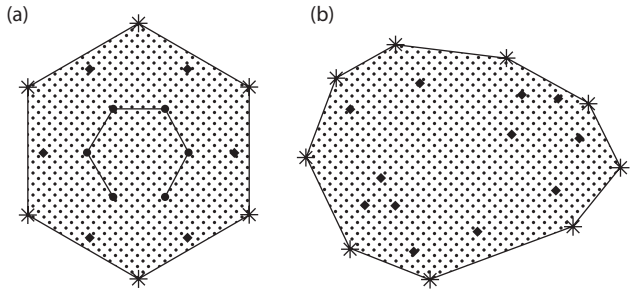

FIGURE 7.8 Illustrative plan view of the three nodal networks: (a) in a perfectly ordered state and (b) in the normally disordered state (except for the mind domain network). The proposed size scale change from network to network is ~10^{10}.

various stages of ordering to eventually become a relatively perfect 4-dimensional periodic lattice. The closest analogue to this in the world of materials science is *superlattice* formation in a host lattice of atoms. Let us now proceed with the description of the fully ordered state of these three nodal networks.

For NN_R, this first superlattice to NN_M has uniquely identifiable nodal points at $\lambda_R \sim 10^{-17}$ m and, at a 3-space level, is also of a close-packed hexagonal type but rotated counterclockwise by 90° with respect to NN_M (see Figure 7.8a). In fact, the NN_R are located at certain sites in the NN_M separated by ~10^{10} primary sites and have their own unique identifiable nature. The second superlattice, NN_D, is also formed from uniquely identifiable nodal points at a spacing of $\lambda_D \sim 10^{-7}$ m. It is a superlattice to the NN_R and, at a 3-space level, is also of the hexagonal close-packed type but rotated counterclockwise a further 90° with respect to the NN_R. Figure 7.8a represents an illustrative picture of these three nodal structures in perfect lattice form (but with much reduced spacing between the superlattice nodal points). However, relative to the sites in the NN_M lattice, those in the NN_R lattice are thought to have a spacing ~10^{10} times larger while those in the NN_D lattice have a spacing ~10^{20} times larger.

Figure 7.8b illustrates how the situation might look when defects and disorder of the NN_R and NN_D are present. As already stated, order–disorder transformations are thought to be involved in the two coarsest networks so they can exhibit amorphous, polycrystalline, or single crystal type of character. Here, one grain is thought to differ from another by the orientation of some special nodal point property, for example, special spin vector, tensor, and torsion.

These grids of nodal points are unique in that the waves traveling through the networks exhibit qualities of consciousness as distinct from energies. The conversion from consciousness to energies occurs at the nodal points themselves. It is also thought that the major components of life energy for humans are radiated from the NN_R and NN_D. Thus, the larger is the size or number of regularly spaced radiators in the array, the greater will be the amount (and fidelity) of the information transferred from the NN_M as well as energy transferred to the human from the NN_R and NN_D making the individual more conscious and more vital.

The structural character of the nodal networks is thought to be influenced by three main forces

1. Cosmological scale forces driven from higher dimensional realms
2. Individual human internal harmony versus disharmony
3. Collective humanity's internal harmony versus disharmony

When all the forces are beneficial, the NN form relatively perfect lattices of very large extent (e.g., Figure 7.8a) and humans manifest amazingly large consciousness and energy densities. When the reverse occurs, the NN form an almost amorphous arrangement and humans manifest only very small amounts of consciousness and life energy. In between, the NN structure is polycrystalline (e.g., Figure 7.8b) and the larger the size of the average NN grain, the greater will be the amount of consciousness and life energy flowing through the individual.

Generally, from the perspective of this model, a saint has reached a high state of inner self-management at mental and emotional levels so that the body substance radiation fields are harmonized and synchronized. This supports a superlattice ordering process to occur at the NN level so that grain growth occurs and the average NN grain size increases. Such individuals manifest an abundant energy output even with negligible physical food intake. Their Qi-Prana pumps are optimally functioning.

Figure 7.7 has been used to express the various energy bands involved in this model. Here, one can discriminate the classical physical reality (positive energy states) from the vacuum reality (negative energy states), once one defines the zero energy state as being located in the middle of what we will label the *Dirac energy gap.* This choice of zero energy state is historical and arbitrary. In the new paradigm, it would seem more reasonable to shift it to the bottom of Figure 7.7. Then, all of the energies in the diagram are positive. The presently described quantum mechanical reality is thought to include this classical physical reality plus some aspects of the upper band of the vacuum reality.

The experimentally observed reality, which this chapter has largely focused on, includes the classical physical reality (D space), the mathematical modulus of the upper band (R space) of the vacuum reality, plus both the deltron activation function from the middle vacuum reality band and the intention imprint "boundary condition" imposed on the lower vacuum reality band. The details of the nodal network structures in Figure 7.8 are intimately related to the details of the energy levels in the energy bands of Figure 7.7. One goal of the present work is to expand our current quantum mechanical perspective via the "biconformal base-space interpretation" so as to develop a quantitative predictability of experimentally observable events that incorporates (i) the details of both the magnetic and the electric monopole substance levels, (ii) the intention imprint as a boundary condition (BC) imposed on R space, and (iii) a parameterized version of the deltron activation function. Sometime in the distant future, we will have

learned enough to expand the perspective sufficiently that the intention imprint, BC, can be moved to the NN_M level and the deltron activation function can be expressed in much more fundamental terms. Then we will have created a level of physics that truly incorporates the human qualities of emotion and mind into observable reality.

In the U(1) gauge experimental world, one doesn't detect any significant object shape effects, at least not for objects of macroscopic size. Presumably, this is because the magnitude of the effect in normal cases is so small that it is down amongst the noise for the current levels of measurement accuracy. This could be interpreted to mean that the shape's R-space modulus is small because the cosmic background level of deltron coupling is quite small. For a system in a linear regime of deltron coupling, the deltron effect would cancel out of the normalized modulus[4] and this becomes a baseline pattern effect for the particular shape.[4] To empower the pattern to have a marked physical measurement contribution, through enhanced deltron activation, this additional factor must be incorporated into the theory in a mathematical fashion. At our present level of understanding, we simply define the deltron activation factor as $C_\delta\,(k, t,\ldots)$, where the dots represent other, as yet, undelineated variables, and we incorporate it into Equations 7.11a and 7.11b, which describe the R-space modulated Fourier transform, $F(k)$, for the particular D-space quality distribution, ρ_s, in a material plus the inverse Fourier transform to convert from the R-space quality distribution to its equilibrium D-space counterpart.

$$T: \qquad \hat{F}(k) = \frac{1}{(2\pi)^{1/2}} \int_{\text{D space}} \hat{\rho}_s C_\delta e^{i2\pi sk}\, ds \quad (7.11a)$$

$$T^{-1}: \qquad \hat{\rho}(s) C_\delta = \frac{1}{(2\pi)^{1/2}} \int_{\text{R space}} \hat{F}(k) e^{-i2\pi sk}\, dk \quad (7.11b)$$

Here the superscript ˆ notifies us that enhanced deltron activation is being taken into account. Equation 7.11 can also be used when only the cosmic background level of deltron activation, $C_\delta = C_{\delta_0}$, is present. In such a case, C_{δ_0} can be treated as a constant and brought out from under the integral sign, so it disappears in the expression for the normalized modulus.[4]

APPLICATIONS IN THE ELECTROPHYSIOLOGY AREA

The main portion of this and the previous chapter has focused on three aspects of the larger reality: (i) the coarse particulate level, (ii) the fine information wave level, and (iii) the deltron coupling medium from the domain of emotion. These can be thought of as three unique layers of substance in the human body with particular infrastructure development and features of all three are present and convoluted together in every type of electrophysiological measurement made by today's medicine. If we could deconvolve these three aspects, bioelectromagnetic medicine would have made an enormous step forward. Well, the mathematics is now available to allow us to do just that. It will not be laid out here, but it has been demonstrated by recent publications.[5,6]

Let us use electroencephalography measurements to illustrate the principle. At present, we take time-dependent electric voltage measurements at N unique spatially separated points on the head and immediately Fourier transform this $V(r_j, t)$, $j = 1, 2,\ldots, N$, data to obtain a frequency domain representation. We then use this result as a diagnostic tool. However, this raw data is a type of mixture from three different layers in the human so the diagnostic power is not as great as it might be. In references 5 and 6, respectively, we have shown (i) how to take spatially varying data and calculate its complementary spectral amplitude profile at the R-space level and (ii) how to take time-varying data and calculate its complementary spectral amplitude profile at the R-space level. Combining this same type of analysis procedure into a 4-space distance-time set of data, the full four-dimensional R-space spectral amplitude profile that generated this data set can be calculated. In addition, the general equations also allow one to calculate the deltron activation function profile yielding this particular D-space and R-space result. Now, with this addition, the same experimental data-gathering procedure provides explicit information on (i) the patient's D-space coarse particulate brain, (ii) R-space fine information wave brain, and (iii) one aspect of the emotion domain brain.

Such mathematical procedures can also be applied to all other electrophysiological measurements on the human body so that future medicine will be able to experimentally manifest a richer perspective on the state of health and pathology for the "whole" human.

ACKNOWLEDGMENT

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8 Magneto-Metabolic Therapy for Advanced Malignancy and Cardiomyopathy

Demetrio Sodi Pallares and Paul J. Rosch†*

CONTENTS

The evolution of a novel and highly effective treatment approach for the treatment of metastatic malignancy, pancreatic cancer and terminal cardiomyopathy based on the efficacy of polarizing solution and a low sodium diet in acute myocardial infarction is discussed. Illustrative case histories are provided demonstrating the dramatic benefits derived from the additional administration of electromagnetic fields to this regimen. The mechanisms of action responsible for these rewards are explained as well as implications for future applications.

EDITOR'S NOTE

Demetrio Sodi Pallares passed away on August 12, 2003, at the age of 90. He was the son of the famous lawyer and Secretary of State of Mexico, Demetrio Sodi Guergue, and he was the grandson of another famous lawyer, Jacinito Pallares, and he is survived by five sons, including Mexican Senator Demetrio Sodi. An internationally recognized cardiologist and one of the world's authorities on electrocardiographic interpretation, he was the author of 16 books and more than 300 scientific papers and the recipient of over 100 honorary degrees.

I first became acquainted with Demetrio Sodi Pallares 45 years ago as a result of having been awarded a Fellowship at Hans Selye's Institute of Experimental Medicine and Surgery at the University of Montreal in 1951, shortly after the publication of his magnum opus *Stress*. Selye and I developed a close professional and personal relationship and collaborated on several articles and projects over the next three decades. In exploring the role of stress in experimental myocardial infarction, he had demonstrated that the damage was magnified when animals had been previously sensitized by a high salt diet and/or the administration of adrenal cortical hormones like desoxycorticosterone that caused sodium retention. Potassium supplementation had a protective effect and he told me that a Dr. Sodi Pallares was able to subsequently confirm this in such a convincing fashion in humans that Selye replaced all his salt shakers with potassium chloride. It tasted terrible on those occasions when we had dinner at his home but he was confident it would help protect him from a heart attack. Following my internship and residency at Johns Hopkins and postgraduate training at Walter Reed, I entered private practice and at Selye's insistence, succeeded Joel Elkes, former Chairman of the Department of Psychiatry at Hopkins, as President of The American Institute of Stress in 1978.

Our First International Montreux Congress on Stress in 1988 included a session entitled "Electromagnetic Energy Effects on Psychophysiologic Function." It was chaired by Björn Nordenstrom who discussed "The Use of Electrical Energies in the Promotion of Healing and Treatment of Cancer" and included presentations by Norman Shealy and Saul Liss on "The Effect of Electromagnetic Energy on Brain Neurotransmitters" and Boris Pasche on "The Physiological effects of Low Energy Emission Therapy (LEET)." This segment attracted so much interest that we included similar sessions at subsequent events. I had been involved with the development of the Symtonic LEET device and was so impressed with the results of double-blind studies showing its efficacy in insomnia and anxiety that I decided to devote a day to the use of magnetotherapy for the treatment of stress related disorders at our 1997 Ninth International Montreux Congress on Stress. I was anxious to attract leading investigators in this area and particularly any whose research could provide clues about magnetotherapy mechanisms of action. I made some inquiries and two colleagues immediately suggested that I invite a Dr. Sodi Pallares of Mexico City to discuss his remarkable results in patients with advanced metastatic malignancy.

I told them that I was familiar with Demetrio Sodi Pallares, a cardiologist who had now become world renowned for developing a "polarizing solution" to prevent cardiac damage. In the 1960s, I routinely administered this intravenous drip containing potassium chloride and insulin in hypertonic glucose (Figure 8.1) as soon as possible to all my acute heart attack

* Deceased.
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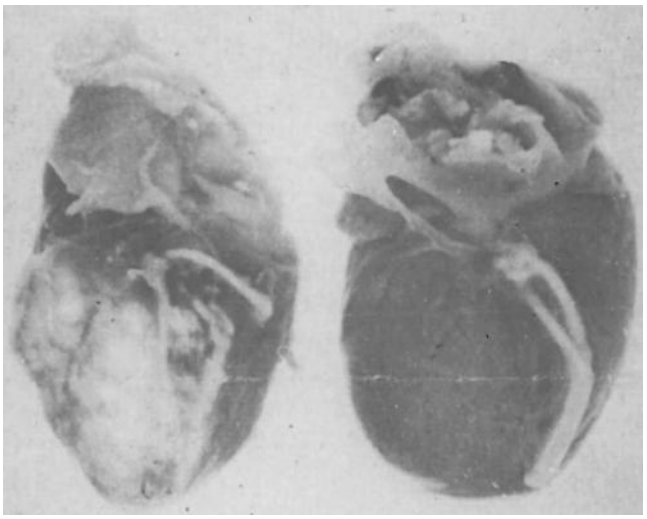

FIGURE 8.1 Cadioprotective effect of potassium chloride. Left: Massive necrosis visible as a white patch on the surface of the left ventricle following ligature of the left coronary artery in a control rat. Right: Complete prevention of the necrosis by pretreatment with KCL in a litter made exposed to the same procedure.

patients as did most other cardiologists I knew. There seemed little doubt that it significantly reduced complications of shock, arrhythmia, and congestive failure and shortened duration of hospitalization. However, as this Sodi Pallares would now probably be over 80, it did not seem likely that he was still treating patients, much less using magnetotherapy to cure cancer. I assumed that this might be his son or some other relative and wrote to him requesting additional information and related the Selye anecdote.

I was pleased to receive a prompt and very gracious response indicating that he was indeed the same Demetrio Sodi Pallares. His letterhead listed his specialty as "Cardiology and Magnetotherapy," which was like getting a letter from Mike DeBakey indicating "Cardiovascular Surgery and Magnetotherapy." He went on to describe his current research interests and willingness to participate in the congress, where he gave a superb presentation. Demetrio, or Sodi as he is usually referred to, has provided us with updates at subsequent congresses of his astounding achievements, not only in patients with seemingly hopeless cancers, but also in patients with terminal cardiomyopathy and other disorders. We became good friends and cooperated in other presentations; he asked me to co-author this chapter in a narrative fashion based on our conversations and provided written material.

He had initially become interested in the antagonistic roles of sodium and potassium in 1944 when his mother developed marked edema of the lower extremities, enlargement of the liver, and tremendous abdominal distention due to ascites. The diagnosis was heart failure due to coronary arteriosclerosis and her electrocardiogram showed a left bundle branch block. In those days, this usually meant a life expectancy of not more than 2 years but it would have been much less for his mother in view of her serious heart failure. She was receiving the standard treatment of mercurial diuretics, digitalis, and a low cholesterol diet but she was allowed to have sodium rich foods that were low in fat. The aggressive diuretic therapy required to reduce her fluid retention caused severe cramps and left her feeling exhausted. At the time, Sodi was involved in experimental electrocardiographic investigations at Mexico's National Institute of Cardiology and when he inquired as to why she had to receive so many injections of the mercurial diuretic, his professors explained that it was to eliminate sodium chloride. He asked why they allowed her to eat foods rich in salt and was told that his mother had to be on a low cholesterol diet to delay the atherosclerotic process and that the injections would get rid of the salt.

He was not satisfied with this answer and, although he had little appropriate background, decided to develop a diet for her that would eliminate any food with a sodium content higher than 100 mg/100 g. As it turned out, this was fortuitous, as he ended up with a diet that was not only low in sodium (around 360 mg) but also 10 times higher in potassium, and he did not realize how important this would prove to be. His mother followed the diet faithfully, was able to discontinue her medications, and went on to live a normal life for another 15 years. He began prescribing this dietary regimen for patients with other cardiovascular problems and found that most with congestive failure could be stabilized and usually only required digitalis and/or diuretics if they had acute pulmonary edema. The same was true for many others with essential hypertension, and it was not unusual for angina to disappear in weeks or even days after following the diet. Exhilarated about his results, he tried to convince other physicians to try the diet in their patients to see if they got the same benefits. However, his colleagues not only did not share his enthusiasm but also criticized him because his diet was rich in cholesterol like egg yolk, unsalted butter, and other fats that would surely accelerate the progression of atherosclerotic deposits. In addition, he had had relatively little experience in clinical cardiology and was invading other fields not related to the electrocardiographic research he had been assigned, which would not be tolerated by authorities of the National Institute of Cardiology.

In retrospect, we now know that dietary cholesterol and fat have relatively little effect on either serum cholesterol or the development of obstructive atheroslcerotic plaque and that this diet actually proved to have a favorable effect on lipid profiles. Sodi went on to become a superb clinical cardiologist, authored some 20 cardiology texts, including over a dozen on the electrocardiogram alone, and his continued successes with the low salt diet only served to strengthen his belief in its benefits.

In spite of this opposition, he recommended it whenever he could and was encouraged by Hans Selye, who visited the Institute in 1959 during the International Symposium of Arteriosclerosis being held in Mexico City. Selye presented his experiments demonstrating the damaging effects of sodium as well as the cardioprotective effects of potassium in animals subjected to stress. Compared to control animals, more extensive myocardial infarcts were seen in those who

had been on a high sodium diet and given adrenal corticoids. Potassium supplementation markedly reduced or prevented myocardial necrosis as seen in Figure 8.1.

As this could be demonstrated in animals with normal coronary arteries, it proved that myocardial infarction was not always due to obstruction of a coronary vessel that deprived the myocardium of oxygen. At the time, *heart attack, coronary occlusion,* and *myocardial infarction* were often used interchangeably as if they were synonymous. However, it is now clear that atherosclerotic occlusion of a coronary vessel, which occurs gradually, does not always result in a myocardial infarction and conversely, that myocardial infarction can result from excess catecholamine effects in the absence of coronary occlusion or even ischemia. This is not infrequent in pheochromocytoma and has also been reported as a complication of sympathomimetic drugs (isoproterenol, amphetamines), increased sensitivity to MAO inhibitors, and deaths related to sudden emotional stress, where characteristic "contraction bands" can be seen in the myocardium.[1,2]

Selye's presentation also fell on deaf ears as it was contrary to current dogma and many felt that what happened to rats under laboratory conditions had little relevance for people. In commenting on this several years later, Selye wrote:[3]

> The very fact that scientists of so many countries have contributed to this monograph on metabolic cardiopathies bears witness to the great change in outlook that has been placed in the interpretation of pathogenesis of heart disease during the last decade. Barely eight years ago, in September 1959, at the International Symposium on Arteriosclerosis and Coronary Disease in Mexico City, I tried to prove that infarcts, like cardiac necroses, can be produced without vascular obstruction, that is, by combined treatment with electrolytes or corticoids and stress. At that time, with the notable exception of Dr. Sodi Pallares, few of the participants were prepared to believe that such metabolic factors could play a role in the genesis of true cardiac infarcts in man.….Although the functional effect of many electrolytes upon the heart has long been known, the finding that sodium increases and potassium and magnesium diminish the susceptibility to cardiac necroses was also received with the greatest reserve.

But what was the mechanism of action that explained the harmful effects of sodium and the benefits of potassium? Why did administering sodium cause fluid retention in patients while potassium did not, as both were monovalent cations? In an acute myocardial infarction, three zones of injury can be distinguished. In the central portion of the damaged area, there is a core of necrotic tissue and dead cells due to the absence of oxygen. This is surrounded by an area of severe injury composed of cells that will die unless the metabolic derangement can be stopped or reversed. The damage lessens progressively in the periphery of this section that gradually merges into a larger third zone of cells that are less ischemic. Here, structural damage is not as impressive, and although function is impaired compared to adjacent normal tissue, the abnormalities are reversible.

Sodi demonstrated that in experimental infarction produced by ligature of the left coronary artery in dogs, he could show a clear and consistent correlation between the degree of damage and intracellular concentrations of sodium and potassium as one progressed through these three zones from healthy muscle. The higher the concentration of sodium, the greater the degree of damage, but the reverse was true for potassium. Compared to normal tissue, intracellular sodium in the ischemic area increased around 50%, compared to over 200% in the intermediate area of injury and more than 300% when the central necrotic core was reached. There was a corresponding decrease in potassium of 5% in ischemic tissue, 10% in the intermediate injury zone, and 18% in the necrotic area. Although these figures varied with the location and size of the infarct, they showed the same consistent interrelationships.

Were these abnormalities in sodium and potassium merely a reflection of the degree of damage or could they possibly contribute to it? Was increased intracellular sodium the cause of cellular injury? All atoms have shells orbiting around them filled with electrons to neutralize the positive charge of protons in the nucleus. The first shell contains two electrons and each successive shell contains eight electrons. The sodium atom has 11 electrons, two in the first shell, eight in the second, but only one in the third that it must get rid of to remain stable. The potassium atom has 19 electrons so it has three shells that are filled and a fourth that has only one electron. In both situations, there is a need to remove the extra electron by finding an atom with a shell that needs more electrons to be filled. When this happens, one of the protons in the nucleus is not balanced and these atoms now become monovalent positive ions or cations (Na^+ and K^+). A molecule of water (H_2O) consists of two atoms of hydrogen, each having a positive charge, and 1 atom of oxygen that has a negative charge. As the radius of the potassium ion, or the distance from the center of the nucleus to the external orbit, is greater than the radius for sodium it is easier for water molecules to cluster around the sodium ion. When the number of intracellular sodium ions increases, they attract more molecules of free water than potassium does and the resultant swelling of the cell interferes with normal function.

The concentration of sodium within the cell is normally much lower than in the extracellular fluid, and the reverse is true for potassium, but what was responsible for this? His further investigations revealed that under healthy conditions, there is a powerful mechanism that constantly pumps excess sodium out of the cell. Because the concentration of sodium ions outside the cell is much higher than inside, a gradient in polarization is produced across the cell membrane known as the *sodium electrochemical potential*. He found that the difference in this gradient decreased progressively as one moved from healthy tissue to zones of increased injury and that this was reflected in the electrocardiogram as illustrated by the typical changes of ST segment depression seen in ischemic tissue noted in Figure 8.2.

This progressive decline in the polarization gradient with increased injury mirrored the changes in sodium and potassium alterations noted above were also reflected in the electrocardiogram. As intracellular sodium increased, so did the

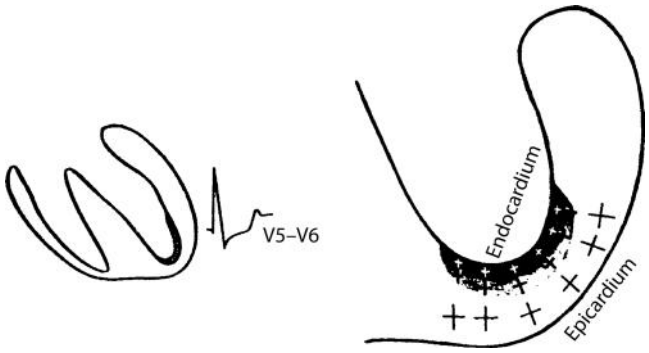

FIGURE 8.2 Schematic representation of subendocardial ischemia of the left ventricular wall. The electrocardiogram shows significant S-T segment depression in leads V5–V6.

volume of water in the cell, causing it to swell so that normal function was disrupted. These concomitant changes and correlations are summarized in Figure 8.3.

Sodi concluded that increased intracellular sodium caused damage to cardiac muscle fiber cells and that as this became more pronounced, there was a corresponding progressive diminution of the gradient of polarization across the cell membrane and a diminished ability to function optimally. This can be seen more clearly in Figure 8.4 taken from his book *Deductive and Polyparametric Electrocardiographic Interpretation*.[4]

He immersed himself in studying physics, biochemistry, bioelectrical phenomena, cybernetics, and anything else that might help him understand why his dietary regimen had such cardioprotective effects. This might allow him to convince his colleagues and other physicians of its benefits and more importantly help him learn how to improve his treatment results. The correlation between a healthy cell and its ability to maintain an electrical potential gradient across the cell membrane was consistent and impressive, and by now his mastery of electrocardiographic interpretation made it relatively easy to monitor this. He knew that according to the laws of thermodynamics, energy is neither created nor destroyed. It can only be transformed and that during its conversion from one form to another, some energy is degraded, or "lost" with respect to its availability to do work. This degradation, which is called *entropy,* applies to all chemical, electrical, and mechanical energy transformations, including those in biological systems.

Albert Einstein used the illustration of a roller coaster to explain the different forms of mechanical energy and entropy in a closed system.[5] As the car is pushed to the highest point of the track during the first steep rise, it acquires potential energy as it progressively resists the force of gravity as shown in Figure 8.5a. As it subsequently accelerates down the first bend towards earth, this stored potential energy is steadily converted into kinetic energy, the energy of motion as seen in Figure 8.5b. When the car ascends the second upward incline, kinetic energy is again progressively transformed into potential energy, and this sequence of energy transformation events is repeated over and over with each successive

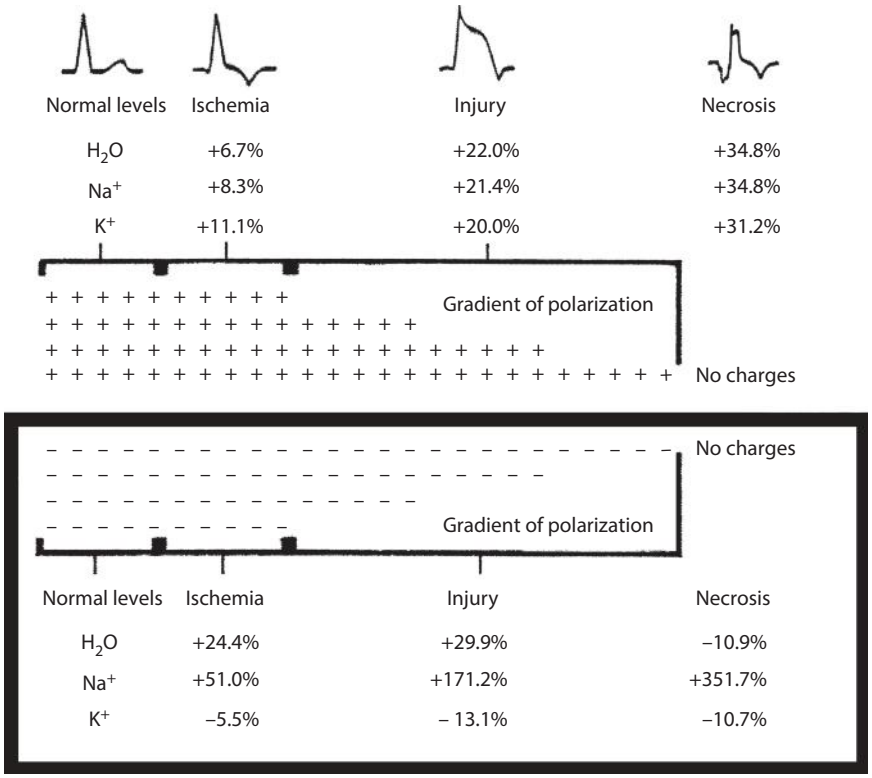

FIGURE 8.3 Schematic representation of a recent myocardial infarction showing the progressive change in intracellular and extracelullar concentrations of sodium (Na^+), potassium (K^+), and water (H_2O) as well as the decline in gradient of polarization from normal to ischemic to injured to necrotic tissue with characteristic corresponding ECG changes.

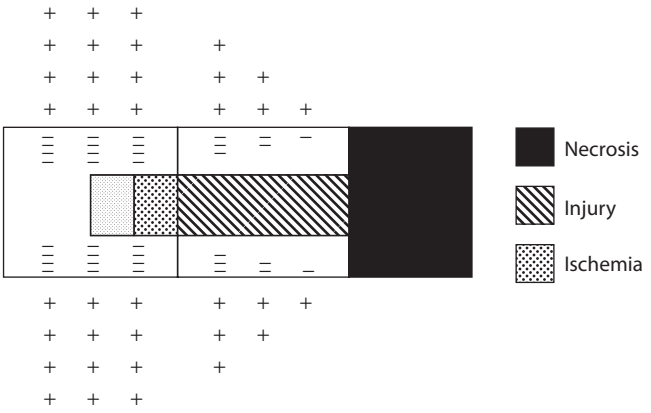

FIGURE 8.4 Following an acute myocardial infarction there is a progressive decline in the difference in electrical potential across the cell membrane that is closely related to the degree of injury and intracellular sodium concentration. Much like a battery, heathy tissue maintains a gradient of about 90 mV, whereas no gradient can be detected in necrotic or dead tissue. As this polarization gradient diminishes, so does the ability to do work, and the amplitude of contraction of muscle fibers progressively declines.

loop. However, the height reached (potential energy) and the speed of the descent (kinetic energy) progressively diminishes due to entropy, and the car finally stops moving.

If this transfer of energy was absolutely complete without any diminution in its ability to perform work, then the car would always attain the same height on the ascending loop and the same speed during its descent, and we would have perpetual motion. However, we all know that this does not happen because of friction. The friction between the wheels of the car and the rails they ride on create heat. Although this is another form of energy (entropy), it is not available to help the car do its work. Instead, it is conducted to connecting structures, or back into the environment by radiation or convection, during which, some of it is also degraded. The amount of heat, which in this example depends upon the degree of friction or resistance, represents a loss in energy to perform the work of the car. If the surface of either the wheel or the rail becomes damaged so that smooth and continuous contact cannot be maintained, then there will be a corresponding decrease in kinetic and potential energy because of increasing entropy. The total amount of energy remains the same, but the difference between its forms progressively diminishes since entropy keeps increasing over time. As the laws of thermodynamics also govern biological activities, all three forms of energy in Einstein's roller coaster analogy must be present in the heart. From Sodi's perspective, kinetic energy was the same as what was referred to as *free energy* in biological systems, which was supplied by Adenosine triphosphate (ATP). The free energy concentrated in the phosphate bonds of one molecule of ATP furnishes about 7600–7800 cal. Potential energy was primarily represented by glycogen and triglycerides stored in heart muscle. Under emergency conditions due to fever, trauma, or severe emotional stress, the potential energy in these compounds is converted to ATP free energy similar to the conversion of potential to kinetic energy in the roller coaster. During all cardiac metabolic activities, some energy cannot be converted to do work and these calories (entropy) are dissipated to surrounding tissues.

Sodi reasoned that in heart muscle tissue, entropy is produced when sodium enters the cell, and as this increases, the electrical potential across the cell membrane diminishes and disappears when the cell dies. Under healthy conditions, the power for pumping sodium out of the cell comes from the energy rich phosphate bonds of adenosine triphosphate (ATP). The production of ATP diminishes as intracellular concentrations of sodium rise so that the energy to perform work declines correspondingly. This is what happens when the cell membrane is damaged following a myocardial infarction and sodium enters the cell causing a reduction in the polarization gradient.

When the cell has to do more work, additional energy from ATP is required and the key to this was ATPase, an enzyme that hydrolyzes the ATP molecule to release the free energy in its powerful phosphate bonds. ATP is also the source of energy for normal activities, such as the sodium pump that maintains the difference in concentrations of intracellular and extracellular sodium and potassium. Sodi had shown that his low-sodium high-potassium diet also helped to keep sodium out of the cell and potassium inside by promoting ATP activities. He reported his clinical achievements in cardiovascular disease in 1960 in the *Canadian Medical Association Journal*, possibly because of Selye's encouragement.[6] By then, he had become aware of a "polarizing solution" consisting of glucose, insulin, and potassium developed by Henry Laborit, a French researcher.[7] It seemed to be even more effective in this regard, because insulin facilitates the entry of glucose and potassium into the cell and when this happens, sodium is driven out, thus increasing the polarization gradient across the cell membrane.

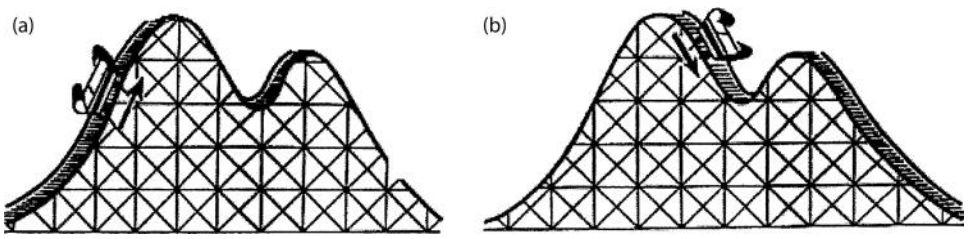

FIGURE 8.5 (a) Ascending the track to acquire potential energy; (b) transformation of potential to kinetic energy.

As this was similar to the results he wanted to achieve with his diet, he decided to investigate the effect of different concentrations of the ingredients of this concoction in experimental myocardial infarction produced by ligating a coronary artery in dogs as he had done in previous experiments. He measured extracellular and intracellular sodium (Na^+) and potassium (K^+), and the best results were seen with an intravenous solution of 20% glucose containing 40 units of regular insulin and 40 mEq of potassium chloride given at a rate of 40 drops per minute. Administering polarizing solution significantly reduced the progressive rise in intracellular sodium and decrease in intracellular potassium that correlated with the degree or injury as depicted in Figure 8.6.

Polarizing solution also prevented the damage due to experimental myocardial infarction in dogs, as illustrated in Figure 8.7.

Encouraged, he studied the effects of administering polarizing solution to patients with acute heart attacks and other cardiovascular disease and was gratified by the clinical numerous benefits it provided as well as significant improvement in electrocardiograms. He reported these results in the early 1960s[8,9] and the rest is history. Cardiologists and researchers all over the world confirmed his results and sent him letters of congratulations. Eugene Braunwald, who would later become one of the most celebrated American cardiologists, Chief of Medicine at the Peter Bent Brigham Hospital with a chair named for him at Harvard, an award established in his name by the American Heart Association and numerous other honors, received a $100,000 grant to study the effects of polarizing solution in experimental infarction. He and his associates corroborated the results Sodi had reported 10 years previously[10] and subsequently confirmed its clinical benefits.[11] Others also reported a decrease in morbidity, mortality, and complications such as arrhythmias.[12–14] Studies of polarizing solution effects in experimental infarction in dogs,[15] pigs,[16] and rats,[17] confirmed its ability to boost ATP production and improve free fatty acid metabolism[18] and to protect against hypothermic global ischemia by scavenging free radicals.[19]

As Sodi's fame increased, it seemed that the authorities and his colleagues at the Institute became increasingly envious and jealous, rather than praising and supporting his efforts. Instead of improving things, the antagonism to his research increased and became so intense that he was forced to leave the Institute in 1975 and enter private practice to continue his investigations. Over the next decade, Sodi and his associates were able to show conclusively that his polarizing solution speeded up recovery from myocardial infarction, corrected arrhythmias, significantly reduced mortality rates in shock, and boosted ATP and cellular energy mechanisms sufficiently to benefit other conditions including myocarditis, cardiomyopathy, and hepatitis. These results were also confirmed by others in nuclear magnetic resonance studies, patients with diabetes and chronic ischemic cardiomyopathy, as well as clinical trials that acknowledged his seminal contributions.[20–23] The use of polarizing solution increased all over the world, but it was often administered in a haphazard or reckless fashion so that optimal or consistent results were not achieved. In other instances, extravagant claims were made suggesting that it was a panacea, and it was prescribed for inappropriate indications. As new drugs were developed to treat shock, congestive failure, hypertension, inflammation, and various arrhythmias, they were vigorously promoted to doctors by pharmaceutical companies, and the popularity of polarizing solution declined. However, it continued to be used in heart transplant surgery to maintain the integrity of donor hearts,[24] improve the efficacy of mechanical assist devices,[25] and for prophylactic benefits in bypass surgery.[26] There has been a recent revival of interest with large clinical trials confirming that it is the most cost-effective treatment for acute myocardial infarction and can reduce mortality by as much as 66% when damaged cells that are still viable can be restored to normal.[27–30]

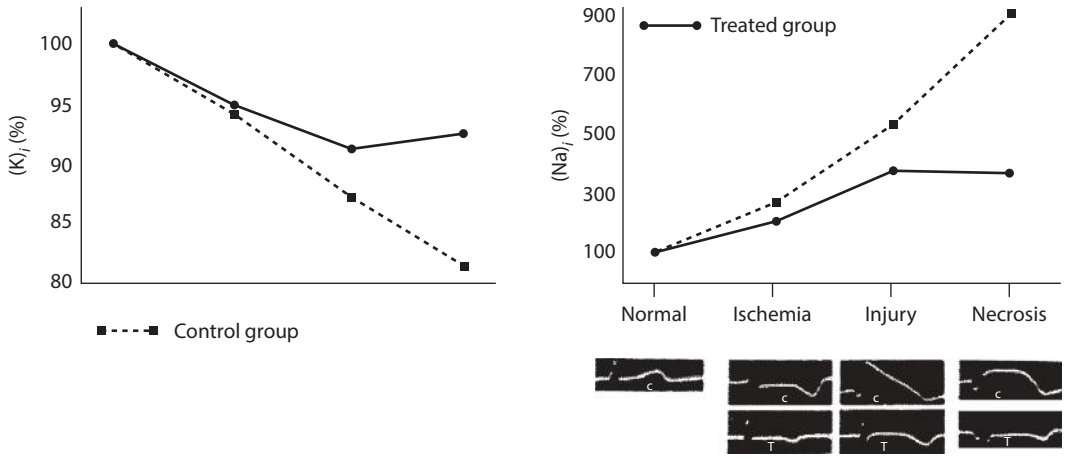

FIGURE 8.6 Progressive increase of intracellular sodium and decrease of intracellular potassium (broken lines) from the periphery of the infarct through areas of ischemia and injury to the central core of necrosis. Polarizing solution significantly diminished this trend as shown with the solid lines.

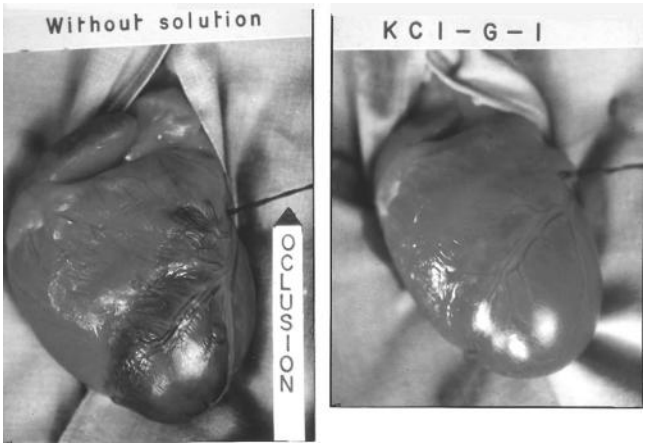

FIGURE 8.7 Reduction in necrosis following myocardial infarction in a dog with intravenous infusion of glucose, insulin, and potassium (polarizing solution).

Polarizing solution was effective because it improved the ability of ATP to provide energy by reducing the entropy produced when sodium enters the cell. As in Einstein's roller coaster illustration, the greater the entropy, the greater the disturbance in the ability to utilize energy to perform work. This principle applies to all forms of energy and all systems but its application to biological processes was first described by the nineteenth century American mathematician-physicist Josiah W. Gibbs. Gibbs conceived the concepts of chemical potential and surface tension and was considered to be one of the world's greatest theoretical physicists by James Clerk Maxwell, who first proposed that electric and magnetic energies travel in transverse waves at the speed of light. One of Gibbs' greatest achievements was devising the equation to express thermodynamic equilibrium in living systems in terms of energy and entropy, and the energy from ATP is often referred to as the *free energy of Gibbs* in his honor. This energy is free for the cell to reproduce itself, manufacture an enzyme or hormone, or use in any way it sees fit. Going back to the roller coaster analogy, it is very much like having a constant source of electricity that the system can use to control the speed of the cars and provide light, heat, or sound as required. As the source of energy for all cellular functions comes from ATP, it follows that when ATP synthesis or hydrolysis is impaired by increased intracellular sodium, no cell can function properly and the ability to correct this should resuscitate those with potentially reversible damage.

If this were so, then Sodi's polarizing solution and dietary regimen should prove beneficial for many disorders other than myocardial ischemia, and this has been supported by numerous observations. Ling, a molecular biologist, did not subscribe to the sodium pump theory but also verified the damaging effects of intracellular sodium[31,32] and later confirmed that a high potassium and low sodium environment could partially restore damaged cell proteins to the normal undamaged configuration using nuclear magnetic resonance tecniques.[33] Ling had a profound influence on F. W. Cope, who proposed a tissue damage syndrome that could occur anywhere in the body in cells deprived of oxygen and/or nutrients for any reason.[34] He regarded the cell as analogous to an ion-exchanger resin granule with structured water in the interstices and potassium and sodium ions associated with fixed negative charges on the protein matrix. In tissues damaged by disease or trauma, there was a configurational change of the protein matrix that resulted in intracellular potassium being replaced by sodium and an abnormal uptake of water by the cell that interfered with ATP production. He advocated diet and medications that could decrease sodium and/or increase potassium concentrations in the body and was later surprised to find that Sodi had already been utilizing this and that Gerson's successful treatment of cancer emphasized this approach.[35]

B. F. Trump and colleagues also found that these characteristics of high intracellular sodium and low intracellular potassium in damaged tissue that could be restored to normal could be demonstrated not only in the myocardium but liver cells exposed to carbon tetrachloride, kidney tubules following the mercuric chloride injection, HeLa cells infected with polio virus, ascitic tumor cells treated with cytolytic antibody, and various malignancies. Trump believed that a wide variety of pathological phenomena ranging from acute cell death to chronic processes like neoplasia, hypertension, and aging were all a common series of cellular reactions.[36,37]

Sodi's interest in cancer was stimulated by the observation that malignant cells were also depolarized because of failure of the pumping mechanism that keeps sodium out. In some instances, intracellular sodium concentration is 300% higher than normal, and as this progresses, the intracelluar concentrations of protons (H^+) and calcium (Ca^{2+}) increase causing swelling of the cell due to water retention. This seriously disrupts mitochondrial function and the ability to synthesize ATP and lowers membrane potential. Cohen had shown that in very aggressive malignancies like mysoarcoma, the polarization of adjacent healthy tissue was 90 mV in contrast to only 10 mV at the center of the tumor. Furthermore, this decrease in membrane potential could be correlated with increased proliferative activity of malignant cells.[38]

Our cells are surrounded by an ocean of salt water very high in sodium and low in potassium that passes through them at a rate of 100 times the cell's volume every second. As healthy cells contain only 7% of the sodium concentration of extracellular fluid, but the concentration of potassium is 342 times greater within the cell, a tremendous amount of energy is required to overcome these very high gradients across the membrane. This energy comes from the hydrolysis of ATP to Adenosine diphosphate (ADP) and phosphorus or to Adenosine monophosphate (AMP) and pyrophosphate with the eventual release of high-energy phosphate bonds. How this was accomplished was not clear until the late 1950s when the Danish biophysicist Jens Christian Skou proposed that an enzyme was responsible.[39] Skou was awarded the

1977 Nobel Prize in Chemistry for discovering Na^+ -K^- ATPase and showing that when bound to the cell membrane, it was activated by an increase in external potassium and/or internal sodium.[40]

Reports that electromagnetic fields could remarkably increase the growth of plants suggested that this was another way to stimulate ATP synthesis, and Sodi investigated this by preparing two small tumblers in which he put five dried beans and a fistful of soil. One was exposed to a pulsating electromagnetic field for 2 h a day for 5 days, and a highly reputable fertilizer was added to the other according to the prescribed instructions. He was surprised to find that the stem of plant subjected to the electromagnetic field increased as much as 10 cm in a day (Figure 8.8a) and was much taller than the fertilized plant (Figure 8.8b). Long term studies showed that the fertilizer was effective in promoting increased growth (Figure 8.9b) but not to the extent achieved with pulsating electromagnetic fields (Figure 8.9a).

Proof that pulsed electromagnetic fields could significantly boost ATP production to provide benefits in other disorders came from a patient with human papilloma virus infection of the cervix that was considered to be a premalignant condition as shown in Figure 8.10a. The Schiller test showed an absence of glycogen. She was treated with a low-sodium diet and exposed to a pulsating magnetic field of 70 G for 2 h daily. After 2 months, there was no sign of disease (Figure 8.10b) and the Schiller test now confirmed the reappearance of glycogen. This is particularly important as large amounts of ATP are required to form glycogen.

Since then, significantly beneficial results have been found with the use of pulsating magnetic fields in osteoarthritis, rheumatoid disease, discoid lupus, multiple sclerosis cardiomyopathies, severe cardiac insufficiency and other

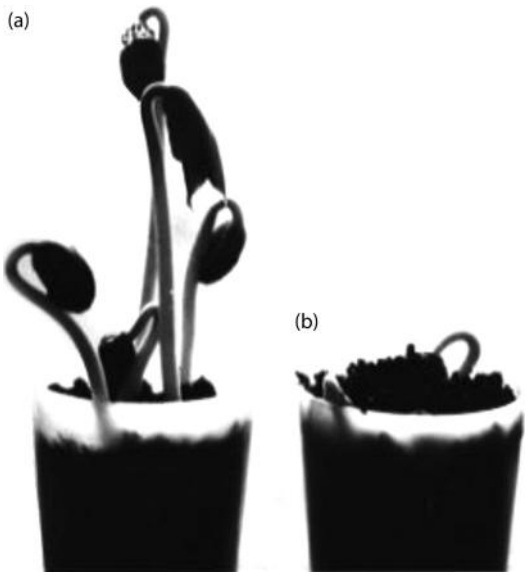

FIGURE 8.8 After a few weeks, (a) with PEMF and (b) with fertilizer.

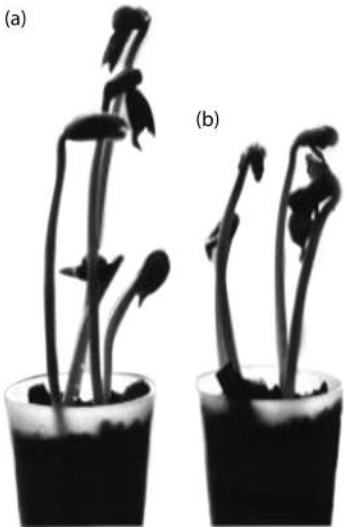

FIGURE 8.9 After months, (a) with PEMF and (b) with fertilizer.

disorders including Kaposi's sarcoma, AIDS, and various malignancies. In most instances, the intensity of the magnetic field ranges between 40 and 80 G, all patients followed the low-sodium diet, and in resistant cases, polarizing solution was also given. Cancer patients generally require 130–150 G. The pulsating electromagnetic field is delivered by a three-section folding pad containing coils in each section on which the patient can lie or use while sitting in a chair to target specific portions of the body. The wave form is a sinusoidal curve with a frequency of 60 Hz for treating both bone and soft tissue. The reason that cancers respond so well has been clarified by the research of Damadian and Cope, who measured Na^+, K^+, and H_2O in various malignancies and confirmed that the increase in intracellular sodium and water and decrease in potassium were similar to the changes noted in a recent myocardial infarction.[41] This had previously been shown by Clarence Cone, who predicted the benefits of restoring intra-cellular potassium but was unaware that Sodi had already demonstrated this.[38] Metastatic bone metastases respond especially well to this treatment.

Space constraints preclude an extensive report on clinical successes in various metastatic malignancies as well as brain tumors and primary lung cancer, but these and other triumphs are described in a book published in 1988[42] that is now being updated and translated into English. It also demonstrates how this protocol can prevent cardiac damage due to chemotherapy and radiation, and is effective in a variety of cardiovascular, dermatologic, and other disorders. Figures 8.11 through 8.13 are representative of the dramatic results achieved in advanced metastatic breast, prostate, and pancreatic malignancies.

Very positive results have been seen in cardiovascular disorders, including congestive failure, hypertension, and especially end-stage cardiomyopathy requiring heart transplantation. In one such case, a 42-year-old male with heart failure resistant to treatment had a biopsy at a leading cardiovascular center that confirmed coagulative necrosis, and

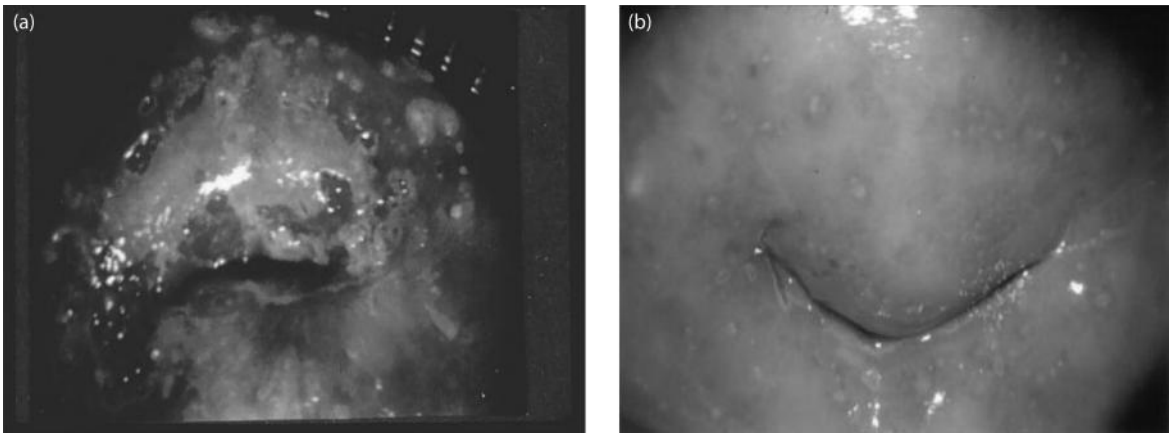

FIGURE 8.10 (a) Premalignant lesions before treatment and (b) disappearance of lesions after treatment.

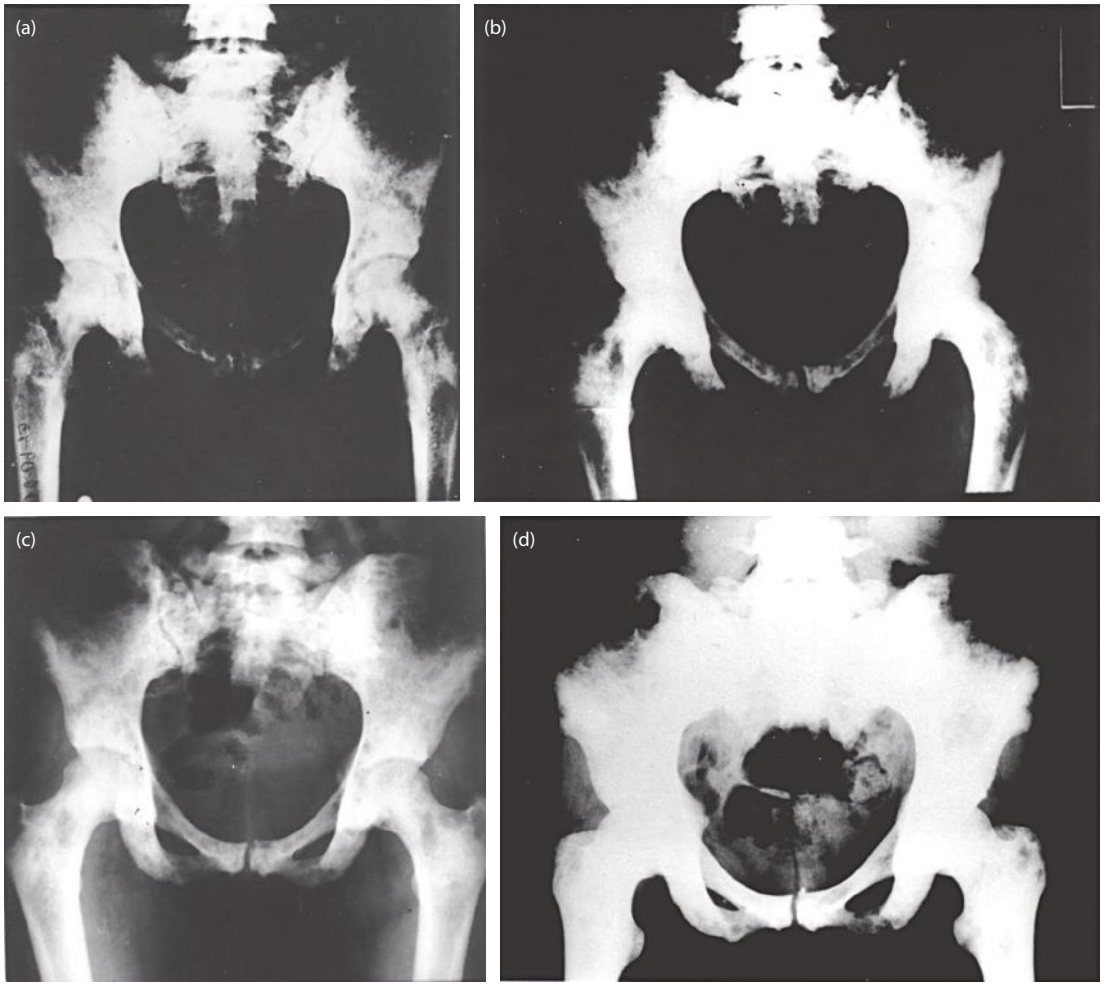

FIGURE 8.11 Thirty-nine-year-old female with bilateral breast cancer treated with chemotherapy and radiation with good results for 3 years but subsequently experienced weight loss, shortness of breath, and recurrent breast tumors. X-ray of the pelvis (a) showed an absence of the pubic bones and ischia and numerous metastases. A pleural effusion of 3000 cm^3 was evacuated, but it was generally felt that she would not last a week. Treatment was started with diet, polarizing solution 5 h daily, and application of a pulsating magnetic field of with intensity between 130 and 170 G. She gained 5 lb over the next 3 weeks, continued to improve, and by 6 weeks, there was evidence of reappearance of the pubic and ischial structures (b). This continued to improve (c), the breast tumors decreased progressively and she felt so well after 25 weeks she asked if she could continue her treatment at home and appropriate arrangements were made. X-rays at that time (d) showed almost complete remineralization.

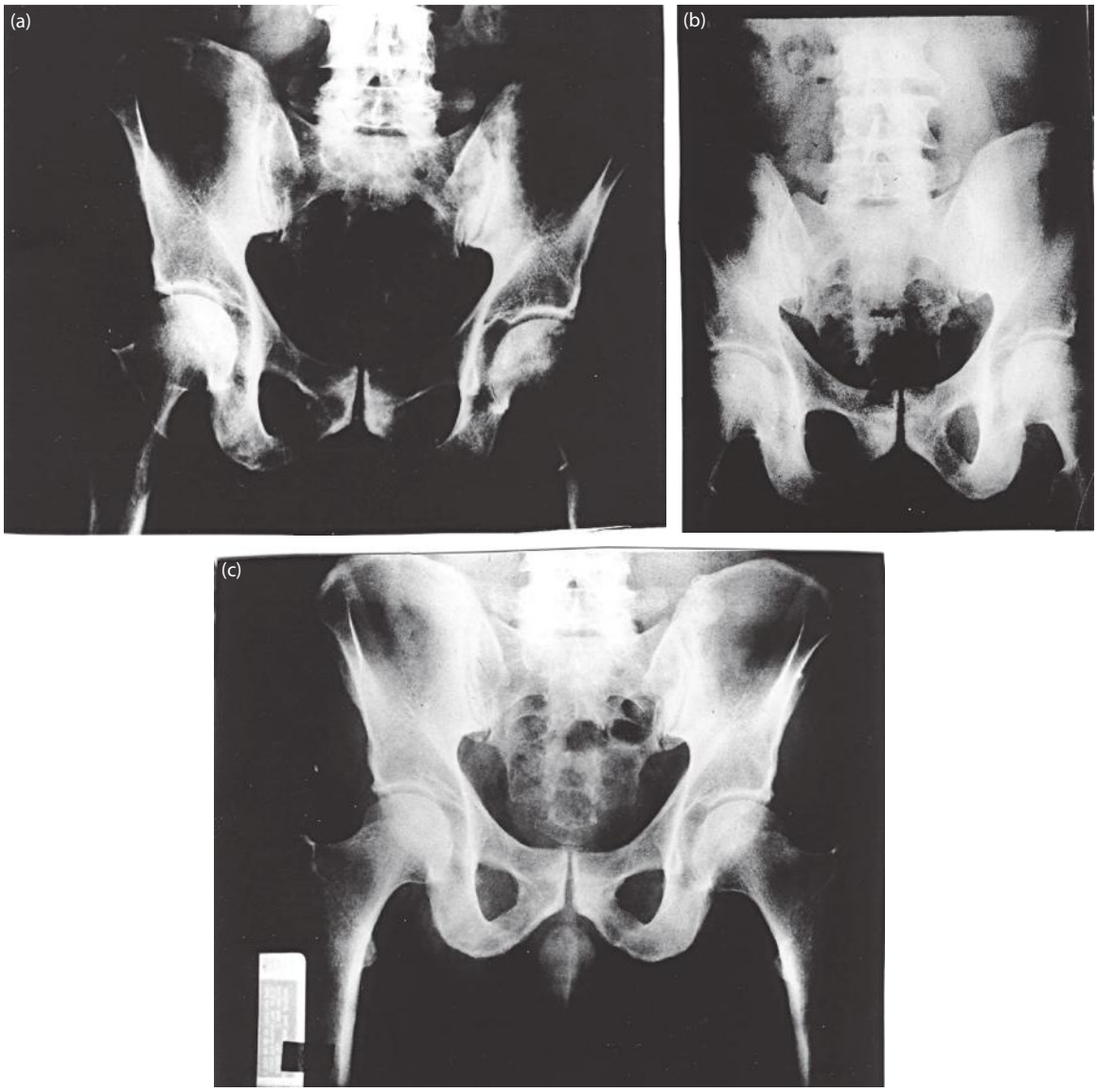

FIGURE 8.12 Seventy-two-year-old male with adenocarcinoma of the prostate and metastases to the ribs and pelvis showing destruction of the pubis. (a) Treatment was started on July 7, 1997 with dramatic improvement in general well-being as well as osteolytic lesions in the pelvis after only 4 days. (b) On July 25 the reduction in metastases was even more impressive. (c) The patient had to return to the United States where he intended to find a physician to continue the treatment, but contact was lost because he was apparently unable to accomplish this. Reduction in metastases was even more impressive.

he was told that only a heart transplant would save his life. While waiting for a donor, he developed increasing shortness of breath, abdominal distention angina, and atrial fibrillation and, when seen, had Grade IV enlargement of the heart on x-ray, and ECG showed left ventricular hypertrophy and subendocardial damage. He was started on diet, 5 h of polarizing solution daily and application of 80-G pulsating magnetic field during this period. After only 2 weeks, shortness of breath, angina, and abdominal complaints vanished and heart size was markedly reduced. His electrocardiogram returned to normal following 18 weeks of treatment, and he continued to improve and he was discharged. When contacted 3½ years later, he stated he was in excellent health and living a completely normal life and taking no medication, although he continued to follow the diet. Figure 8.14 shows the response of another patient who was treated with the same protocol.

There seems little doubt that this regimen can be improved as it is based on an empiric approach. In some instances, variations in the strength of the polarizing solution and the pulsed electromagnetic field have produced better results, and optimal treatment probably varies with each patient. Unfortunately, we do not have objective parameters to determine this, but advances in measuring biofield characteristics may prove useful. It is also likely that supplementation with ubiquinone (coenzyme Q10) could provide additional benefits since it is a crucial component of the electron transport chain of the Krebs cycle that is required

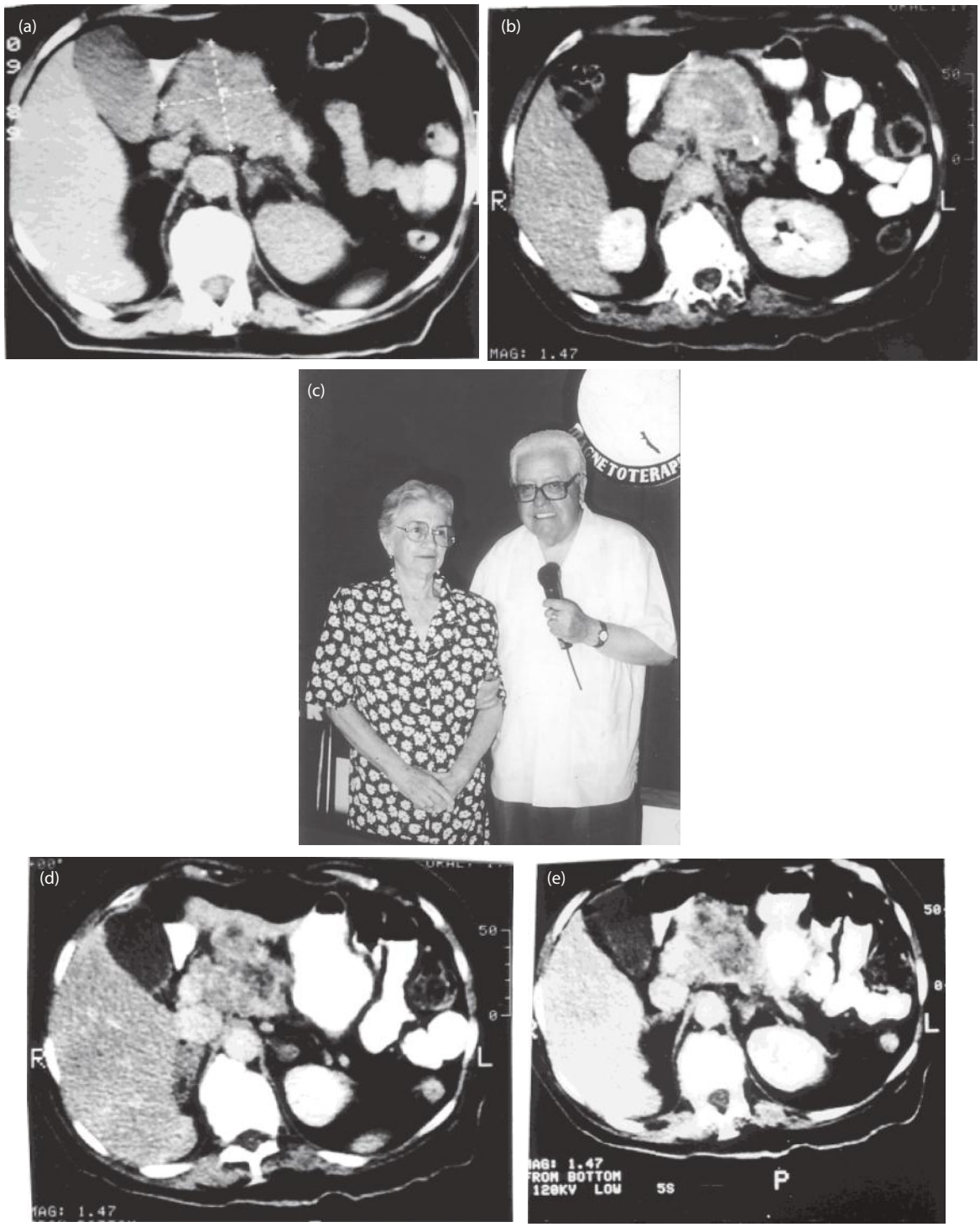

FIGURE 8.13 Seventy-five-year-old female seen on March 29, 1998 complaining of progressively severe abdominal pain, weight loss, and fatigue for a month. Tomography revealed a malignancy of the body and head of the pancreas with invasion of regional lymph nodes (a and b). She was started on diet, received polarizing solution twice weekly along with daily application of 150 G to the affected area. She improved rapidly with respect to relief of pain, return of energy, and weight gain, and her general condition was excellent 24 months later. (c) She continued to do well and tomograms at 36 months showed no increase in the tumor size and necrotic areas could be seen (d and e). She was seen by an oncologist who told her that the original diagnosis must have been an error as nobody with this type of pancreatic cancer lives for 3 years, furthermore, she could eat as much salt as she wanted and she could discontinue the treatment. The patient was pleased with this opinion and took his advice but died shortly thereafter.

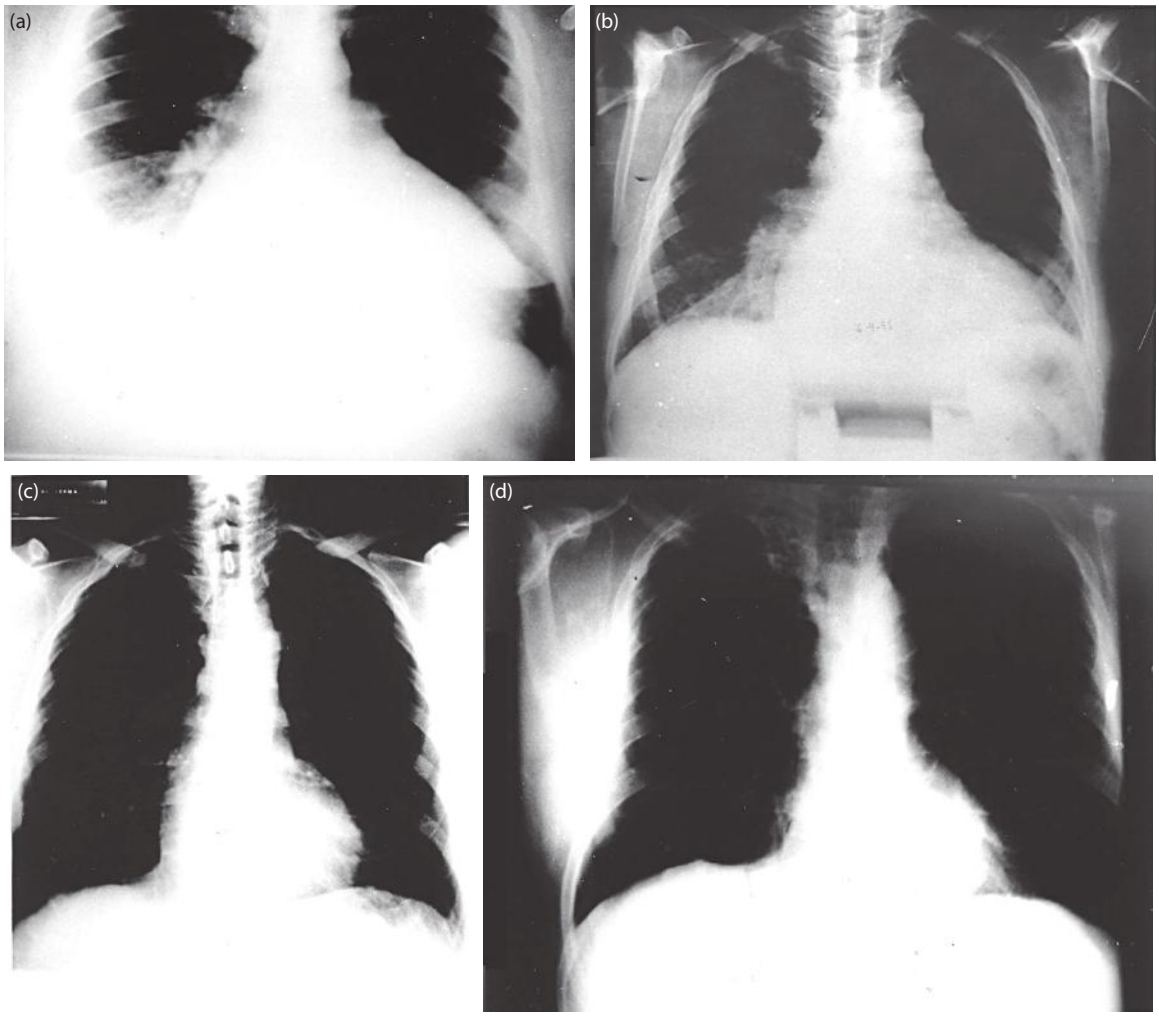

FIGURE 8.14 (a) Before treatment, (b) after 2 months, (c) after 6 months, and (d) after 7 months.

for ATP synthesis and oxidative phosphorylation. Our hope is that others will confirm the benefits of this magnetotherapy-metabolic-thermodynamic approach and find ways to improve it.

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9 Is There an Electrical Circulatory System That Communicates Internally and Externally?

Paul J. Rosch and Björn E.W. Nordenström*

CONTENTS

> There is evidence of an electrical circulatory system in the body that is reminiscent of ancient Chinese concepts of meridians that conduct *Qi* (ch'i) energy through prescribed pathways (meridians) in the body in an orderly fashion. In this analogy, the antagonistic and complementary components of yin and yang may be thought of as positive and negative electricity. Similar energy communication conduits may help explain such well acknowledged but poorly understood phenomena as the placebo effect, the power of a strong faith in spontaneous remission of cancer and energy fields that can emanate from chi gong masters and faith healers that appear as auras with Kirlian photography and other imaging techniques.
>
> Dr. Björn Nordenström claims to have found in the human body a heretofore unknown universe of electrical activity that's the very foundation of the healing process and is as critical to well being as the flow of blood. If he is right, he has made the most profound biomedical discovery of the century.

So began the April 1986 cover story in *Discover Magazine* about Björn Nordenström's amazing "cures" of patients with lung and breast tumors based on his theory of biologically closed electrical circuits. It went on to note that some distinguished scientists and physicians believed that if his findings were confirmed by others they would prove to be as important as William Harvey's description of the circulatory system. Some compared his 1983 book[1] explaining his results and theories to Harvey's 1628 treatise on how blood circulates through the body.[2] Clinicians who tried to wade through Nordenström's massive tome often had difficulty deciphering the complex electrical schematics and equations that formed the underpinnings of his theory. Others failed to grasp its potential implications. However, the few who did appreciate this as well as the thoroughness of his research were laudatory in their praise and tried to promote his efforts, as evidenced by the following unusual book review by Morton G. Glickman, MD, Professor of Diagnostic Radiology, Yale University School of Medicine, that appeared in *Investigative Radiology* (Vol. 19. Sept/Oct/No. 5, 1984):

> It has not been the policy of *Investigative Radiology* to publish book reviews. However, the work by Nordenström reviewed below presents such fundamental and far-reaching concepts that a review was deemed desirable in order to call this book to the attention of those who read *Investigative Radiology.* The importance of the concepts presented in Dr. Nordenströms book cannot be overemphasized. Those who are interested in fundamental biological observations will be fascinated by the logical progression of this most imaginative work: *Biologically Closed Electric Circuits,* Björn E. W. Nordenström, MD, 1983 (Nordic Medical Publications, Arsenalsgatan 4, S-1ll 47 Stockholm, Sweden).

This remarkable book introduces a new physiologic concept that could solve many long-standing biologic problems. This far-reaching concept evolved from a series of ingenious experiments that began with the author's search for the explanation of a curious pattern that he observed on a chest x-ray about 30 years ago. His investigations carried him well beyond the original problem and produced original insights into such fundamental processes as wound healing, organ development and differentiation, and extra-cellular fluid dynamics. The primary direction of the book is understanding the interaction of malignant tumors with their surrounding tissues. It leads on the one hand to a possible mechanism of carcinogenesis and on the other to a proposed new mode of therapy of malignancies. Dr. Nordenström has discovered a new circulatory system that is based on spontaneously occurring electrical potentials. Potential gradients have long been known to develop in normal organs as a result of metabolism and in injured or diseased tissue because of hemorrhage or necrosis. The investigations detailed in this book reveal that these potentials are more than just a source of error in bioelectric measurements, that, in fact, they drive electric current through what the author calls biologically closed electric circuits (BCEC).

Blood plasma and interstitial fluid are examples of ionic media capable of effectively conducting current. Blood vessel walls and the cells and membranes that surround interstitial spaces insulate these conducting media from their surroundings. Plasma and interstitial fluid are electrically joined across capillary membranes. Thus, blood vessels and interstitial spaces function as insulated electric cables that carry current and transport charged particles over short and

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long distances. Other BCEC probably also exist, but the book examines this particular circuit in detail, documenting its existence and function with a series of experiments using physical analogs of biologic organs and organ systems, animal models, and tumor and tissue specimens obtained at autopsy or surgical resection. The resultant hypotheses are tested in a series of careful and humane diagnostic experiments and therapeutic trials performed on consenting human volunteers with malignant diseases.

Credit should be given to Dr. John Austin who spent many hours revising the manuscript. The book is written in a lucid, concise prose style and presents its material in approximately chronologic order. Thus, the reader is shown the stepwise development of this complex concept in what must be very close to the way that the author himself arrived at his conclusions. This method of presentation tantalizes the reader as it builds from the proposal of a simple hypothesis to its experimental documentation to the next hypothesis, and gradually, but convincingly, expands the reader's understanding as the investigations progress to more and more basic levels of biologic insight. Like most significant scientific innovations, the ideas are simple and, once proposed, the reader must wonder why something so obvious took so long to surface. Yet the originality or the hypotheses, the thought processes that led to them, and the experiments that prove them are astounding.

In the mid-1950s, Dr. Nordenström observed a peculiar series of radiating and circumferential patterns surrounding a primary carcinoma of the lung on a chest radiograph. He called this pattern corona structures, because of the similarity to the corona of the sun. A prospective study over several years revealed that corona structures were present with considerable frequency around pulmonary malignancies, pulmonary granulomas, and even hamartomas. The book begins the analysis of these structures with a careful description using radiographs of many patients and using serial radiographs of the same patient. The alteration of corona structures with time and the disappearance of some of them with the development of pneumothorax led Dr. Nordenström to postulate that some parts of this radiographic pattern resulted from an unexplained effect of pulmonary masses on distribution of lung water. Thus began a series of experiments that resulted in his conclusion that fluctuating electrical potentials originating within lung masses could alter extracellular fluid dynamics. The author demonstrated that electrical potentials do exist within lung masses by performing a series of measurements in patients undergoing needle biopsy. After preliminary experiments, he succeeded in reproducing corona structures in dogs by implanting artificial "tumors" that produced potential gradients similar to those measured in human pulmonary masses.

The text proceeds to an investigation of the anatomy and physiology of these phenomena and leads to the development of the concept of energy conversion over BCEC. Along the way, explanations of a number of other biologic phenomena are proposed. After demonstrating that electrical potentials are spontaneously generated in organs such as the spleen, and that potentials of this magnitude lead to formation of fibrous tissue at electrical interfaces, the author postulates that organ capsules and other fibrous surfaces such as pleura and peritoneum are formed by BCEC.

Platelets and leukocytes carry a surplus of fixed electronegative surface charges. Thus, a spontaneously occurring positive polarity in injured tissue results in accumulation of platelets and then thrombosis of capillaries surrounding a site of injury. This mechanism can also account for attraction of leukocytes to a site of positive electrical potential in injured or diseased tissue.

To test the possibility that BCEC alter the tissue environment around tumors in organs other than the lung, the author undertook a series of experiments with human and animal breast tissue and human breast neoplasms. He demonstrated in a series of mammograms that corona structures similar to those that surround lung masses are present quite commonly around tumors of the breast. Spontaneous electrical potentials occur in breast tumors, just as in lung masses, and have a similar effect on tissue water distribution. However, the abundant fat in breast tissue permitted some even more surprising observations. Histologically normal human breast fat obtained from mastectomy specimens, when subjected to electrophoresis, developed fibrosis similar to the desmoplastic reaction that surrounds breast tumors. Within this desmoplastic tissue, structures developed that were histologically similar to primitive ductal and vascular channels. The author suggests that this may explain the mechanism by which tumor angiogenesis occurs. Similar *in vitro* experiments produced microcalcifications similar to those found in breast malignancies in previously normal breast fat.

This seminal work opens important new subjects for research and may ultimately explain many heretofore inexplicable biologic phenomena. However, it is more than a scholarly report of a massive research effort. It is an interesting, often exciting account of a brilliant mind in vigorous action. It leaves the reader exhilarated.

A year later, a second article appeared in the *American Journal of Roentgenology*, probably the most prestigious journal in the field. It was a rewrite of one of Nordenström's lectures, again accompanied by a comment from the editor who similarly stated that its publication was unconventional and required the following explanation. The work was unique in that unlike the multiauthored papers that such a complex subject usually required, this represented the effort of just one individual, Björn Nordenström. "He alone is responsible for the original concepts, the experiments, the analysis, and the text. Although employing modern terms and instruments, his performance is in the tradition of the pioneer scientist: complete and isolated immersion in the research." While a final judgment on the merit of Nordenström's theory would be premature, the work was "imaginative, experimentally ingenious and provocative" and deserved serious examination by the medical community.

Despite this and other accolades, Gary Taubes, the author of the lengthy *Discover* cover story was surprised to find during his extensive research that few cancer specialists and even radiologists knew anything about Nordenström's research or

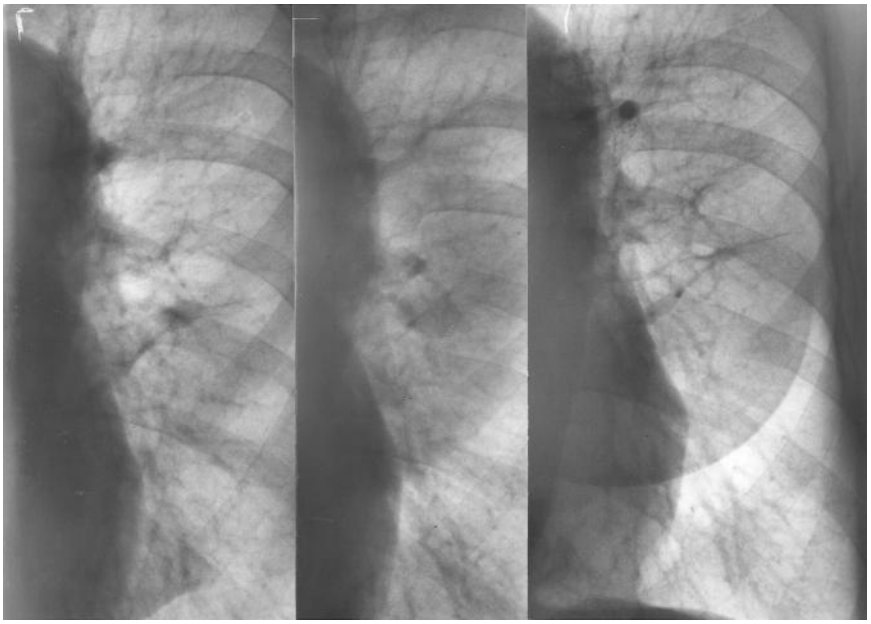

FIGURE 9.1 Sixty-six-year-old patient with metastatic ovarian cancer to the lung.

recognized who he was, much less interested in determining whether he was right or wrong. This, despite the fact that he had pioneered the development of the percutaneous "skinny needle" biopsy technique that all surgeons and interventional radiologists relied on. In addition, Nordenström was Chairman of the Department of Radiology at the prestigious Karolinska Institute and Chairman of the Nobel Assembly that selects the Nobel Laureate in Physiology or Medicine.

Whether Björn Nordenström's BCEC concept is correct, there is little doubt that his treatment protocol based on this can be very effective. I had asked him to chair a session on "Electromagnetic Energy Effects On Psychophysiologic Function" at our 1998 International Congress on Stress in Montreux, Switzerland. It included papers on "The Effect of Electromagnetic Energy on Brain Neurotransmitters" by Norman Shealy and Saul Liss, and "The Physiological Effects of Low Energy Emission Therapy" by Boris Pasche, all of whom who have also contributed chapters to this volume. Björn's own presentation on "The Use of Electrical Energies in the Promotion of Healing and Treatment of Cancer" described one patient with a history of ovarian cancer and another with adenocarcinoma of the breast who had subsequently developed metastatic pulmonary lesions. These patients were considered inoperable and one had large lesions in both lungs. Nevertheless following treatment, the tumors gradually disappeared and both were well 8 and 10 years later with no evidence of metastatic disease. Figure 9.1 shows chest x-rays of the ovarian cancer patient when first seen and 8 months and 2 years following a single painless course of treatment that was completed in 1 day. When last heard from a few years ago, this individual was approximately 90 years old, in good health, and without any evidence of cancer. How could such miraculous results be explained?

According to Nordenström's theory, the body's electrical communication system can be compared to a battery in which the circuit is driven by separation of oppositely charged ions. Once the circuit is closed, long distance current flows through the conducting cables and within the battery, ions drift across the permeable barrier as shown in Figure 9.2.

When tissue is damaged by injury or malignant growth, there is a buildup of positively charged ions in the affected area, whereas adjacent healthy tissue is negative. As a malignant

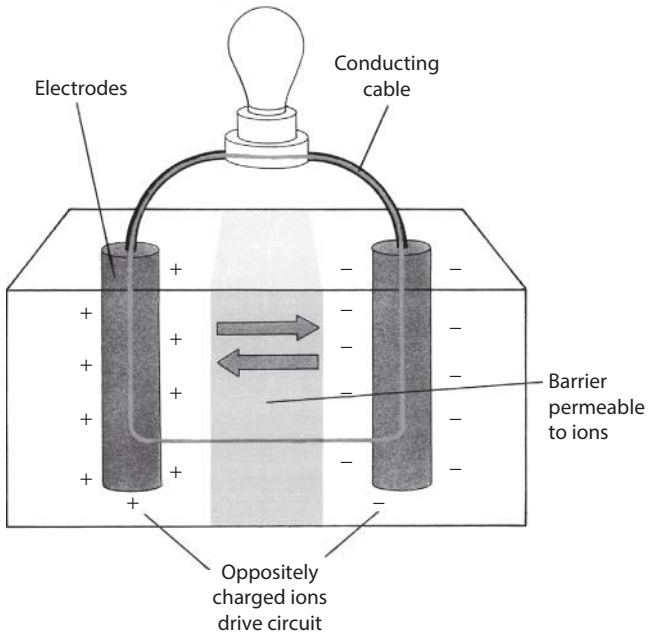

FIGURE 9.2 Nordenstrom's biologically closed electrical circuit (BCEC): a biological battery.

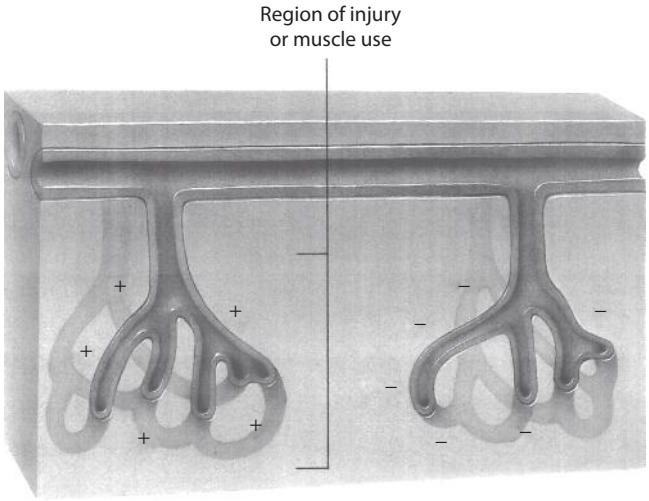

FIGURE 9.3 Cancer tissue develops a positive charge.

tumor grows, its inner cells are cut off from the circulatory system and they slowly perish. This cell death leads to chemical changes and the production of positive electrical potential in the tumor compared to adjacent tissue as seen in Figure 9.3.

This separation of charge sets the stage for the flow of electricity as the tumor's progressive positive charge polarizes nearby tissue, thus turning on the long-distance circuit. Ions flow through blood vessels linked to the tumor as well as percolating throughout the tissue around the tumor as indicated in Figure 9.4.

Nordenström's biologically closed electrical circuits are driven by the accumulated charges, which, unlike those in a battery, constantly oscillate between positive and negative. The larger vessels act like insulating cables and the blood plasma functions as a conductor. In permeable tissue around the tumor, the fluid between cells conducts ions and capillary membranes function as electrodes, as shown in Figure 9.5.

A key component of BCECs are the natural electrodes found in capillary walls. The membranes of the capillary wall cells are known to be charged, causing ions to circulate through the cells

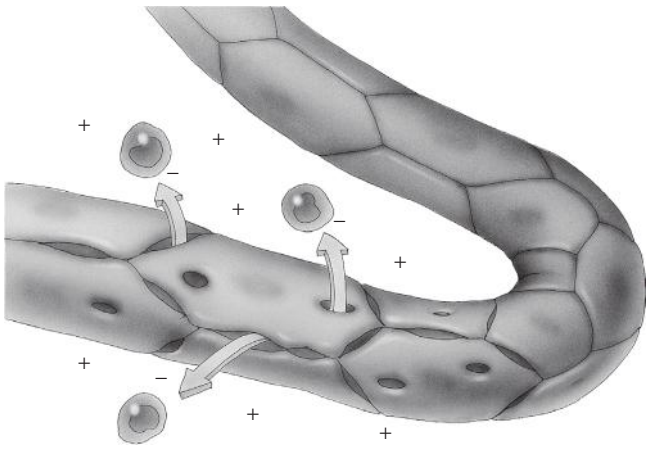

FIGURE 9.4 How the biologically closed electrical circuit is activated.

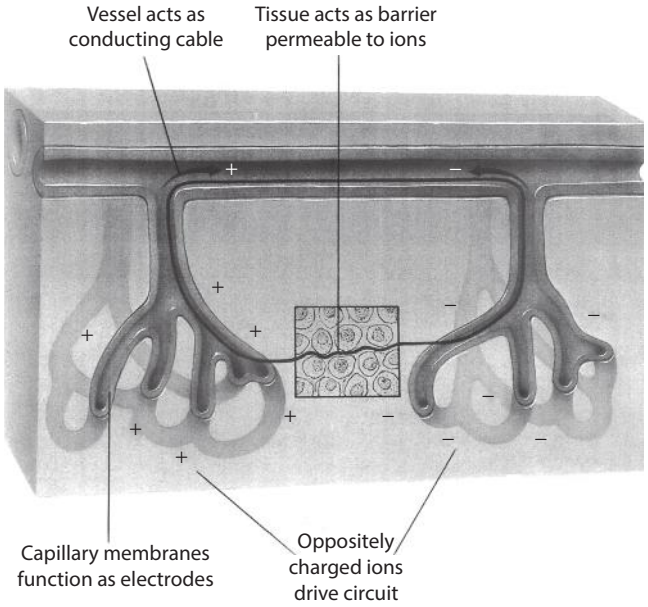

FIGURE 9.5 How current flows through the blood stream.

via gates and vesicles and between the cells via pores, as shown in Figure 9.6. Electrons cross over and enzymes can bridge to close this local circuit. Nordenström discovered that arterial capillaries contract when subjected to an electric field caused by the accumulation of positive charges at a site of tissue injury. As a consequence, the pores and gates close, blocking the ionic current and the ions flow through the blood stream and along the capillary walls, thus switching on the long-distance circuit.

In contrast, venous capillaries do not contract in an electrical field. Ions and charged white blood cells that are attracted or repelled by the changes in electrical potential at sites of injury migrate through the pores of adjacent venous capillaries as shown in Figure 9.7. This causes an oscillation of electrical potential at injury sites creating an ebb and flow of ions that Nordenström believed was critical for the healing process.

He arrived at these conclusions by initially measuring the electric potential or voltage of lung tumors by using the skinny needles he had introduced as electrodes. A positive electrode was inserted into the tumor and a negative one into adjacent normal tissue as illustrated in Figure 9.8. He found that the coronas around malignant tumors seen on x-rays occurred during their electropositive phase; spikes appeared on the surface of the tumor and water moved into the surrounding tissue dehydrating the tumor and forming a series of radiating structures and arches.

By running current into the tumor, Nordenström was able to amplify and prolong the electropositive phase of the existing circuit. He postulated that this would trigger a variety of tumor-fighting effects, including attracting white cells and producing acid at the center of the tumor and the accumulation of water at the negative electrode as shown in Figure 9.9.

Since his initial presentation, Björn has provided us with updates on his research at subsequent congresses, and we

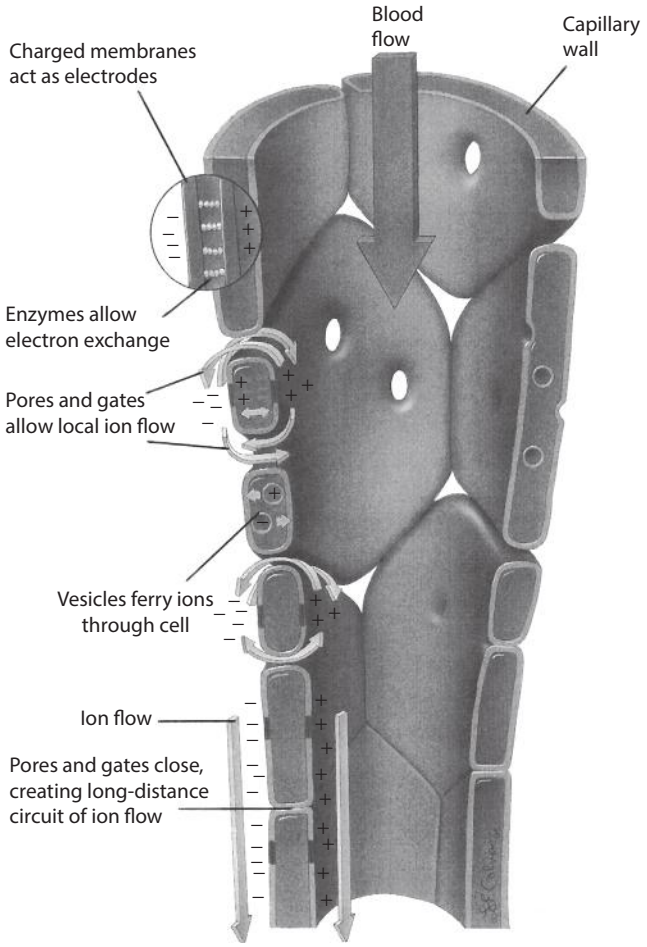

FIGURE 9.6 Capillaries close the circuit.

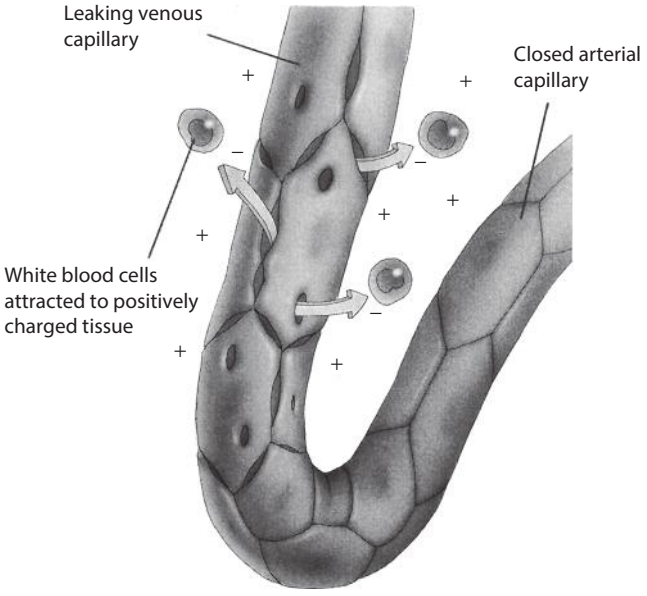

FIGURE 9.7 Venous and arterial capillary activities at sites of injury and cancer.

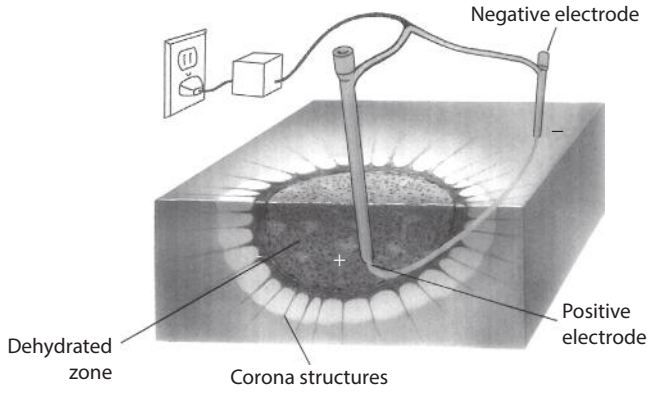

FIGURE 9.8 Inserting the electrodes. Using skinny needles inserted into the tumor (positive electrode) and adjacent normal tissue (negative electrode), it was found that the coronas around malignant tumors seen on x-rays occurred during their electropositive phase; spikes appeared on the surface of the tumor, and a series of radiating structures and arches were formed as water moved into the surrounding tissue and the tumor became dehydrated.

have become good friends. His results in metastatic lung malignancies and cancer of the breast and other organs have now been confirmed by others in over 10,000 patients. In his 1998 book,[3] he explained how the BCEC principle can be utilized to show how biological systems can interact with internal and external electromagnetic fields and asked me to provide a concluding afterword explaining on how this might relate to ancient concepts of *Qi* (ch'i), yin, and yang. I had invited him to contribute a chapter to this book but his progressive illness has now made this impossible. Consequently, I have attempted to synopsize some of his recent thoughts and these are expressed in my afterword. I asked Björn to review this for accuracy and to add any additional comments.

I chose to begin my chapter for his last book with this quotation from Claude Bernard: "To be astonished at anything, is the first movement of the mind towards discovery."

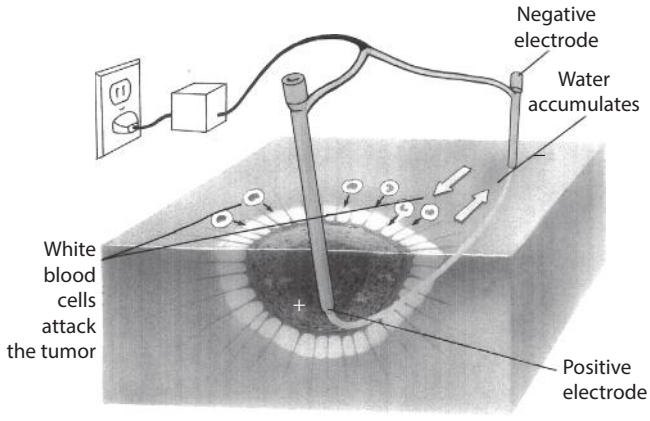

FIGURE 9.9 Attacking the tumor. Running current into the cancer prolongs its electropositive phase facilitating a variety of anticancer activities such as attracting tumor-fighting white cells and producing an acidic condition at the center of the tumor as water accumulates at the negative electrode.

I felt this was most appropriate as it was his amazement and bewilderment about the curious corona like halos around malignant tumors he had seen on chest x-rays that set Björn off on a quest that has occupied almost five decades of multidisciplinary research. He had published a few papers confirming that the electrical characteristics of lung cancers differed from normal tissue, but there was little response or interest in this. Undaunted, he continued his research, which eventually led him to the conclusion that the body had an additional communication or "electrical" circulatory system not previously appreciated. In 1979, he began writing a book entitled *Biologically Closed Electrical Circuits: Clinical, Experimental and Theoretical Evidence for an Additional Circulatory System* to explain this. The final product was a large handsome volume of over 350 pages replete with elaborate artwork, diagrams, x-rays, and reproductions of gross and microscopic pathology, many of which were in color. However, the medical publishing houses were not at all interested in this, probably because they thought it would not be profitable, and they were correct. Nordenström had to raise $50,000 to finally publish it himself in 1983, and of the 2000 copies printed, only 200 were sold over the next 2 years. Since then, an additional 1000 have been purchased with the majority of the remainder being donated to libraries, institutions, and interested individuals.

My interest in Bjorn's research stemmed from my involvement in studying relationships between stress and cancer. I had been awarded a Fellowship in 1951 to study with Hans Selye, who coined the term *stress* as it is commonly used. Selye had demonstrated in thousands of experiments that when laboratory animals were subjected to severe and prolonged stress there was an immediate activation of the body's defense mechanisms or alarm reaction, followed by a stage of resistance, during which these were maximized, and a final stage of exhaustion, in which defenses diminished and disappeared. He referred to this three staged response as the general adaptation syndrome and observed that during its course, pathologic changes could be seen in tissues and organs indistinguishable from those seen in patients suffering from various diseases, including hypertension, myocardial infarction, nephrosclerosis, peptic ulcers, and rheumatoid arthritis. He suspected that stress could contribute to such disorders in people and referred to them as diseases of adaptation.

Selye and I had developed a close personal and professional relationship and continued to collaborate after I resumed my medical training and entered private practice. However, I was surprised when he invited me to participate in a 1977 conference entitled "Stress, Cancer, and Death," being cosponsored by his International Institute of Stress and the Sloan-Kettering Institute. I explained that although relationships between stress and cancer were of great interest to me, I did not have the background to prepare a proper presentation as I was preoccupied with caring for patients and had not been actively involved in research activities for over 20 years. However, Selye was insistent and reminded me that I had first suggested to him during my fellowship that certain malignancies might also represent diseases of adaptation. While initially skeptical, he now agreed, based on a personal experience as well as basic science studies and clinical reports he had assembled, which he wanted me to review. He promised to put the resources of his institute at my disposal, and a week later, I received a very large packet of reprints dealing with various intriguing aspects of this complex subject. The challenge was irresistible and I contributed a paper that was subsequently published in the Sloan-Kettering Cancer Series devoted to the conference.[4] In his preface to this volume, Selye noted, "Perhaps, as Paul Rosch of New York has suggested, cancer might even be an attempt by the human organism to regenerate tissues and organs and even limbs, as lower animals are able to do spontaneously."[5] I had pointed out that the response to physical injury or loss in lower forms of life was purposeful regeneration. Studies in cancer patients showed that the onset of malignancy often followed the death of a spouse or loss of some other important relationship. Perhaps this initiated a similar stimulus to regenerate new tissue that had gone awry and resulted in neoplasia that was now, not only no longer purposeful, but also potentially lethal.

The conference proceedings generated a great deal of interest, and my chapter attracted numerous inquiries and correspondence from researchers with similar views who supplied additional supportive information. The authors were invited to provide an update for an expanded second edition that also included contributions from others on various relevant topics. I had become particularly interested in the unexplained phenomenon of spontaneous remission in cancer and other deadly disorders and the health promoting properties of a firm faith, and discussed this in my revised chapter entitled "Some Thoughts on the Endemiology of Cancer."[6] The focus here was not on the role of environmental carcinogens but rather on factors residing in the host that might influence susceptibility to stressful emotional stimuli. The chapter following mine in this 1988 update was by Yujiro Ikemi, a respected Japanese researcher, who had been attempting to integrate Eastern and Western biospychosocial approaches to understanding and treating disorders, especially those that seemed to be stress related.[7] He had thoroughly studied well-documented cases of spontaneous remission in cancer and presented his findings at our 1995 International Congress in Switzerland, where he was honored for his contributions. Ikemi confirmed that the common denominator in these patients was a strong belief system and a very positive expectation of a favorable outcome.[8] Others had also reached this conclusion,[9] but how were these benefits mediated? What mechanisms were involved?

Research in the flourishing field of *psychoneuroimmunology* had shown that emotional distress could lower immune system resistance to cancer, which seemed an attractive possibility, but this hardly proved that stress could cause cancer. In addition, nobody knew exactly what the immune system consisted of or where it was located, as it had numerous components and could be assessed in various ways. There were

rapid humoral responses as well as delayed, cell-mediated processes, each with several markers whose significance was not clear. Immune system *function* or *competency* can be measured by numerous criteria, including different antibodies in blood, saliva, and urine and various cytokines or specialized leukocytes with descriptive names suggesting possible functions, such as "natural killer," "helper," and "suppressor" cells. Others are represented by an "alphabet soup" of confusing letters, numbers, and symbols that are used to monitor immune system competency in AIDS, such as CDF4+ and CDF4+/CDF8+ ratios and NK-associated CD16+ (leu11) leu7– and CD16+ (leull) leu7+ lymphocyte subsets, the inducer subset (CD45RA+ CD4+) that activates suppressor–cytotoxic CD8+ cells, etc. During stress, varied responses have been observed, including a reduction in cytokines that stimulate both Th1 responses and macrophages (interleukin (IL)-2, IL-12, IFN-(γ)) as well as an increase in cytokines that promote the growth and differentiation of Th2 and B-lymphocytes (IL-4, IL-10).

Immune system status is also often measured by older techniques such as macrophage activity by chemiluminescence following stress or responses involving properdin, opsonins, and complement C3. There are assays for ILs, interferons (IF), tumor necrosis factors (TNF), and transforming growth factors (TGF). Much of the research on the effects of stress is based on the effects of mitogens such as phytohaemagglutinin (PHA) or concanavalin A (ConA) that stimulate T-cell production. However, it is not known whether such *in vitro* studies accurately reflect changes that have clinical significance or mirror *in vivo* immune responses. In short, it is quite likely that the same stressor could result in an increase, decrease, or lack of effect on "immune system resistance" depending on the criteria selected. Different types of stressors might have differing effects on the same system and the intensity and duration of the stimulus could also affect responses.

The more I tried to study how stress affected the immune system, the more confused I became. The traditional explanation of stress-immune system responses as being mediated by activation of the hypothalamic-pituitary-adrenal cortex axis and humoral neuropeptide messengers did not seem to apply, as there were no studies to support such a cause-effect relationship between emotional stress and malignant growth. I had wondered whether there might be some other energy communication pathway that might be relevant. In the final analysis, when hormones or small neuropeptides reached their specialized receptor sites on cell walls, the message was ultimately transmitted to the interior of the cell by a feeble electrical stimulus. Thus, electroencephalography (EEG) waves might not merely reflect the noise of the machinery of the brain but signals being sent to specialized receptor sites in the body through unknown pathways. I postulated this in the concluding chapter entitled "Future Directions in Psychoneuroimmunology: Psychoelectroneuroimmunology?" I was asked to contribute to *Stress, the Immune System and Psychiatry.*[10] In his foreword to this book, my friend Bob Ader, who coined the term *psychoneuroimmunology,* had also emphasized that future progress in this field would require "careful research, new methodologies, and communication between scientists in traditionally distinct fields."[11]

By this time, I had come to the conclusion that cancer was a disease of adaptation to civilization due to faulty communication and lack of a feeling of control. There was abundant support for cancer as a disease of civilization. Dr. Albert Schweizer, the renowned humanitarian, theologian, medical missionary, and Nobel Prize recipient wrote[12]:

> On my arrival in Gabon in 1913, I was astonished to encounter no cases of cancer. I cannot, of course say positively that there was no cancer at all; but like other frontier doctors, I can only say that if any cases existed, they must have been quite rare. In the course of the years, we have seen cases of cancer in growing numbers in our region. My observations incline me to attribute this to the fact that the natives are living more and more after the manner of the whites.

The celebrated anthropologist and Arctic explorer, Vilhjalmur Stefansson, in his book, which was actually titled *Cancer; Disease of Civilization?*, emphasized the absence of cancer in the Eskimos during his visits to various North Polar communities but a subsequent increase in the incidence of the disease as closer contact with white civilization was established.[13] In *Cancer; A Disease of Either Election or Ignorance*, William Hays commented on this as follows[14]:

> A study of the distribution of cancer, among the races of the entire earth, shows a cancer ratio in about proportion to which civilization living predominates; so evidently something inherent in the habits of civilization is responsible for the difference of cancer incidence compared with the uncivilized races and tribes. Climate has nothing to do with this difference as witness the fact that tribes living naturally will show a complete absence until mixture with more civilization, even so does cancer begin to show its head.

One of the most persuasive arguments is to be found in Alexander Berglas' *Cancer; Its Nature, Cause and Cure.* Throughout this book runs the theme that cancer is a disease from which primitive peoples are relatively or wholly free, and that[15]

> We are threatened with death from cancer because of our inability to adapt to present day living conditions. Over the years, cancer research has become the domain of specialists in various fields. Despite the outstanding contributions of scientists, we have been getting farther away from our goal, the curing of cancer. This specialized work, and the knowledge gained through the study of individual processes, has had the peculiar result of becoming an obstacle to the whole. More than thirty years in the field of cancer research have convinced me that it is not to our advantage to continue along this road of detailed analysis. I have come to the conclusion that cancer may perhaps be just another intelligible natural process whose cause is to be found in our environment and mode of life.

This concept was hardly new and was possibly first proposed in Tanchou's *Memoir on the Frequency of Cancer*, delivered in 1843 to the French Academy of Sciences.[16]

> M. Tanchou is of the opinion that cancer, like insanity, increases in a direct ratio to the civilization of a country and of the people. And it is certainly a remarkable circumstance, doubtless in no small degree flattering to the vanity of the French savant, that the average mortality rate from cancer in Paris during 11 years was about 0.80 per 1000 living annually, while it is only 0.20 in London! Estimating the intensity of civilization by these data, it clearly follows that Paris is four times more civilized than London!

I was able to cite numerous additional supportive writings in "Stress and Cancer: Disorders of Communication, Control and Civilization" with 254 references that endorsed the other opinions suggested in this title.[17]

With regard to being a disorder of communication, Selye had also noted in his preface to the proceedings of the 1977 conference on stress and cancer that "the ultimate health of the organism, like that of society, appears to depend on how well or appropriately its constituent units communicate with one another."[5] This was essentially a paraphrase of Claude Bernard's dictum that the health of the organism depended on its ability to maintain the constancy of the milieu intrieur (internal environment),[18] which Walter Cannon later described as homeostasis.[19] In discussing the importance of communication, Selye had previously written in his best seller, *Stress Without Distress*, "the indispensability of this disciplined, orderly mutual cooperation is best illustrated by its opposite—the development of a cancer, whose most characteristic feature is that it cares only for itself."[20] However, it seemed to me that good health depended not only on good communication within the milieu intrieur but also with the external environment and that this held true for all the hierarchy of living systems ranging upward from a cell, tissue, organ, and person to a family, corporation, nation, or culture. Maintaining good health as well as life itself depends entirely on good communication—both between the components of the system as well as with the external environment.

But exactly how did communication take place within the body? The nervous system relays information by direct contact as adrenergic or cholinergic molecules are released at nerve endings and synapses. Hormones and neurotransmitters are carried via the circulation to specific receptors at sites distant from their point of origin. Much less is known about the immune system, although it is clear that its conversations include both humoral and hardwired connections. However, in the final analysis all of the messages are eventually transmitted by means of weak energy transfers across cell membranes that occur at an atomic rather than molecular level. It had also become clear that the cell membrane was much more than a mere protective shield studded with receptors for antibodies and other small molecules that acted like keys to open special locks. The cell wall had now emerged as a powerful signal amplifier that provides an interactive window through which the cell can sense and respond to environmental changes. Some substances pass freely back and forth through certain channels, whereas the cell wall is an impenetrable barrier for others. When designated molecules fit into special receptor sites, a subtle signal produces a sudden change in the electrical potential between the interior of the cell and its external environment, allowing a new channel to open for a thousandth of a second. During this brief period, although millions of ions may pass back and forth, the total current generated is only a few billionth of an ampere.

As previously proposed, I believe that cell membranes may also have receptor sites for subtle energy signals that react exactly as they would to chemical on molecular stimuli. Electrical stimulation of highly specific areas in the pain pathway produces analgesia and microinjections of morphine at these precise sites have an identical effect. Electrical stimulation or injecting morphine a few millimeters away has no effect. However, combining suboptimal doses of morphine or electrical stimulation that alone are too weak to reduce pain results in a synergistic effect that does provide analgesia. This suggests that for some receptors, the effects of weak electrical stimulation are congruent with those of molecular stimuli. Furthermore, the specific locations at which either chemical or electrical stimulation relieve pain are exactly the sites of action of the opiatelike endorphins, the body's natural pain relievers.[21] It seemed highly plausible that these and other receptor sites could readily respond to feeble electromagnetic signals generated internally.

Stress is difficult to define as it is a highly personalized phenomenon that differs for each of us. Things that are distressful for some people may be pleasurable for others and we respond to stress differently. Nevertheless, all of our experimental and clinical research confirms that the feeling of having little or no control is always distressful. That also happens to be a good definition of the cancer cell. It is a cell that is out of control because it does not communicate properly with its neighbors or the rest of the organism, as Yamasaki so elegantly demonstrated.[22]

> Cancer can be regarded as a rebellion in an orderly society of cells when they neglect their neighbors and grow autonomously over surrounding normal cells. Since intercellular communication plays an important role in maintaining an orderly society, it must be disturbed in the process of carcinogenesis. Evidence suggests that blockage of intercellular communication is important in the promotion process of carcinogenesis.

A domineering, dogmatic determination, firm, forceful faith, fighting spirit, and an aggressive positive attitude all reflect the development of a strong sense of control. They are also common themes in reports of patients who triumphed over seemingly fatal malignancies.[23–25] Could this message of control be communicated to cancer cells through unsuspected energy pathways to curb their undisciplined activities?

Anecdotal, but irrefutable reports of cancer cures from shrines, faith healers, laetrile, coffee enemas, acupuncture,

macrobiotic diets, and other alternative treatments are difficult to explain. There are numerous reports of cancer regression through the use of various stress reduction or mind altering techniques, including intense meditation, visual imagery, and hypnosis.[26–37] Yet, like spontaneous remission, all these cures are extremely rare, and benefits are entirely unpredictable in any given patient. Here again, having a strong faith in anything the individual believes in that provides a sense of control might be the reason. But how are the salutary rewards of faith healing, "therapeutic touch," or the placebo effect mediated? Is there such a thing as psychic healing? How can one explain the well-documented benefits associated with the development of strong social support in patients with cancer and other disorders?[38–43] Conversely, what are the mechanisms involved in the numerous reports of reactivation of dormant cancer following an extremely stressful event, particularly the loss of a loved one?[44–47] No consistent immune, neuroendocrine, or central nervous system changes have been demonstrated in connection with such responses suggesting that they are mediated via other pathways.[48,49] Is it possible to harness this subtle energy or to learn how to emulate, simulate, or stimulate it to attain the vast potential for self-healing that resides in all of us?

A related issue is whether communication or signaling exists between people, other forms of life, or nature through pathways and mechanisms that have not yet been delineated. How does any of this relate to cancer as a disease of communication and control? I believe that Björn Nordenström may have provided a piece of this puzzle. While his 1983 book concentrated on the "vascular-interstitial closed circuit" (VICC), he subsequently demonstrated that there are numerous circuits ranging in size from meters to microns that utilize both ionic and electronic electricity, and produce electromagnetic fields with varying frequencies, amplitudes, and wave lengths. He believes that *Qi*, the energy of life in ancient Chinese medicine is analogous to or perhaps the same as the electromagnetic energy found in biologically closed electrical circuits. Its yin and yang components may be thought of as the positive and negative electrical charges of closed circuit ionic flow. During health, *Qi* flows through prescribed pathways (meridians) in the body in an orderly fashion, and VICC and other interstitial channels may be thought of as corresponding to these meridians. *Qi* energy is also believed to project as a corona emanating from the extremities that can be visualized with Kirlian photography.

Nordenström provides other analogies with ancient Oriental concepts of how *Qi* in nature can affect human health, performance, and possibly aging. Lifespan varies greatly in animals, plants, as well as different tissues in humans. It is believed that the life of a cell is genetically predetermined by limiting the number of times it can divide and reproduce. This process of programmed cell death, called *apoptosis*, is specific for each cell. He has described how biomagnetic forces can influence either regression (apoptosis) or proliferation (regrowth and survival) by explaining how a tree preserves its life during the cold winter through altering metabolic activities that sacrifice its leaves in the fall. In the spring, apoptotic regression is replaced by proliferative regeneration, when energy preserved in the tree is activated by heat to again produce the same kind of leaf. He illustrates how even a leaf that is dead still has energy in the form of a corona around it that can be seen with Kirlian photography. This repetitive cycle of death and rebirth that is guided by the same energy constantly takes place in other systems. In the Chinese view of nature, they provide balance in the Sheng and Ke cycles of ongoing regeneration and destruction for the five elements as depicted in a diagram I provided for my afterword chapter.[50]

Nordenström believes that although *Qi* and EMF energies are essentially the same entity that this is not appreciated because of semantic problems. He also believes that these forces flowing in closed biological circuits play a crucial role in the transformation of nonbiological substance into biological matter. However, theories do not have to be correct—only facts do. Some theories prove to be meritorious because of their heuristic value, in that they stimulate others to discover new facts that lead to better theories. Whether Nordenström's theories will prove to provide insights into ancient Oriental concepts of *Qi* and its flow through meridians remains to be seen. It has been reported that stimulation of an acupuncture point in the foot results in EEG changes that exceed the speed of sound. This and many of the other phenomena described above cannot be explained by any known biological mechanisms but could be consistent with the BCEC concept.

Are the forces or energies in magnetic fields, as well as those involved in faith healing, therapeutic touch, consciousness, intentionality, and BCECs also some manifestation of *Qi*? Albert Einstein believed that there was an underlying order to the organization and operation of the universe based on mathematical principles. He proposed not only that electromagnetism and gravity were different aspects of the same force but that all the four forms of energy were interrelated, and scientists have been trying to prove this unified field theory ever since. Is *Qi* a fifth form of energy that will prove to be the glue that binds all of the others together?

The Chinese sage Lao Tsu described *Qi* as follows:

> "Look, it cannot be seen—it is beyond form
> Listen, it cannot be heard—it is beyond sound
> Grasp, it cannot be held—it is intangible."

Is the human mind capable of comprehending *Qi*? Or, like infinity, and the lack of distinction between energy and matter at subatomic levels, is it impossible for us to visualize what *Qi* represents with respect to its composition and the manner in which it functions?

It is now obvious that subtle signals and energies can exert powerful psychophysiologic effects despite the fact that they are nonthermal, which would appear to violate the laws of thermodynamics. Various presentations at our International Congress support the belief that weak energies generated in the brain as well as the heart can have internal as well as external physiologic effects that cannot be explained by known communication pathways. These include energy fields or auras

emanating from the hands of healers that were readily visualized with Kirlian and other imaging techniques, but only while they are engaged in their activities. Subjects blinded to the presence of such healers also reported sensations of heat or tingling in different parts of their body corresponding to sites under the healer's hands several inches away. When the position of the healer's hands moved to other areas, these sensations consistently shifted to coincide with this. In addition, the ability of certain healers to produce voltage surges of 100 V in the EEG waves of subjects several feet away who were unaware of the purpose of the experiment or the healer's presence was illustrated as had been previously reported.[51]

The external force generated by *Qigong* practitioners, also vividly demonstrated at our congress, is thought to have electromagnetic components. This is supported by studies using a cell free myosin phosphorylation system with high sensitivity to magnetic fields that exhibited the same response to the energies emanating from two *Qigong* masters.[52,53] Clinically, *Qigong* has been found to be effective in treating reflex sympathetic dystrophy and other complex pain syndromes.[54] Similarly, therapeutic touch and other energetic practitioners have demonstrated their ability to relieve pain,[55,56] promote wound healing,[57] increase hemoglobin levels,[58,59] and produce structural changes in DNA and water,[60] in addition to other measurable activities.[61] As also presented at our congress and discussed elsewhere in this book, Tiller has demonstrated that intentionality can change the pH of a solution and alter the incubation time of fruit fly larvae. Furthermore, this energy can be stored on a computer chip for future use and other applications.

The brain or mind is not the only source of energy. The heart's electromagnetic field is estimated to be 5000 times stronger than that of the brain and can also be measured several feet away from the body with SQUID-based magnetometers.[62] Congress presentations by McCraty and co-workers have demonstrated that this field can influence cerebral and cardiovascular function of other individuals in direct physical contact or even a few feet away as assessed by ECG and EEG recordings and as also explained in this volume and elsewhere.[63] These observations have been independently confirmed by others[64] who have proposed that the heart actually plays the major role in generating as well as integrating the flow of energy in the body.[65]

All of the above is consistent with an emerging paradigm that posits some form of subtle energy communication system in the body that can also detect and respond to external environmental energies or signals. This could help to explain such widely acknowledged but poorly understood phenomena as the placebo effect, faith healing, the power of a strong faith in spontaneous remission in cancer, the salubrious effects of certain olfactory, auditory, visual and tactile stimuli, and certain psychokinetic observations. The proposal that the level or orderly flow of energy in the body determines health and illness and that it is influenced by environmental forces has surfaced over the years as *Qi*, chakras, prana, archaeus, the aether, animal magnetism, Odic force, orgone, and other constructs in different cultures.[66,67] If such forces do indeed exist, is it possible they are being drowned out by man-made energies that we are unable to appreciate but are readily detected by FM and AM radio receivers, sonar, radar, and devices that can measure microwaves, electromagnetic fences, and other forces that pollute the atmosphere?

Acupuncture points known since antiquity have electrical properties quite different from sites a few millimeters away even though no distinctions can be seen with electron microscopy. This can be readily demonstrated by injecting radioactive technetium, and these electrical characteristics can be influenced by mental processes.[68] The potential to cure disease and enhance health by harnessing such natural energies, as well as similar forces that can be artificially generated, seems enormous. Highly sophisticated technologies may now make it possible to achieve this goal and to integrate ancient Eastern and current Western concepts of health and illness. As also suggested by Mitchell in this volume, quantum physics and quantum mechanics may provide insights into possible mechanisms of action that cannot be explained by Newtonian physics.

I have attempted here to provide a brief introduction to some of Björn's concepts and regret that his health did not permit him to take a more active role in this presentation. I am very grateful to his son, Professor Jorgen Nordenström, for crafting a chapter entitled "The Paradigm of Biologically Closed Electric Circuits (BCEC) and Its Clinical Applications" consisting of excerpts from some of Björn's publications that provides more detailed information. Professor Xin YuLing and colleagues from China have also contributed a chapter, "Electrochemical Therapy of Tumors," detailing their experience in over 9000 patients with various malignant and benign tumors.

As noted in the *Discover* cover story, some scientists have compared Björn Nordenström's accomplishments to William Harvey's discovery of how blood circulates in the body. In *The Discoverers*, Daniel Boorstin portrayed the state of medicine before Harvey described the circulatory system in 1628 as follows[69]:

> Any physician who had labored to learn the academic languages and had become the disciple of some eminent professor of medicine had a heavy vested interest in the traditional lore and accepted dogmas…To attack this citadel demanded a willingness to defy the canons of respectability, to uproot oneself from the university community and from the guild.

Boorstin noted that Michael Servetus, who described the pulmonary circulation of the blood in one of his theological tracts, was burned at the stake by Calvin in 1553 for this heresy. However, Harvey led a charmed life. After completing his medical education in Padua, the leading center for anatomical studies, he returned to England in 1602 and married Elizabeth Browne, the daughter of one of the Queen's physicians. Harvey himself obtained a fellowship at the Royal College of Physicians and he was appointed as a physician to the court of James I. He later became personal physician to his successor, King Charles I, who not only encouraged but also generously supported his research

into the circulatory system. Although Harvey's 1628 treatise created an uproar, he was regarded as a respected medical leader and at the time of his death in 1657, his medical and scientific genius were widely celebrated throughout England and Europe.

In contrast, Björn Nordenström has struggled and labored alone for over four decades, personally performing every experiment, with no financial support and at great personal expense. Although renowned for his radiological accomplishments, it seems unlikely that his BCEC concept and its implications will be adequately recognized in his lifetime. As previously indicated,[50] he may have also opened the door to a greater understanding of how we can communicate with other living systems to improve health and harmony in nature. He is the epitome of the true scientist, described by Jules Henri Poincar as follows: "The scientist does not study nature because it is useful; he studies it because he delights in it, and he delights in it because it is beautiful. If it were not beautiful, it would not be worth knowing, and if nature were not worth knowing, life would not be worth living."

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Section III

Subtle Energies

Theories and Therapies

10 Life Is Water Electric

*Mae-Wan Ho**

CONTENTS

New evidence suggests that the L-field is generated by, and embodied in, the quantum-coherent liquid crystalline water that makes up to 70%–90% of organisms and cells and is essential for life.

Water forms quantum coherent domains at ordinary temperatures and pressures. Within organisms, coherent domains become stabilized as liquid crystalline water on the vast amount of membrane and macromolecular surfaces, effectively aligning the entire body electrically to form a single uniaxial crystal. This liquid crystalline water makes life possible by enabling proteins and nucleic acids to act as quantum molecular machines that transform and transfer energy at close to 100% efficiency. It provides excitation energy to split water in photosynthesis, releasing oxygen for the teaming millions of air-breathing species that colonize the earth, at the same time generating electricity for intercommunication and the redox chemistry that powers the entire biosphere.

Living water is the means, medium, and message of life.

LIFE, THE UNIVERSE, AND EVERYTHING

In his book *Science and the Modern World*[1] first published in 1926, Alfred North Whitehead (1861–1947) showed how the mechanical laws that describe objects with 'simple location in space and time' utterly fail to represent natural processes, and argued it is only possible to know and understand nature as an organism. He wrote (p. 100): "The concrete enduring entities are organisms, so that the plan of the whole influences the very characters of the various subordinate organisms which enter into it. In the case of an animal, *the mental states enter into the plan of the total organism and thus modify the plans of the successive subordinate organisms until the ultimate smallest organisms, such as electrons, are reached*" [italics added].

Whitehead's organisms include *everything* in nature, from the universe to galaxies, stars, planets, plants, animals, human beings, bacteria, right down to fundamental particles; they are bundles of electromagnetic activities—"vibratory organisms"—endowed with a kind of primal consciousness that experience their environment in acts of "prehensile unification," and most important of all, evolve as the result of the experience.

Whitehead was remarkably prescient, as evidence has been accumulating since the latter half of the twentieth century that our universe is 99.999% electric plasma. Gigantic plasma currents and their magnetic fields are constantly engaged in creating super-galaxy clusters, galaxies, and stars, in direct contradiction to the conventional Big Bang theory based solely on gravity and Einstein's theory of general relativity.[2]

I have taken Whitehead's philosophy to heart. Not only is nature an all-encompassing electromagnetic super-organism, but the knower is also an electromagnetic organism maximally sensitive and responsive, fully engaged in mind and body, intellect and feeling to other organisms, ultimately to all nature.

THE ELECTRODYNAMIC ORGANISM ATTUNED TO THE COSMOS

There is substantial evidence that living things are fundamentally organized by electric fields and electromagnetic activities. Whitehead's concept of a "plan of the body" that modifies the motion of electrons within it anticipates

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the discovery of physiologist Harold Saxton Burr at Yale University, who began his work in the 1930s.

Burr's book, *The Blueprint for Immortality,*[3] first published in 1972, offers a grand vision described on the book's back cover:

> This is a breakthrough book—the first *comprehensive* account ever published of one of the most important scientific discoveries of this century. It reveals that all living things—from men to mice, from trees to seeds—are moulded and controlled by 'electrodynamic fields', which can be measured and mapped with standard modern voltmeters.
>
> These 'fields of life', or L-fields, are the basic *blueprints of all life on this planet*. Their discovery, therefore, is of immense significance to all of us.
>
> To every man and woman in this troubled age it gives the comforting certainty that life is no accident and that all of us are integrated parts of the Universe, subjected to its laws and *sharing in its purpose and destiny…the Universe has meaning and so have we*.
>
> Since measurements of L-field voltages can reveal physical and mental conditions, doctors will be able to use them to diagnose illnesses *before the usual symptoms develop* and so will have a better chance of successful treatment.

Burr and his many collaborators over a period of 40 years documented L-fields in diverse organisms including eggs and seeds; and dramatic changes in L-field potentials closely correlated with growth, development, mental states, and key physiological events such as ovulation and cancer.

Burr attached electrodes to trees and simultaneously recorded electric potential differences in the atmosphere and in the earth continuously for 25 years. The records showed that the air and earth potentials fluctuated in phase with the trees' potentials. Statistical analysis revealed well-known diurnal rhythms in all four records, as well as the lunar cycle and the 11-year cycle of solar activity. These findings leave little doubt that trees in particular are sensitive to electric and electromagnetic fields from earth and outer space, acting as antennae to the universe. Trees connect us to the universe. This may be why a walk in the woods or being near to woods and forests is beneficial to health.[4]

Earth's magnetic field comes from the electric current generated in the conductive layer of molten iron in its outer core moving across the sun's magnetic field, which in turn generates a magnetic field. Birds, bees, amphibians and other animals are known to depend on earth's magnetic field for navigation. There are reports that animals and humans in environments shielded from earth's magnetic field aged faster, died more readily, suffered stress and pains, and pathological changes in the liver, kidneys, white blood cells, and urinary bladder.[5]

Earth also has an electromagnetic spectrum or Schumann resonance named after Winifred Otto Schumann (1888–1974) who predicted them in 1952. Schumann resonances are standing waves created in the space between the surface of the earth and the conductive ionosphere, and naturally excited by lightning discharges. Schumann resonances range between 3 and 60 Hz, appearing as distinct peaks at 7.83, 14.3, 27.3, and 33.8 Hz. These same frequencies are prominent in human brain waves and strongly correlated with different mental states. Evidence suggests that humans and other organisms actually synchronize their biological rhythms to the Schumann frequencies.[6,7]

Earth's electromagnetic activities are strongly affected by those of the sun. The beautiful northern lights are generated during periods of intense solar activity, or magnetic storms, when the solar wind carrying hot energetic plasmas of ionized particles from the sun increases in density and speed. The ionized particles are trapped by earth's magnetic field and accelerated towards its magnetic poles. Collisions between these ions and atmospheric atoms and molecules (mainly oxygen and nitrogen) cause light to be emitted as the excited atoms relax back to the ground state. Both higher and lower than average levels of solar and geomagnetic activities are associated with adverse health and psychological impacts on humans worldwide, possibly due to the suppression of the pineal gland secretion of melatonin as biological rhythms are desynchronized. This is also partly why artificial electromagnetic emissions from mobile phones, wireless, and high tension power lines are having dire effects on humans and wild life.[8–11]

THE LIFE-FIELD

Burr's L-field could be measured from the surface of the body or the egg or seed, and detected away from the body surface, as when measurements were done on salamanders in water. This was sign of a true field effect, as the field was not shorted out by water. When the salamander was rotated under the electrodes positioned some millimeters away, it acted like a dynamo as expected of a rotating electric field, giving a sine wave of rising and falling potentials.

L-fields of all organisms share some common features, such as a positive potential at the anterior, versus a negative potential at the posterior. However, the entire field is made up of subsidiary or local fields specific to the body plan (see Figure 10.1).

The L-fields are not static; Burr and his collaborators found L-fields changing slowly, increasing in strength during development to a plateau in adulthood, and declining gradually as the organism ages.

The precise nature and origin of L-fields are not yet known, and it would take rather more sophisticated equipment to map them out properly. However, they are almost certainly actively maintained by electric currents within the body, forming closed circuits, rather than static DC fields. These electric currents give rise to magnetic fields that can be detected outside the human body including the brain, and form the basis of magneto-encephalography (MEG), the mapping of brain activity with very sensitive superconducting quantum interference devices (SQUID) magnetometers.[13]

L-fields were confirmed by other laboratories working independently of Burr, and later by orthopedic surgeon/researcher Robert Otto Becker (1923–2008), who also documented DC potential changes during wound healing and regeneration in animals and humans. Notably, he showed

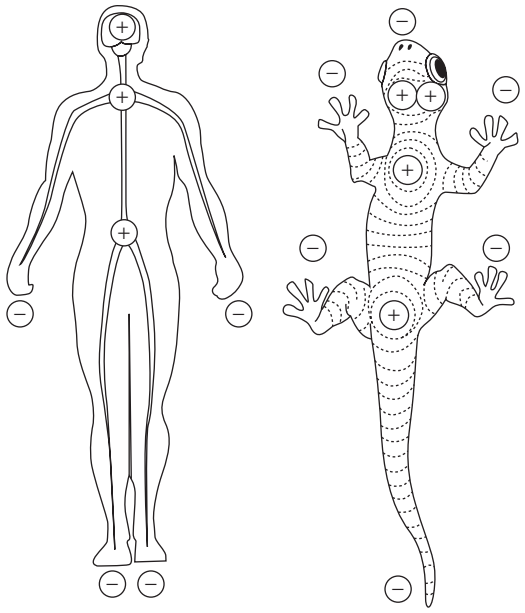

FIGURE 10.1 L-fields of humans and salamanders, measured by Robert O. Becker. (From Becker RO, Selden G. *Electromagnetism and the Foundation of Life*. New York: Harper; 1985. With permission.)

that potential changes from regenerating and nonregenerating organisms differ markedly from each other (see Figure 10.2).

Becker's findings were described in numerous scientific papers, and in one of the most gripping, moving accounts of scientific discovery, *The Body Electric*,[12] published in 1985, 5 years after his research lab was shut down by scientists and politicians in a bid to silence his warnings on the health hazards of electromagnetic fields from overhead high tension power lines and other electrical installations. (This debate has continued to the present day over "nonthermal effects" including brain cancer resulting from mobile phone use and other electromagnetic smog in our environment; see Reference 14.)

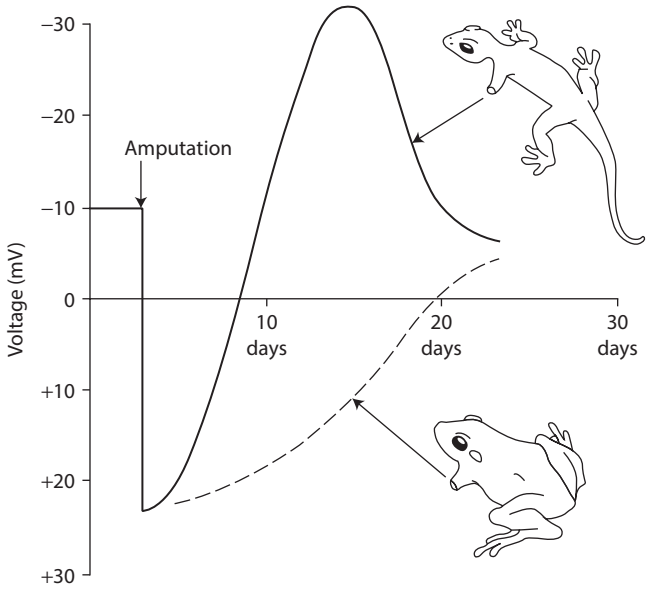

FIGURE 10.2 Electric potential changes at the cut end of the stump after amputation in salamander (top), which regenerates its amputated limb, and frog, which does not. (From Becker RO, Selden G. *Electromagnetism and the Foundation of Life*. New York: Harper; 1985. With permission.)

Becker knew that electromagnetic fields, when used accurately with the correct polarity, at the right time and place, and at the extremely weak levels characteristic of living organisms, could indeed help to heal persistent wounds and fractures, and even regenerate severed fingertips and nerves. However, exposures to inappropriate electromagnetic fields were likely to cause abnormal growth and cancer. Electromagnetic fields are a powerful, double-edged weapon, and must be used with utmost care and precision based on accurate knowledge from painstaking research; only then could it help restore the lives of people often reduced to utter despair.

Becker's discoveries anticipated by decades the recent findings on the transformation of differentiated cells into stem cells during healing and tissue regeneration, and by manipulations of gene expression in the laboratory.[15] Research is now also focused on enhancing stem cell repair *in vivo* without transplant by using drugs to encourage the process.[16] There has been no investigation on the effect of electric fields on the recruitment of stem cells thus far.

Today, it is possible to track electric potential changes in cells and embryos, and it is widely acknowledged to be involved in development, differentiation, regeneration, and cancer. But they are interpreted solely, and mistakenly, in terms of membrane potential of cells[17] with a major emphasis on identifying downstream gene activities, while important questions on the nature of the electrodynamical life-field and its relationship to health and disease are largely forgotten.

The most exciting serendipitous new discovery at Tufts University is the "face" of the frog roughed out in potential differences very early in development when the embryo is still a shapeless ball of cells with very few anatomical features.[18] A team led by Dany Adams used a combination of voltage and pH sensitive dyes to follow the development of *Xenopus* embryos under a microscope fitted with a time-lapse camera. It recorded "never-before-seen" dynamic patterns of electrical potentials on the outermost cell layer. These are clear signs of electrodynamic processes determining body structures that appear much later on (more on this later).

THE L-FIELD IS STORED ENERGY

Burr's insight was no less remarkable.[3] He surmised that the L-field reflects the energetic status of the organism; in particular, he assumed correctly that the energy flux of organisms is associated with the chemical flux of metabolism, but the L-field represents energy *stored* in potential differences across the body. Variations in the L-field, therefore, reflect variations in the flow of energy in the system. He wrote[3] (p.71):

> If this assumption is true, it follows, then that by studying potential differences during rest and during activity a record

> could be made of a general level of immediately available energy, as represented by algebraicly summated boundary potentials.
>
> In the face of the demand for activity this reservoir of potential energy could be tapped. When the biological system is at rest, the potentials could be recorded as DC potentials, but when protoplasm is thrown into any kind of activity, such as neural transmission, muscle contraction and similar events, the first sign of that activity would lie in the sudden withdrawal from the reservoir of electrical energy; in other words, a drop in potential difference. Then, mobilization of chemical properties might be expected to re-establish the original level of the potential difference.

The concept of *stored* energy is the key to living organization as emphasized in my book, *The Rainbow and the Worm, The Physics of Organisms.*[19] Stored energy is *coherent* energy, and the mobilization of coherent energy can be made with as little dissipation as possible, giving rise in the ideal to the zero-entropy quantum coherent organism (to be explained later).

As consistent with Burr's observation, a drop in "membrane potential"—depolarization—precedes many important cellular events including growth and regeneration.[17]

ELECTRODYNAMIC ACTIVITIES AND PATTERN FORMATION

The L-field is separate from, and independent of, the action potentials of the brain or the electrical discharges from the heart measured respectively in electroencephalograms (EEGs) and electrocardiograms (ECGs). In fact, evidence already available to Burr[3] suggested that EEGs and ECGs are controlled by variations in the L-field, which would show up as baseline potential changes under the action potentials of the EEGs and ECGs, had they not been filtered away (!) in most readings as noise or a nuisance rather than important physiological and psychological information. For example, Burr and colleagues discovered that high potential differences measured between the left and right index figures might be predictive of mental instability.

Evidence that action potentials reflect global field potential changes also came from early embryonic development.

By far the most important unsolved problem in biology is how a relatively featureless egg can transform into a shapely highly differentiated organism in the process of development. I was among a very small number of scientists who believe electrodynamical processes are fundamentally involved in pattern formation.

We carried out several series of experiments described in a paper published more than 20 years ago,[20] which provided evidence of highly coherent electrodynamic processes responsible for *generating* body pattern during early development.

For our experiments, we collected synchronously developing batches of freshly laid fertilized eggs from *Drosophila*. The first series of experiments was carried out in the laboratory of electrophysiologist Charles Nicholson at New York University Medical School, who patiently taught me how to make microelectrodes to record the electrical activities from individual developing embryos without damaging them. The embryo, with its shell (chorion) removed, was attached by hydrophobic interaction between the vitelline membrane and the plastic surface of a petri dish. It was immersed in insect Ringer to keep it from drying out. The electrode was carefully inserted into the anterior or posterior polar pocket inside the vitellline membrane without puncturing the embryo.

The results were amazing. A series of action potentials from 1 to 30 Hz appeared at least as early as 40 min from the start of development and persisted for hours thereafter (see Figure 10.3). During most of the period in which pattern determination takes place, there is little or no cellular organization.

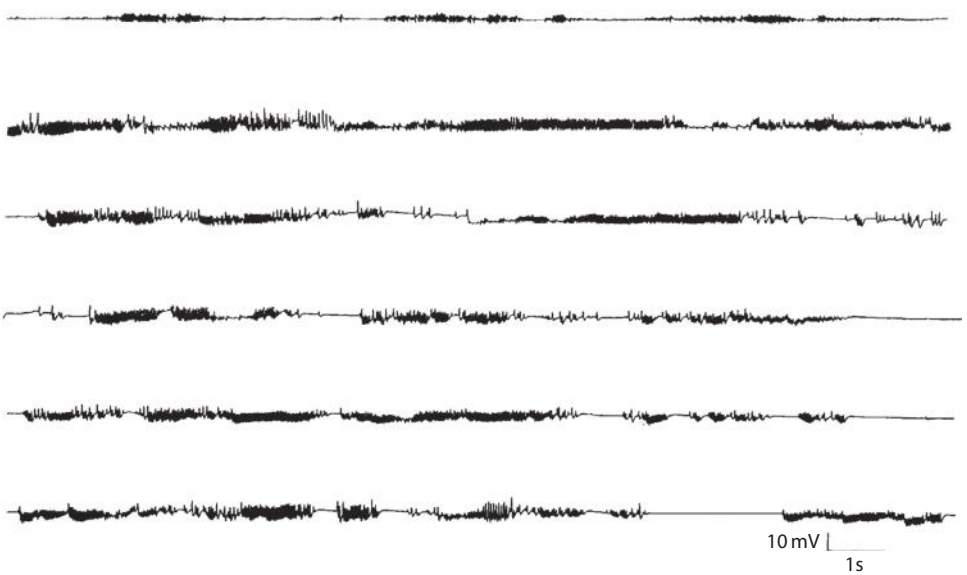

FIGURE 10.3 Action potentials at successive later time segments at nuclear migration stage (43–53 min from start of development). (From Ho MW et al. *J Sci Expl* 1992;6:59–77.)

The trace typically starts with clusters of 2, 3, or 4 volleys of discharges (about 30 Hz) each lasting 1 or 2 s, punctuated by 2–3 s of relative quietude. The volleys increase in amplitude and tend to coalesce into a continuous train. The peak amplitudes are about 10–12 mV. The highest frequency of the spikes are about 30 Hz, but can be as low as 15 or 3 Hz. Characteristically, the baseline potential shifts underneath the spiking activities, often coinciding with the start and end of the volleys, strongly suggesting that those shifts are global in extent, and both initiate and end the volleys.

In the second set of experiments carried out in my own laboratory, we exposed the synchronously developing batches of fertilized eggs for 30 min to weak static magnetic fields (0.5–9 mT) at different times during the first 3 h of development when pattern determination is known to occur. This resulted in high proportions of body pattern abnormalities 24 h later, when the first instar larvae would have normally hatched. The most frequent type of abnormalities is uniquely associated with exposure to static magnetic fields, and consists of variously twisted configurations of the segmental pattern. As static magnetic fields were used, the effects must have been due to moving electrical charges or more likely global field dynamics. As the energies in the weak magnetic fields were many orders of magnitude below the thermal threshold of random molecular motion, there could have been no effect unless the electrodynamical processes were highly coherent.[19–21]

In the third series of experiments done in the laboratory of Fritz Albert Popp, who taught me almost everything I know about quantum physics, the flies were induced to lay eggs in a quartz cuvette, then gently removed. The cuvette with freshly laid eggs was placed in a light-tight chamber connected to a sensitive photon counter, and the photons emitted were recorded with or without a single flash of white light (l min, 4 W/m^2). Photon emission changed with developmental time, which was not unexpected. Remarkably, when embryos less than 40 min old were stimulated with light, an entirely new phenomenon appeared that has never been observed before: intense light flashes were re-emitted, thousands of times stronger than the baseline. The flashes can be extremely brief (<1 s) or prolonged (minutes to hours), and can appear any time from 1 to 20 min, and up to 8 h after light stimulation.[19,20] The results are reminiscent of super-radiance in quantum optics, a collective resonant emission involving many, if not all individuals within the synchronously developing population.

These results together provide evidence of electrodynamical activities accompanying pattern formation that are coherent over the whole embryo and entire populations of embryos. It would be great to look at these embryos again with voltage sensitive dyes.

I was prompted to revisit these old forgotten findings on coming across a paper by Alexis Pietak from Kingston, Ontario in Canada[22] proposing a new mechanism for morphogenesis: the formation of resonant electromagnetic modes in a dielectric microwave resonator.

Resonant modes are standing wave patterns formed when a wave is confined within a resonator and subjected to reflection from internal boundaries where incident and reflected waves combine. This is something like the Schumann resonances generated in the cavity between the earth's surface and the ionosphere (see above), but on a much smaller scale of 0.1–1 mm, the dimensions of eggs and primordia. Consequently, the frequency of the electromagnetic waves involved is much higher, in the microwave to submillimeter range or GHz (10^9 cycles per second). Using the mathematical technique of finite element analysis Pietak produced resonant modes (in ellipses and a sphere) (Figure 10.4) whose patterns resemble different kinds of leaves.

As Pietak noted, this type of mechanism is not restricted to generating leaf patterns. The *Drosophila* egg is a long ellipse, and successive horizontal resonant modes are reminiscent of stages in the process of segment determination as revealed by the famous gene transcript patterns, which are most likely involved in downstream processes of pattern formation.

Pietak emphasized that "the model rests on the validity of biological coherence theories as described by Fröhlich…and/or quantum field theorists." Herbert Fröhlich (1905–1991)[23] proposed that organisms are condensed matter systems, and can be pumped by metabolic energy into states of coherent excitations (resonant modes) in analogy with the solid-state laser. Quantum field theorists Emilio Del Giudice and colleagues propose that interaction between ambient electromagnetic fields and soft condensed matter such as liquid water creates coherent domains oscillating in phase with the electromagnetic field.[24] I have described the work of Fröhlich in the *Rainbow Worm*[19] and quantum field electrodynamics is treated in some detail in my new book[25] *Living Rainbow* H_2O, both providing extensive evidence for the quantum coherence of organisms.

Field theories of morphogenesis go back at least to the 1920s associated especially with Alexander Gurwitsch (1874–1954) in Russia and Paul Weiss (1898–1989) in Austria, but they were rather vague (see the review in *Order and Life*[26] by Joseph Needham [1900–1995]). A significant advance was made by John Totafurno and Lynn Trainor (1921–2008) in a paper published in 1987[27] using a vector-field model to predict baffling results of salamander limb regeneration. In these experiments, a limb was amputated, and the regenerating cell mass was transplanted and/or rotated, leading to abnormal limb regrowth that were determined by the way the cell mass was transplanted. A vector-field has both orientation and continuity, and any disturbance to the field lines need to be smoothed out and reconnected, with the result that extra limbs are generated in certain transplants.

I suggested that the morphogenetic field could be "written"—like memory—in liquid crystalline orientation patterns,[19,28] which in turn determine gene transcription patterns and growth, the latter reinforcing cellular memory, and committing the cell to differentiation along a developmental pathway.

Liquid crystals are well-known to respond to electric and magnetic fields in generating patterns, as well as in changing their alignments.[28] Thus, resonant electromagnetic modes

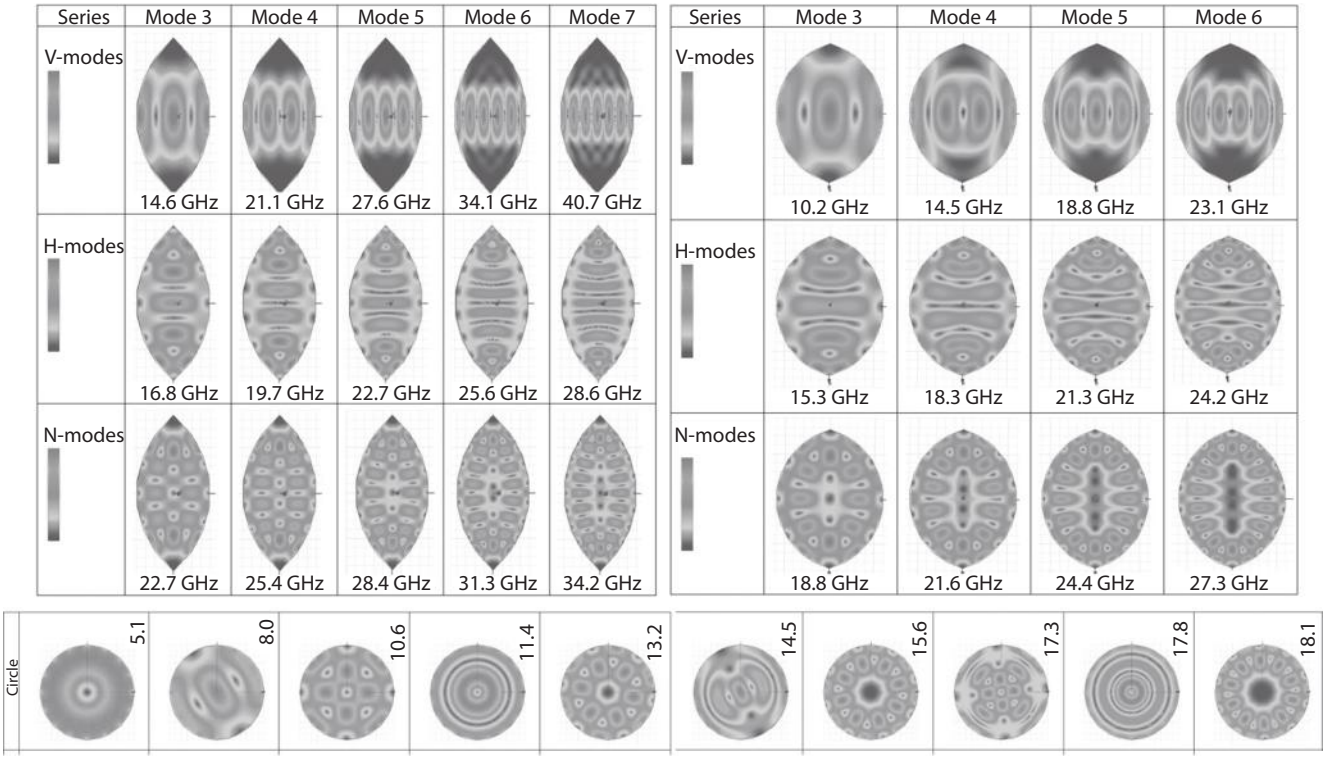

FIGURE 10.4 **(See color insert.)** Resonant modes in elliptical and spherical resonators generated by finite element analysis and the resonant frequencies in GHz; V, vertical, H, horizontal, N, nodal. (Rearranged from Pietak AM. *J Phys Conf Ser* 2011;329:012012. doi:10.1088/1742–6596/329/1/012012.)

generated in the *Drosophila* embryos could give rise to segmental patterns in the liquid crystalline cortex of the early embryos, which result in the well-known gene transcription patterns that lead in turn to the differentiation of the initially cryptic pattern. Static magnetic fields could indeed have a dramatic effect on the liquid crystalline patterning by resonant electromagnetic modes, and hence on the body pattern.

Despite substantial evidence on the existence of L-fields, and the fundamental importance of electrodynamic processes in living organization and function, there is still little clue as to how the L-field is generated and where it resides. I shall present evidence that liquid crystalline water in living organisms is both the body electric and the L-field.

THE ORGANISM IS ONE UNIAXIAL LIQUID CRYSTAL

The tantalizing evidence of a coherent electrodynamic field involved in pattern formation from our experiments[20] suggested that we should be able to *see* some sign of coherence, specifically, a birefringence indicative of ordered alignment of liquid crystalline molecules in the early embryo.

Birefringence is an optical property of a crystal or liquid crystal with atoms or molecules aligned by electric polarity, so that plane-polarized white light (consisting of many wavelengths vibrating in a single direction) is split into two perpendicularly oriented rays, one travelling slower than the other. When the two rays are recombined with a second polarizer (the analyzer), the component wavelengths of light interfere constructively or destructively. That is how the rainbow colors are generated. In order to amplify the birefringence, it is usual to add a full wave-plate—the wavelength of green light—to the system, giving the characteristic pink background (Figure 10.5).

I had been working with *Drosophila* for over 15 years, yet I was completely unprepared for what greeted me as I peered

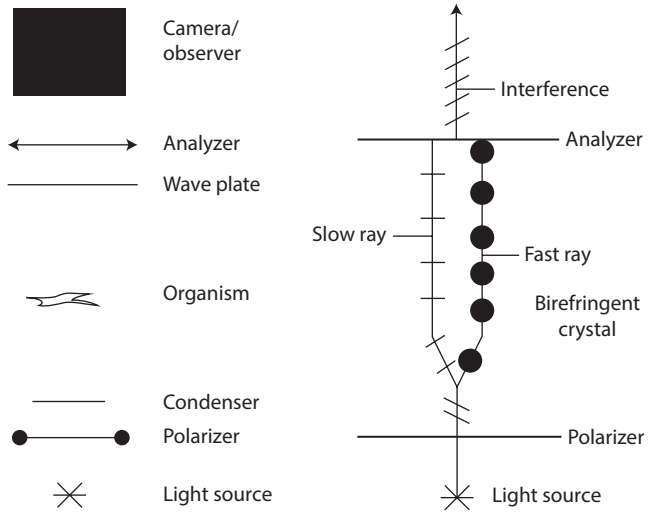

FIGURE 10.5 Polarizing light microscope (left) and birefringence (right).

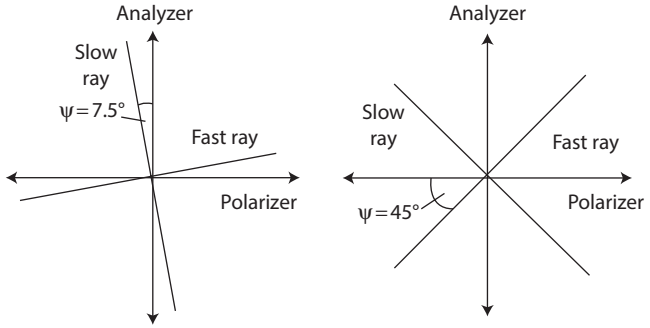

FIGURE 10.6 The new setting stumbled upon that is especially good for biological liquid crystals.

down the polarizing microscope. A little larva was crawling out of its egg, carrying a rainbow inside. Even the fully developed larva was coherent, and coherent beyond our wildest dreams. That is what the dancing rainbow inside its body was telling us, only it took a while to figure that out. That sublime vision was the immediate inspiration to writing.[19] *The Rainbow and the Worm, The Physics of Organisms*.

Because the expert in charge of the polarizing microscope was away, my colleague Michael Lawrence and I stumbled upon a new setting that was especially good for viewing biological liquid crystals. Instead of positioning the vibrating directions of the full wave plate at 45° to the polarizers, we placed it at a small angle of 7.5°[29–31] (Figure 10.6). The brilliant rainbow colors tell us that all the liquid crystalline molecules in the cells and tissues of the body are aligned, and more importantly, moving coherently together. As light vibrates much faster than the molecules can move, the orderly alignment of the molecules remains apparent to the light passing through. In fact, the most active parts are the brightest, indicating that the molecular motions are the *most* coherent.

Not only that, the entire organism is electrically polarized from head to tail, behaving optically as a single uniaxial crystal, like quartz. This is the life-field unveiled. Only, it is not just the macromolecules that are polarized; instead it is the water making up 70%–90% by weight of cells and tissues that is polarized together with all the macromolecules, as our detailed analysis showed.[31,32] In fact, it is the water that makes all macromolecules liquid crystalline, because living water, aligned along the abundant surfaces of membranes and macromolecules is itself liquid crystalline.[19]

LIQUID CRYSTALLINE WATER IS LIFE

Liquid crystalline water softens the macromolecules, making them flexible and enabling them to act as *quantum molecular machines* that transfer and transform energy at close to 100% efficiency. If organisms were working even with the efficiency of electronic machines say, our laptop computers, already much enhanced (in both sensitivity and efficiency) over ordinary machines, such as the motor-car, the amount of heat generated would burn them up before you could say "Christopher Robin!"[33] The energy transactions in living cells and tissues are much denser than those in a laptop (at least a billion times as dense), therefore, organisms *have* to be a lot more efficient; in other words, they have to approach the zero-entropy quantum coherent state.[19,34]

The archetypal quantum molecular machine is the enzyme. Enzymes speed up chemical reactions in organisms by a factor of 10^{10}–10^{23}. And they cannot do that without water. Water giving flexibility to proteins reduces the energy barrier between reactants and products and increases the probability of quantum tunneling by a transient compression of the energy barrier.

The *Rainbow Worm*[19] presents empirical evidence and theoretical arguments that the organism is quantum coherent, and that liquid crystalline water plays the lead in creating and maintaining the coherence of organisms.

However, the full extent to which life, and probably the universe and everything depends on water is still unfolding. Astronomers now think that water is the most abundant substance in the universe, and it may be present at the birth of the universe. In July 2011, two groups of astronomers in the United States discovered the largest, most distant reservoir of water—equivalent to 140 trillion times the water in earth's oceans—surrounding a massive black hole in a quasar more than 12 billion light-years away.[35] The conventional (big bang cosmology) view of quasars with hypothetical supermassive black holes and their supposedly enormous distance from us is seriously open to question,[2,36] but the presence of water is not in doubt. Could it be that the universe too, is powered by water electricity, as organisms are powered by water electricity? This makes Whitehead's[1] vision of the universe as an organism all the more remarkable.

I wrote a sequel to *Rainbow Worm* dedicated to water in living organisms in[25] *Living Rainbow H_2O*, which synthesizes recent findings in the quantum physics and chemistry of water that tell us why it is so fit for life. Water is "the means, medium and message of life, the beautiful rainbow within that mirrors the one in the sky." Already further new evidence has turned up since the book was published, and I shall bring the story up to date.

WATER IS WEIRD AND WONDERFULLY FIT FOR LIFE

The water molecule is a dipole with separated positive and negative charges associated with the oxygen and the two hydrogen atoms, respectively, therefore, it can engage in dipole interactions with other molecules of water or other dipoles (see Reference 25 and references therein). However, it seems to prefer to hydrogen bond most of the time, where the hydrogen atom of one molecule is shared between two oxygen atoms in neighboring molecules. The preferred configuration is a tetrahedron in which a molecule accepts two hydrogen atoms and donates two hydrogen atoms to neighboring molecules. It is estimated that at ordinary temperatures and pressures, over 90% of the water molecules are hydrogen-bonded, although the hydrogen bonds flicker on and off randomly in a matter of pico (10^{-12}) seconds.

BOX 10.1 MAJOR ANOMALIES OF WATER (SEE REFERENCE 37 AND REFERENCES THEREIN)

- Neighbors of oxygen form gases with hydrogen at ordinary temperatures and pressures, but water boils at 100°C and only freezes at 0°C under standard atmospheric pressure, which means organisms are composed of and bathed in liquid water on earth.
- Water has a high heat capacity and high thermal conductivity, thereby preventing temperature fluctuations, enabling organisms to better control their body temperature, and large bodies of water, such as oceans and seas, to serve as heat reservoirs, thereby moderating our climate.
- Other liquids increase in density on becoming solid, but ice is lighter than water and floats on it, most fortunately for fish and other aquatic inhabitants.
- Liquid water can be supercooled below 0°C without freezing, but on heating, the supercooled liquid does not expand like other liquids; instead, it contracts to a maximum density at about 4°C; this is very important for the hydrological cycle[38] as it plays a key role in rainwater percolating underground to refill the aquifers.
- Water's compressibility atypically decreases with increasing temperature reaching a minimum at about 46.5°C.
- At ordinary temperatures below 35°C, increasing pressure results in decreased viscosity, facilitating flow, again at odds with other liquids.

Water is notorious for a host of anomalous properties (see Box 10.1), due to its propensity to form hydrogen bonds, and the same anomalies are widely regarded as precisely the qualities that make water fit and essential for life.

QUANTUM DELOCALIZATION OF HYDROGEN BOND

The key to water's remarkable properties is the hydrogen bond interconnecting water molecules, which is usually regarded as classical and electrostatic; but many observations are inconsistent with that picture.

Nobel laureate chemist Linus Pauling (1901–1994) in 1935 was the first to suggest that the hydrogen bond and covalent bond in ice may switch places in view of residual entropy (randomness) existing even at very low temperatures,[39] and thus, the hydrogen bond must be at least partly covalent.

In 1999, researchers at Bell Labs New Jersey in the United States, the European Synchrotron Radiation Facility of Grenoble in France, and the National Research Council of Canada in Ottawa teamed up to study the hydrogen bond in ordinary ice Ih with inelastic x-ray scattering at the Grenoble facility.[40] Beams of x-rays are bounced off electrons so both the energy of the electron and the x-ray are changed. The team investigated the intensity of scattering as a function of energy or momentum (Compton profile) at different orientations of a carefully prepared slab of ice. They found that the results were in good agreements with the predictions based on a fully quantum mechanical model, while predictions based on the classical electrostatic model did not agree with the data at all.

In the same year, Sander Woutersen and Huib Bakker at FOM-Institute for Atomic and Molecular Physics in Amsterdam used time-resolved pump-probe laser spectroscopy to investigate liquid water at room temperature and pressure. The experiments revealed resonant intermolecular transfer of OH-stretch excitations mediated by dipole-dipole interactions that are faster than the classical Förster mechanism would predict.[41]

A few years later, Huib Bakker and Han-Kwang Nienhuys at FOM showed that not only the electrons of the hydrogen bonds fail to conform to the classical electrostatic model; the protons too are quantum mechanical. Using ultrafast femtosecond (10^{-15} s) pulses of infrared light to excite and probe the O-H covalent bond vibration in *liquid* water,[42] they found that only quantum mechanical calculation of the vibrational wave functions could reproduce the experimental absorption spectrum.

The excited proton can be found simultaneously—delocalized—at the O−H bond distance from either of two neighboring oxygen atoms (belonging to two different water molecules). This delocalization increases the probability of proton transfer (I will come back to that later). The energy of excitation to the delocalized state is less than 20% of the O−H bond energy. These results show that liquid water has quantum properties, and may even be quantum coherent.

QUANTUM COHERENT WATER MAKES LIFE ON EARTH

Standard quantum theory does not predict quantum coherence for liquid water, largely because it ignores both quantum fluctuations and the interaction between matter and electromagnetic field; these are only taken into account in quantum electrodynamics field theory. However, conventional quantum electrodynamics field theory applies only to gases.

Theoretical physicists Giuliano Preparata (1942–2000), Emilio Del Giudice, and colleagues at University of Milan in Italy, extended conventional quantum electrodynamics theory to the condensed phase of liquids. They showed that interaction between the vacuum electromagnetic field and liquid water induces the formation of large, stable coherent domains (CDs) of about 100 nm in diameter at ordinary temperature and pressure, and these CDs may be responsible

for all the special properties of water including life itself[43–46] (see Reference 47 for a more accessible description). In particular, they showed that the propensity to form tetrahedral directed hydrogen bonds is a *consequence* of the excited state of water in the coherent domains that would not happen if not for interactions with the ambient electromagnetic field.

The CD in water is a resonating cavity produced by the electromagnetic field that ends up trapping the field because the photon acquires an imaginary mass, so the frequency of the CD electromagnetic field becomes much smaller than the frequency of the free field with the same wavelength.

Under ambient conditions, water is an approximately equal mixture of coherent domains surrounded by incoherent regions. (It is more accurate to say that the water molecules are dancing between the tetrahedral configuration corresponding to the CDs and nontetrahedral configuration, so both the CD and non-CD molecules are interchangeable.) This picture, according to Del Giudice and colleagues, is reflected in the many observations supporting a two-state model of liquid water.[48]

The special thing about water is that the coherent oscillation occurs between the ground state and an excited state at 12.06 eV, just below the ionizing threshold of water at 12.60 eV. In liquid water, the CD of about 100 nm diameter contains millions of water molecules, and nearly a million almost-free electrons—forming a plasma—that can be readily donated to electron acceptors. And this is why water is the means of life: it is this property that enables water to fuel the dynamo of life. Water is the basis of the energy metabolism that powers all living processes; it is both the chemistry and the electricity of life.

The abundant life on earth, including you and me, depends on photosynthesis in green plants, algae, and cyanobacteria that traps the energy of sunlight by means of chlorophyll (the green pigment in chloroplasts) to split water into hydrogen, electrons, and oxygen (Equation 10.1). This gives life access to an enormous, practically unlimited energy source, and perhaps more importantly, liberating oxygen for the evolution of air-breathing organisms including us that filled the earth with teaming millions of species. (If, as astronomers tell us, water is the most abundant substance in the universe, could there be abundant extra-terrestrial beings similar to us in the universe?)

$$H_2O \rightarrow 2\ H^+ + 2\ e^- + O \qquad (10.1)$$

Equation 10.1 says it all. The hydrogen ion (protons) and electrons go to reduce (or fix) carbon dioxide into carbohydrates, and biomass of photosynthetic organisms, which serve as food for herbivores, and down the food web to include the vast majority of air-breathers that break down carbohydrates with oxygen in mitochondria to obtain energy for growth and reproduction, regenerating carbon dioxide and water. This completes the living dynamo of photosynthesis and respiration, the magic roundabout that turns inanimate substances into living organisms.

However, it takes lots of energy to split water, 12.6 eV, to be precise, and requires an energetic photon in the soft x-ray region, which would destroy life, and is not what green plants and cyanobacteria use. They use mainly red and to some extent blue light in the visible spectrum.

More than 50 years ago, Nobel Laureate Albert Szent-Györgyi, the father of biochemistry suggested[49] that water at interfaces was the key to life. He proposed that water at interfaces, such as membranes in the excited state, requires considerably less energy to split than water in the ground state. A sign of the excited water is that a voltage should appear at the boundary between interfacial water and bulk water, which was indeed observed not long after Szent-Györgyi predicted it (see Reference 44). This property of water enables energy transfer to take place in living organisms. Most, if not all, water in living organisms is interfacial water, as it is almost never further away from surfaces, such as membranes or macromolecules, than a fraction of a micron.

A vivid demonstration of interfacial water was achieved by Gerald Pollack's research team at the University of Washington, USA.[50,51] Using a hydrophilic gel and a suspension of microspheres just visible to the eye, they showed that interfacial water apparently tens of microns or even hundreds of microns thick forms on the surface of the gel. This excludes the microspheres as well as other solutes, such as proteins and dyes, and hence, it is referred to as an "exclusion zone" (EZ).

EZ water is about tenfold more viscous than bulk water, it has a peak of light absorption at 270 nm, and emits fluorescence. Del Giudice and colleagues[45] suggest that EZ water is in fact a giant coherent domain stabilized on the surface of the attractive gel. Inside the cell, the EZ would form on surfaces of membranes and macromolecules, as envisaged by Szent-Györgyi.[49] Because coherent water is excited water with a plasma of almost free electrons, it can easily transfer electrons to molecules on its surface. The interface between fully coherent interfacial water and normal bulk water becomes a "redox pile." In line with this proposal, EZ water does indeed act as a battery, as Pollack's research team demonstrated.[52,53]

THE SUPERCONDUCTING ELECTRIC CURRENTS OF LIFE

The core chemistry of life is reduction-oxidation or redox reactions that transfer electrons between chemical species, and the movement of electrons is nothing if not an electric current. However, water electricity is special in that it also involves the movement of positive charges associated with protons.[54] Water conducts protons by a special kind of jump conduction down a chain of water molecules connected by hydrogen bonds. A proton leaps on one end of the chain, and a second leaps off at the other, while electrons are displaced in the other direction.

Some time ago, researchers at Drexel University, Philadelphia, the University of Illinois, Chicago, USA, and the Tokyo Institute of Technology, Japan, demonstrated for the first time the formation of structured water confined in carbon nanotubes less than 5 nm in diameter, that was completely different from the more ordinary looking water

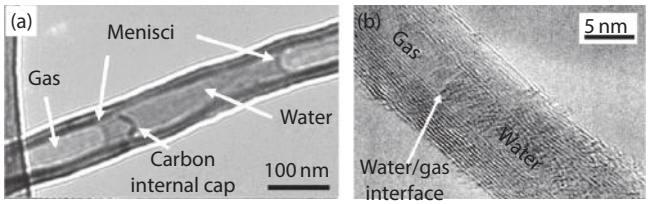

FIGURE 10.7 Structured water confined in narrow nanotube (right) compared with ordinary water in wide nanotube (left). (Rearranged from Ye H, Naguib N, Gogotsi Y. *JEOL News* 2004;39:2–7.)

confined in larger nanotubes[55,56] (Figure 10.7). I suggested that water confined in the small diameter nanotube, being more ordered, could be superconducting because proton jump-conduction could occur simultaneously down multiple chains of hydrogen-bonded water molecules.[57]

Later, Gary Fullerton and colleagues offered a convincing model of liquid crystalline nanotubes of water interwoven with the triple-helix molecules of collagen molecules in the collagen fibres[58,59] (Figure 10.8), which again suggested to me that such a water structure in the extracellular matrix could also be superconducting.

As mentioned earlier, the proton is actually in a delocalized quantum state even in bulk water under ambient conditions. Proton delocalization has been confirmed for water confined in nanotubes (see Reference 60 and References therein). Delocalized protons mean proton jump conduction[54] can be *very* fast indeed.

Greatly enhanced proton conduction has been observed for water confined in Nafion fibres. Nafion is a synthetic polymer used as a proton exchange membrane. The proton conductivity of fibers with diameters >2 μm was similar to the bulk Nafion film (~0.1 S/cm). However, when the fiber diameter was <1 μm, proton conductivity rose sharply with decreasing fiber diameter and reached 1.5 S/cm for the 400 nm diameter fiber, at least an order of magnitude higher than the bulk Nafion film, or silicon, a semi-conductor. Conductivity of the fiber also increased a hundredfold as relative humidity rose from 50% to 90%; in comparison, conductivity of the bulk film increased only tenfold.[61]

Nafion channels form inverse micelles with hydrophilic groups facing the cavity and hydrophobic groups facing out, which most resemble the condition inside the living cell. In the cell, the interstices between fibers of the cytoskeleton and cytoplasmic membranes form inverse micelle nanospaces and channels that drastically alter enzyme/substrate relationships and enzyme activity compared to bulk phase thermodynamic models that still dominate conventional cell biology (see Chapter 18 of *Living Rainbow H_2O*[25]). The inverse micelle model may be even more relevant to the extracellular *milieu* of multicellular animals, which is traversed by collagen fibers consisting of fibrils interwoven with nanotubes of water[59] (Figure 10.5). These water channels aligned with collagen fibers are most likely the anatomical correlates of the acupuncture meridians of traditional Chinese medicine, as I and David Knight first suggested in 1998[62] and the hypothesis is still very much alive and untested.[63]

Proton and electron currents coursing inside cells and over different extracellular distances deliver physical and chemical messages concerning the redox status. This sets in motion the requisite chemical reactions that restore local and global energy balance, as well as the peripheral chemistry and forms the basis of the highly nuanced passions and feelings that make life so exciting for organisms (as opposed to computers, which therefore cannot feel).

THE ELECTROMAGNETIC LANGUAGE OF CELLS AND MOLECULES

One important final question is how do cells and molecules actually find one another? Conventional wisdom says hormones and receptors, cell-cell recognition molecules, and lock-and-key principle for molecules that somehow bump into each other at random.

Actually, molecules find each other by electromagnetic fields, by resonating to common frequencies.[2] Molecules that react together were found to share a common frequency; which is how they can attract each other (see Reference 64 and references therein). This makes even more sense in the context of quantum coherent water.

Del Giudice and colleagues[44] argue that water CDs can be easily excited, and are able to capture surrounding electromagnetic fields to produce coherent excitation in the frequencies of the external fields. This, in turn, enables selective coherent energy transfer to take place. All molecules have their own spectrum of vibrational frequencies. If the molecule's spectrum contain a frequency matching that of the water CD, it would get attracted to the CD, and become a guest participant in the CD's coherent oscillation, and settle on the CD's surface. Furthermore, the CD's excitation energy would become available to the guest molecules as activation energy for the chemical reactions.

Is it possible that cells as a whole also intercommunicate by means of electromagnetic and electric signals? This is completely uncharted territory as far as conventional cell biology is concerned. It is the water in us that gives us life, and makes us sensitive to electromagnetic fields; there is a distinct possibility that we are sensitive to the fields of other organisms as we are sensitive to fields of the sun and the earth (see earlier), and possibly also from distant stars; all without our conscious knowledge. There is good evidence that clusters of galaxies and stars in our universe are interconnected in plasma current circuits spanning hundreds of millions of light years (see Reference 2 and References therein). It would not be surprising if galaxies and stars, too, intercommunicate by electromagnetic fields of intergalactic dimensions.

TO CONCLUDE

Life is quantum electrodynamical through and through, and water is at the heart of it all. A whole new vista has opened up thanks to all the dedicated water scientists who have contributed to this vision: Emilio Del Guidice, Gerald Pollack,

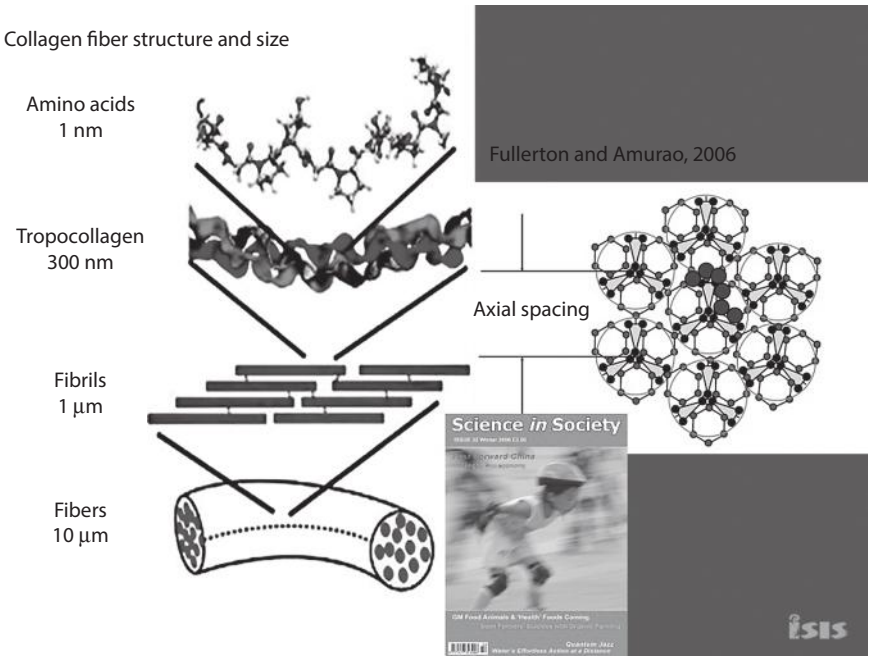

FIGURE 10.8 **(See color insert.)** Collagen water structure revealed.

James Clegg, Gilbert Ling, Philippa Wiggins, Walter Drost-Hansen, Norio Ise, Martin Chaplin, Ludwig Edelmann, Gary Fullerton, Ivan Cameron, Frank Mayer, and many others. Our adventures have only just begun.

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11 Why Biological Water Differs from H_2O and Acts Like a Battery

*Gerald H. Pollack**

CONTENTS

Why do fair weather clouds form puffy white shapes? Why do your joints work without squeaking? Why do sprained ankles swell within seconds? How can you get energy from water?

Answering these questions requires an understanding of water. Given its simplicity and pervasiveness through nature, many presume that water must be completely understood, but in fact, precious little is known about how water molecules line up—until recently.

Students learn that water has three phases: solid, liquid, and vapor. But there is something more: in our laboratory at the University of Washington we have uncovered a *fourth* phase. This phase occurs next to water loving (hydrophilic) surfaces. It is surprisingly extensive, projecting out from surfaces by up to millions of molecular layers. And it exists almost everywhere throughout nature, including your body.

This newly identified phase of water has been described in a recently released book: *The Fourth Phase of Water: Beyond Solid, Liquid and Vapor.*[1] The book documents the basic finding and presents many applications beyond the ones mentioned above. It also deals with water's well-recognized anomalies, turning those anomalies into easily explained features.

The existence of a fourth phase may seem unexpected. However, it should not be entirely so: a century ago, the physical chemist Sir William Hardy argued for the existence of a fourth phase, and many authors over the years have found evidence for some kind of "ordered" or "structured" phase of water. Fresh experimental evidence not only confirms the existence of such an ordered, liquid-crystalline phase, but also details its properties. It is more viscous, dense, and alkaline than H_2O and has more oxygen as its formula is H_3O_2. As a result, it has a negative charge and, like a battery, can hold energy as well as deliver that energy when needed. These properties explain everyday observations and answer questions ranging from why gelatin desserts hold their water to why teapots whistle.

The presence of the fourth phase carries many implications. Here, I outline some basic features of this phase, and then deal with several of those implications, including energetic aspects. I will touch on atmospheric science and then focus on some biological and health applications.

DOES WATER TRANSDUCE ENERGY?

The energy for building water structure comes from the sun. Radiant energy converts ordinary bulk water into ordered water, building this ordered zone. We found that all wavelengths ranging from UV through visible to infrared can build this ordered water. Near-infrared energy is the most capable. Water absorbs infrared energy freely from the environment; it uses that energy to convert bulk water into liquid crystalline water (fourth phase water)—which we also call "exclusion zone" or "EZ" water because it profoundly excludes solutes. Hence, buildup of EZ water occurs naturally and spontaneously from environmental energy. Additional energy input creates additional EZ buildup.

Of particular significance is the fourth phase's charge: commonly negative (Figure 11.1). Absorbed radiant energy splits water molecules; the negative moiety constitutes the building block of the EZ, while the positive moiety binds with water molecules to form free hydronium ions, which diffuse throughout the water. Adding additional light stimulates more charge separation.

This process resembles the first step of photosynthesis. In that step, energy from the sun splits water molecules. Hydrophilic chromophores catalyze the splitting. The process considered here is similar but more generic: any hydrophilic surface may catalyze the splitting. Some surfaces work more effectively than others.

The separated charges resemble a battery. That battery can deliver energy in a manner similar to the way the

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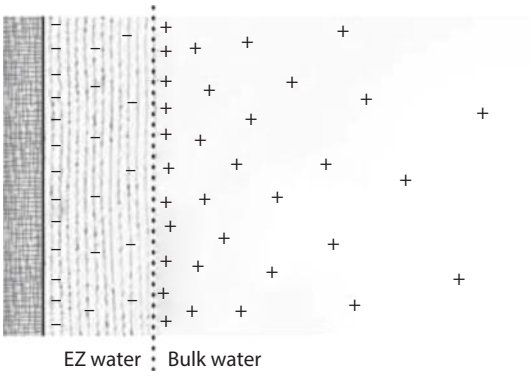

FIGURE 11.1 Diagrammatic representation of EZ water, negatively charged, and the positively charged bulk water beyond. Hydrophilic surface at left.

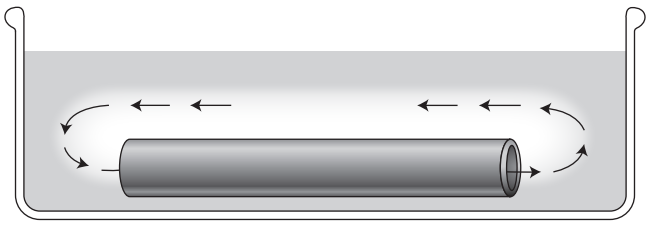

FIGURE 11.2 Practically incessant flow occurs through hydrophilic tubes immersed in water.

separated charges in plants deliver energy. Plants, of course, comprise mostly water, and it is therefore no surprise that similar energy conversion takes place in water itself.

The stored electrical energy in water can drive various kinds of work, including flow. An example is the axial flow through tubes. We found that immersing tubes made of hydrophilic materials into water produces flow through those tubes, similar to blood flow through blood vessels (Figure 11.2). The driving energy comes from the radiant energy absorbed and stored in the water. Nothing more. Flow may persist undiminished for many hours, even days. Additional incident light brings faster flow. This is not a perpetual motion machine: incident radiant energy drives the flow—in much the same way that it drives vascular flow in plants and powers water from the roots to nourish trees taller than the length of a football field.

APPLICATIONS IN BIOLOGICAL FLOW AND ATMOSPHERIC SCIENCE

The water-based energy conversion framework is rich with implication for many systems involving water. These systems may range from biology and chemistry all the way to atmospheric science and engineering. The fourth phase appears nearly everywhere: all that is needed is water, radiant energy, and a hydrophilic surface. The latter can be as large as a slab of polymer and as small as a dissolved molecule. The liquid crystalline phase inevitably builds—and its presence plays some integral role in the system's behavior.

Let me provide a few representative examples.

One example is…you. By volume, two thirds of your cells' content is water. However, the water molecule is so small that making up that two-thirds volume involves 99% of all your molecules. Modern cell biology considers that 99% molecular fraction as mere background carriers of the "important" molecules of life such as proteins and nucleic acids. Conventional wisdom asserts that 99% of your molecules do not do very much.

However, EZ water envelops every macromolecule in the cell. Those macromolecules are so tightly packed that the enveloping liquid-crystalline EZ water largely fills your cells. In other words, most of your cell water is EZ water. This water plays a central role in everything the cell does—as elaborated in my earlier book, *Cells, Gels and the Engines of Life*.[2]

What is new is the role of radiant energy: incident radiant energy powers many of those cellular functions. An example is the blood flowing through your capillaries. That blood eventually encounters high resistance: capillaries are often narrower than the red blood cells that must pass through them; in order to make their way through, those red cells need to bend and contort. Resistance is high. You would anticipate the need for lots of driving pressure; yet, the pressure gradient across the capillary bed is negligible. The paradox resolves if radiant energy helps propel flow through capillaries in the same way that it propels flow through hydrophilic tubes. Radiant energy may constitute an unsuspected source of vascular drive, supplementing cardiac pressure.

Why you feel good after a sauna now seems understandable. If radiant energy drives capillary flow and ample capillary flow is important for optimal functioning, then sitting in the sauna will inevitably be a feel-good experience. The infrared energy associated with heat should help drive that flow. The same if you walk out into sunlight: we presume that the feel-good experience derives purely from the psychological realm; but the evidence above implies that sunlight may build your body's EZs. Fully built EZs around each protein seem necessary for optimal cellular functioning.

A second example of the EZ's central role is weather. Common understanding of weather derives from two principal variables: temperature and pressure. Those two variables are said to explain virtually everything we experience in terms of weather. However, the atmosphere also contains water: it is full of micrometer-scale droplets commonly known as aerosol droplets or aerosol particles. Those droplets make up atmospheric humidity. When the atmosphere is humid, the many droplets scatter considerable light, conferring haze; you cannot see clearly through that haze. When the atmosphere contains only a few droplets, you may see clearly over long distances.

The new book presents evidence for the structure of those droplets. It shows that EZ water envelops each droplet, while hydronium ions occupy the droplets' interior. Repelling one another, those internal hydronium ions create pressure, which pushes against the robust shell of EZ water. That pressure explains why droplets tend toward roundness.

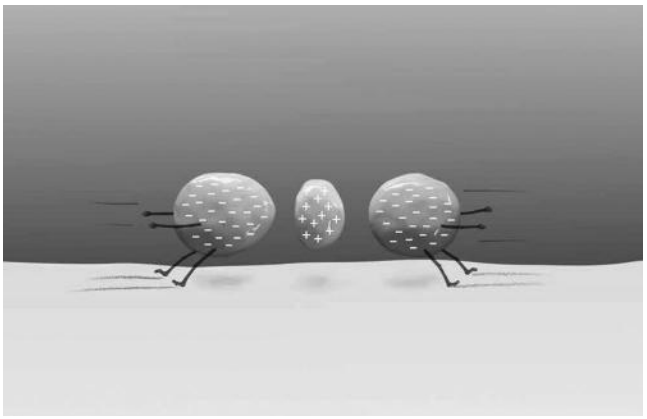

FIGURE 11.3 Like-charged entities attract because of an intermediate of opposite charge.

How do those aerosol droplets condense to form clouds? The droplets' EZ shells bear negative charge. Negatively charged droplets should repel one another, precluding any condensation into clouds. Those like-charged aerosol droplets should remain widely dispersed throughout the atmosphere. However, droplets *do* often condense into clouds, and the question is how that can happen.

The reason they condense is because of the unlike charges that lie in between the droplets. Richard Feynman, the legendary Nobel Prize physicist of the late twentieth century understood the principle, opining that: "like-likes-like because of an intermediate of unlikes." The like-charged droplets "like" one another, so they come together; the unlike charges lying in between those droplets constitute the attractors (Figure 11.3).

The like-likes-like principle has been widely appreciated, but also widely ignored: after all, how could like charges conceivably *attract*? A reason why this powerfully simple concept has been ignored is that the source of the unlike charges has been difficult to identify. We now know that the unlike charges can come from the splitting of water—the negative components building EZ shells, while the corresponding positive components provide the unlike attractors. With enough of those attractors, the negatively charged aerosol droplets may condense into clouds.

These two phenomena, radiant energy-induced biological function and like-likes-like cloud formation, provide examples of how water's energy can account for phenomena not otherwise explained. The fourth phase is the key building block that allows for construction of an edifice of understanding.

PRACTICAL APPLICATIONS

Beyond scientific, the discovery of the fourth phase has practical applications. They include flow production (already mentioned), electrical energy harvesting, and even filtration. I will briefly mention the latter two applications.

Filtration occurs naturally because the liquid crystalline phase massively excludes solutes and particles in much the same way as ice. Accordingly, fourth phase water is essentially solute free. Collecting it provides solute-free and bacteria-free water. A working prototype has confirmed this expectation. Purification by this method requires no physical filter: the fourth phase itself does the separation, and the energy comes from the sun.

Energy harvesting seems straightforward: light drives the separation of charge, and those separated charges constitute a battery. Harvesting electrical energy should be realizable with proper electrodes. This technology development is underway in our laboratory, and has the potential to replace standard photovoltaic systems with simpler ones based on water. More detail on these practical applications can be found in the Pollack laboratory homepage (http://faculty.washington.edu/ghp/).

Practical applications also exist within our bodies, and I present two of them: why your joints do not squeak and why dislocated or sprained joints will swell *within seconds*.

Joints are sites at which bones press upon one another (Figure 11.4). The bones may also rotate, as during deep-knee bends and push-ups. You would think that rotation under pressure might elicit squeaky frictional resistance, but joint friction remains remarkably modest. Why so?

The ends of bones are lined with cartilage. Those cartilaginous materials do the actual pressing. Hence, the issue of joint friction reduces to the issue of the cartilaginous surfaces and the synovial fluid lying in between. How does this system behave under pressure?

Cartilage is made of classic gel materials: highly charged polymers and water; therefore, cartilage is a gel. Gel surfaces bear EZs, so cartilage surfaces should likewise bear EZs. The splitting of water associated with EZ buildup creates many hydronium ions in the synovial fluid. Additional hydronium ions come from the molecules within that fluid, creating their own EZs and protons. Thus, many hydronium ions will lie in the area where two cartilaginous surfaces lie across from one another. The repulsive force coming from those

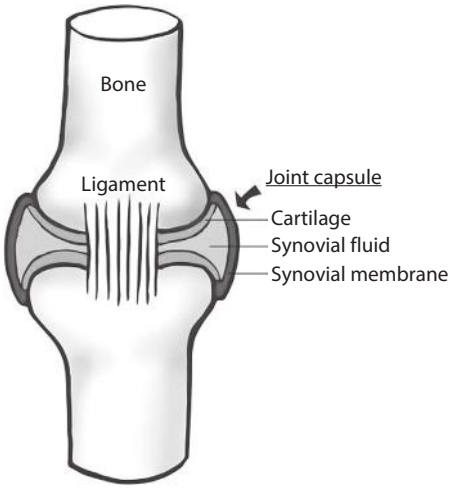

FIGURE 11.4 Enveloping the joint, the capsule ensures that the fluid's hydronium ions do not disperse. The concentrated hydronium ions repel, keeping surfaces apart and assuring low friction.

hydronium ions should keep the cartilage surfaces apart—some investigators maintain that the cartilage surfaces never touch, despite heavy loads. That separation means that any rough spots, or asperities, will never come into contact as the respective surfaces shear past one another, and that in turn means low friction.

For such a mechanism to actually work some kind of built-in restraint should be present to keep the repelling hydronium ions in place. Otherwise, they may be forced out of the local region, thereby compromising lubrication. Nature provides that safety net: a structure known as the joint capsule envelops the joint. By constraining the dispersal of hydronium ions, encapsulation ensures low friction. That is why your joints do not ordinarily squeak.

Regarding swelling, the second issue under consideration, osmosis evidently plays a role. As the cell is packed with negatively charged proteins, the cytoplasm should generate an osmotic draw similar to the osmotic draw generated by diapers or gels. Physiologists know that it does.

A peculiar feature of cells, however, is their relatively modest water content. Compared to 20:1 or higher for many common gels, the cell's water-to-solids ratio is only about 2:1. The many negatively charged macromolecules of the cell should generate a strong osmotic draw; yet the water content in the cell remains surprisingly low. That limited water content may come as a consequence of the macromolecular network's stiffness: cellular networks typically comprise tubular or multi-stranded biopolymers tightly cross-linked to one another. The resultant stiffness prevents the network from expanding to its full osmotic potential.

If those cross-links were to disrupt, however, then the full power of osmotic draw would take effect; the tissue could then build many EZ layers, and therefore, hydrate massively, bringing huge expansion (Figure 11.5). That is what happens when body tissues are injured, especially with dislocations. The injury disrupts fibrous macromolecules and cross-links, eliminating the restraining forces that keep osmosis at bay; EZ buildup can then proceed virtually unimpeded.

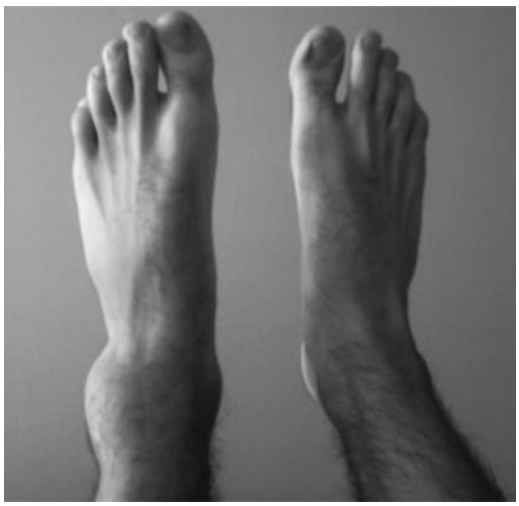

FIGURE 11.5 Example of post-injury swelling.

The reason why swelling can be so impressive is that the cross-link disruption occurs progressively. Breaking one cross-link results in higher stress on neighboring cross-links and, therefore, disruption progresses in a zipper-like fashion. When that happens, the osmotic rush of water into the tissue can continue practically without restraint, resulting in the enormous immediate swelling that is often seen. The tissue will return to normal only when cross-links repair and the matrix returns to its normally restraining configuration.

WATER AND HEALING

During childhood illness, grandmothers and doctors will often advise: "drink more water." In his now-classical book, sub-titled *Your Body's Many Cries for Water: You Are Not Sick, You Are Thirsty*,[3] the Iranian physician Fereydoon Batmanghelidj confirms the wisdom of this quaint advice. The author documents years of clinical practice showing reversal of diverse pathologies simply by drinking more water. Hydration is critical.

Batmanghelidj's experience meshes with evidence of healing from special waters, such as those from the Ganges and Lourdes. Those waters most often come from deep underground springs or from glacial melt. Spring waters experience pressure from above; pressure converts liquid water into EZ water because of EZ water's higher density. EZ water differs from bulk water in that it absorbs light in the UV region of the spectrum, usually close to 270 nanometers. Specimens from the above and from certain spring waters show a spike in this 270-nanometer spectral zone, suggesting that relatively high EZ concentrations could contribute to their therapeutic benefits.

It is the same for mountain water: it too should have high EZ content. Our studies have shown that ice formation requires an EZ intermediate; that is, bulk water does not convert directly to ice, it converts to EZ, which then converts to ice. Similarly for melting: melting ice forms EZ, which subsequently converts to bulk water. Fresh ice melt contains abundant EZ water.

For spring water and fresh ice melt, then, the high EZ content may explain the recognized health benefits. EZ water should rehydrate tissues better than ordinary water because of its higher dipole moment. To appreciate this argument, picture a bean with positive charge localized at one end, negative at the other. The positive end of that dipole orients toward the negatively charged cell, which then strongly draws in that dipole. The larger the dipole, the stronger will be the draw. As EZs contain masses of separated charges, or large dipoles, EZ water should hydrate cells better than ordinary water. That is why EZ water may particularly promote good health.

NEGATIVE CHARGE AND ANTI-OXIDANTS

Humans are considered neutral, but I suggest that we bear net negative charge. Physical chemists reasonably presume that all systems tend toward neutrality because positive charge

attracts negative charge. The human body being one of those "systems," we assume that the body must be neutral.

Not all systems are neutral, however. The earth bears net negative charge, while the atmosphere bears net positive charge. Water itself can bear charge. Anyone watching MIT professor Walter Lewin's stunning demonstration of the Kelvin water dropper (www.youtube.com/watch?v=oY1eyLEo8_A&feature=related), where separated bodies of water eventually discharge onto one another, will immediately see that bodies of water *can* bear net charge. If any doubt remains, then the experience of getting an electric shock from touching certain kinds of drinking water (which my colleagues and I have personally experienced) should eliminate that doubt.

Charges can remain separated if input energy keeps them separated—something like recharging your cell phone battery and creating separated negative and positive terminals. As we constantly absorb external energy from the environment, the theoretical possibility exists that we may bear net charge.

Consider the arithmetic. Cells make up some 60% of your body's mass and they are negatively charged. Extracellular tissues, such as collagen and elastin are next in line, and those proteins bear negative charge and adsorb negatively charged EZ water. Only some of the smaller compartments are positively charged with protons (low pH), and they commonly *expel*: urine, the gastrointestinal system, sweat, and expired air (containing hydrated CO_2 or carbonic acid). They help *rid* the body of positive charge.

Therefore, the arithmetic shows not only that our body bears net negative charge, but also that the body makes every effort to maintain that negativity by ridding itself of protons. It is as though maintaining negativity is a "goal" of life. Plants do it easily: they connect directly to the negatively charged earth; animals need to struggle a bit more to maintain their body's charge, in exchange for greater mobility.

How does our body's negative charge relate to the benefits of anti-oxidants? Answering this question returns us to basic chemistry. Recall that "reduction" is the *gain* of electrons, while "oxidation" means electron *loss*. Oxidation strips molecules of their negative charge, working against the body's attempt to maintain high negativity. To guard against that loss we employ *anti*-oxidants. Anti-oxidants may keep us healthy simply by maintaining proper negativity.

THE FUTURE

Water's centrality for health is nothing new, but it has been progressively forgotten. With the various sciences laying emphasis on molecular, atomic, and even sub-atomic approaches, we have lost sight of what happens when the pieces come together to form the larger entity. The whole may indeed exceed the sum of its parts; 99% of those parts are water molecules. To think that 99% of our molecules merely bathe the "more important" molecules of life ignores centuries of evidence to the contrary. Water plays a central role in all features of life.

Until recently, the understanding of water's properties has been constrained by the common misconception that water has three phases. We now know it has four. Taking into account this fourth phase allows many of water's "anomalies" to vanish: those anomalies turn into predictable features. Water becomes more understandable, and so do entities made largely of water, such as oceans, clouds, and human beings. Even information storage becomes understandable: the crystalline EZ forms a natural substrate for information storage, receipt, and generation—as Jacques Benveniste demonstrated in his pioneering experimental work, and Luc Montagnier and others have followed up.

Various hour-long talks describe these fresh understandings. One of them is a University of Washington public award lecture (www.youtube.com/watch?v=XVBEwn6iWOo). Another was delivered more recently (www.youtube.com/watch?v=JnGCMQ8TJ_g). A third is a recent TEDx talk (http://youtu.be/i-T7tCMUDXU).

A much fuller, well referenced understanding of these phenomena and more appears in the above mentioned new book, *The Fourth Phase of Water: Beyond Solid, Liquid, and* Vapor.[1]

The insights described above arose out of a departure from mainstream science. They were gleaned mainly from simple observations and logical interpretations. I have purposefully ignored the "generally accepted," maintaining some skepticism that all accepted principles are necessarily valid. I believe this skepticism has brought us a long way in our understanding of nature.

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12 Science of Measuring Energy Fields
A Revolutionary Technique to Visualize Energy Fields of Humans and Nature

*Konstantin Korotkov**

CONTENTS

The belief that there are subtle energies in nature as well as humans that interact, which can affect health and behavior has been a basic tenet in Eastern medicine and philosophies for millennia. Western scientists and physicians have largely rejected this because of lack of proof that invisible forces like *Qi* (chi) or *prana* exist. The Chinese sage Lao Tsu, considered to be the father of Taoism, described *Qi* as follows:

> Look, it cannot be seen—it is beyond form
> Listen, it cannot be heard—it is beyond sound
> Grasp, it cannot be held—it is intangible

Suggestions that there is some type of energy similar to this have surfaced sporadically. The medieval physician Paracelsus proposed that a vital force called *archeus* acted like an inner alchemist to sustain life by taking advantage of the *vis medicatrix naturae* (healing power of nature). The seventeenth century mathematician-philosopher Isaac Newton, who was also an alchemist, borrowed some of these ideas in his concept of a mysterious cosmic "aether" that pervaded all space. Two centuries later, Franz Mesmer postulated an invisible "universal fluid" with magnetic properties that circulated throughout the body to provide energy. Disease occurred when this flow was blocked, but health could be restored by swallowing iron filings and applying magnets to the affected area. The magnets were soon discarded, as Mesmer believed the cures were due to his mere presence and the power of his "animal magnetism" when he touched or moved his hands over the patient. Other physicians subsequently proposed analogous healing energies, such as the Odic force of Baron Karl von Reichenbach, Oscar Brunler's biocosmic energy, and, most recently, Wilhelm Reich's orgone. All of these have also been discredited because of lack of proof of their existence, much less any health benefits.

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THE HISTORY AND EVOLUTION OF ELECTROGRAPHY

As might be expected, numerous attempts were made to prove that such energy fields could be identified in humans as well as nature. The first inkling of this was a 1777 discovery by the German physicist and philosopher George Lichtenberg, who reported that when any object was placed in a strong electrical field, a glow could be seen around it. Lichtenberg was able to print images on a plate covered with coal dust that physicists called "Lichtenberg' figures." Interest in photographing electrical fluorescence increased all over the world due to the influence of Nicola Tesla, who demonstrated in 1880 that the application of a high-frequency electrical circuit to the body caused a bright fluorescence to surround it. While this seemed dangerous, it was perfectly safe when special coils were used, that were later called "Tesla coils."

The term "electrography" was coined by the Czech physicist B. Navratil in 1888 to describe photographic images of such energy emanations. A significant advance was made by the talented Byelorussian scientist Jacob Narkevich-Yodko, who developed his own technique for

making electrophotographs. He studied the effects of electrical stimulation on over 1500 fingers of various individuals, plant leaves and grain, and presented his findings to the St. Petersburg Institute of Experimental Medicine in 1892. His results generated so much interest that, in 1893, a conference on electrography and electrophysiology was organized at St. Petersburg University. He was later invited to lecture at numerous European scientific centers, including Berlin, Vienna, Paris, Prague, and Florence. Narkevich-Yodko received medals of commendation at several of these and at the 1900 Congress in France, he was awarded the title of Professor of Electrography and Magnetism.

At around the same time, on the other side of the globe, very similar experiments were being conducted by Landell de Morua, a Brazilian monk. In 1904, he invented an electrographic camera to photograph electrical discharges, which was subsequently modified by others. In 1939, two Czechs S. Pratt and J. Schlemmer published photographs showing a curious glow or aura around leaves. The same year, the Russian electrical engineer Semyon Kirlian and his wife Valentina developed their own technique after observing a patient who was receiving medical treatment from a high-frequency electrical generator. Electrotherapy was popular at the time and they had noticed that when the electrodes were brought near the patient's skin, there was a glow similar to that seen in an electrified tube filled with neon. Kirlian photography consisted of placing photographic film on top of a conducting plate, and attaching another conductor to a hand, leaf, or other part of a plant. When the conductors were energized by a high frequency high voltage power source, the resulting image showed a silhouette of the object surrounded by an aura of light.

The Kirlians published the results of their experiments for the first time in 1958, and in 1961 reported that the characteristics of fingertip auras not only varied in different people, but was also affected by their emotional status.[1] If someone felt very anxious or was in an opposite state of deep relaxation during meditation, there was a corresponding change in the size and intensity of the glow. Their work was virtually unknown in the West until 1970, when two Americans, Lynn Schroeder and Sheila Ostrander, published their book, *Psychic Discoveries Behind the Iron Curtain*.[2] One of the most extensive investigations was carried out at the UCLA Center for the Health Sciences, where Moss and Johnson took more than 10,000 "modified" Kirlian photographs, including the fingertips of over 500 people and over 1000 leaves.[3] They reported that human energy fields were affected by numerous factors, such as ingesting alcohol, performing yogic exercises, and during hypnosis.

They confirmed that the changes were most dramatic when experiencing different emotions and they frequently differed when the researcher and subject were of different genders, as opposed to same sex experiments. A strict authority figure, such as a senior skilled researcher, tended to elicit a much smaller corona compared to a more informal and friendlier assistant of lower status. In studies involving four "healers," their coronas were apt to be much larger and brighter before the healing session than during or after the intervention. In contrast, their patients' coronas increased sharply over their baseline status, suggesting there had been an actual transfer of energy to them from the healer. Dramatic differences in the corona were also found before and after acupuncture treatment. The brightness and clarity of the corona were particularly prominent when needles were inserted at acupuncture points known to be related to the patient's particular complaints. Based on extensive investigations, the researchers concluded that these changes could not be explained by alterations in skin resistance or temperature changes due to peripheral vascular blood flow.

L.W. Konikiewicz, another American researcher, subsequently demonstrated in carefully controlled double-blind studies that he could accurately identify patients with cystic fibrosis, as well as asymptomatic carriers of the gene.[4] He found that the day of the menstrual cycle influenced variations in the brightness of the energy field and that he could use this to identify when ovulation occurred. Subjects taking oral contraceptives had different patterns. He also reported success in detecting cancer and other abnormal conditions in a subsequent book co-authored with L.C. Griff.[5]

Scientific acceptance of Kirlian photography was rather limited because the quality of equipment used by early investigators varied considerably and results were inconsistent as there was no standardization. Things improved when a multidisciplinary group headed by William Eidson, professor of physics at Drexel University in Philadelphia, showed it was possible to image electrical parameters of a specimen in real time, thus making it possible to map human energy fields and any rapid changes. This 6-year project and related research were summarized in a 1976 article in the prestigious journal *Science*.[6] The International Union of Medical and Applied Bio-Electrography was formed in 1987 to help standardize equipment, research methods, and data acquisition.

THE ADVENT OF MODERN BIOELECTROGRAPHY UTILIZING GAS DISCHARGE VISUALIZATION

Gas Discharge Visualization (GDV) technology was developed in Russia by our team in 1995 and has been described in detail in prior publications.[7–10] The GDV device is a state-of-the-art computerized system that has superseded traditional Kirlian photography for several reasons. A major difference is that it allows direct, real-time viewing and analysis of changes in human energy fields as the data is quantified and analyzed by sophisticated software. Because the results are obtained so rapidly, it has become an "express-method" not only for diagnosis, but also for detecting abnormalities that require more detailed investigation. Most importantly, as this technology and the protocols used are standardized, GDV results obtained by different investigators can be compared with reliability. The results are interpreted based on the energy connections of fingers with different organs and systems via meridians that have been used in acupuncture and traditional Chinese medicine for thousands of years.

This approach was first proposed by the German physician and engineer Reinhard Voll in his Meridian Stress Assessment. A variation of this was subsequently developed by the German naturopath and acupuncturist Peter Mandel, who energized certain acupuncture points by using different colored lights to achieve a desired response. Mandel's Energy Analysis Emission diagnostic system utilized Kirlian photography and his Esogetic Colorpuncture therapy is believed to restore *yin* and *yang* equilibrium. All of these modalities, as well as noninvasive laser acupoint stimulation, have been used with varying degrees of success in thousands of patients over the past two decades.[11]

The GDV device is based on the stimulation of photon and electron emissions from an object when it is placed in an electromagnetic field and subjected to brief electrical pulses. This process is called "photo-electron emission" and has been thoroughly studied with cutting edge electronic techniques. The emitted particles accelerate in the electromagnetic field, generating electronic avalanches on the surface of the dielectric (glass) plate in a process called "sliding gas discharge." The discharge causes a glow from the excitement of molecules in the surrounding gas that is constantly measured. Voltage pulses stimulate optoelectronic emissions that are amplified in the gas discharge, and light produced by this process is recorded by a sensitive CCD (charge coupled device) camera that converts it into a colored computer image, or BIO-gram. Data obtained from the fingers of both hands are converted into a human energy field image using proprietary sophisticated GDV (BIO-Well) software.

This technology has extraordinary implications for all health related fields, including conventional as well as complementary or alternative therapies. A comprehensive review of these varied GDV applications can be found in a recent book[12] co-authored with Dr. E. Yakovleva from Moscow Medical University. Research with the GDV device is currently being carried out at universities and research institutes worldwide in medicine, "energy medicine," athletic training, biophysics, parapsychology, and other disciplines.[13–23] We have recently developed a new application of GDV for "Remote Detection of Human Emotions" called "GDV Sputnik."[24,25] GDV has been used in numerous significant research projects that have confirmed its usefulness and reliability and value. Some examples include:

- A presentation at the National Institutes of Health to an audience of 27 recognized experts from U.S. government and academic institutions, including Dr. Leonard Wisneski, author of *The Scientific Basis of Integrative Medicine*.[26]
- A Pennsylvania State University study was conducted by scientists from the National Institutes on Aging, which validated that GDV can be utilized efficiently in high volume venues to provide an accurate and consumer-friendly assessment of health status.[8]
- Significant correlations between GDV indices and heart rate variability (HRV) assessments have been demonstrated by various research groups.[9] HRV is the most accurate, objective measurement of stress and a powerful predictor of sudden death. These observations confirm that GDV reflects autonomic nervous system activity.[7,10]
- GDV has also been the basis of graduate doctoral dissertations in various countries that included research in medical and other technical fields.[16–18]
- Our group has hosted a series of annual international scientific congresses in St. Petersburg during the last two decades that has attracted scientists from 46 countries, all of whom are involved in GDV research. They have reported significant results in diverse areas, including early detection of certain cancers.

As will be seen, GDV technology provides a convenient and user friendly method to assess patients with a wide range of complaints and can also be utilized to assess responses to drugs, meditation, stress reduction therapy or any other interventions.

ENERGY FIELDS—THE GOOD, THE BAD, AND THE UGLY

The energy field of the individual in Figure 12.1 to the left is uniform, has no gaps, holes, or strong outbursts, and is of optimal size. This would likely represent the type of field

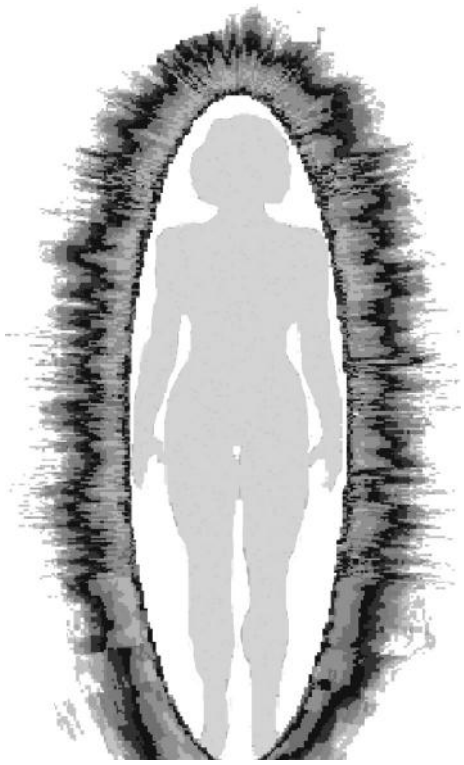

FIGURE 12.1 **(See color insert.)** Human energy field of a healthy person.

seen in someone who not only has no physical problems, but is also not stressed and in a very good mood.

We recognize that it is quite rare for anyone to have absolutely no physical or mental complaints. Most people adapt to problems that only cause mild discomfort under particular circumstances, such as joint discomfort that is weather related or following strenuous exercise. With appropriate dietary and other lifestyle changes and medication when needed, they lead an active life, have few complaints, and would be considered healthy. However, many healthy people may not be aware of asymptomatic weak or abnormal GDV Energy Field findings. In some instances, these could be precursors of dangerous conditions, such as a heart attack or stroke, which might be prevented if appropriate measures were taken, as illustrated in Figure 12.2.

As can be seen in Figure 12.2, abnormalities requiring further investigation may be manifested as outbursts as well as gaps. In both cases, the overall contour is not uniform, and there are marked irregularities at various sites. More sophisticated studies have revealed that gaps in the energy field are very often correlated with microcirculation blockages. In some cases, the differences between energy fields of apparently healthy people and those suffering from chronic problems are so faint that they are difficult to distinguish. An accurate assessment in this and other instances can only be made by an experienced investigator with special training in programs that provide illustrative examples and information. A major purpose of the GDV device is to serve as a screening tool to determine the need for further investigation and to recommend treatment that will provide preventive or therapeutic benefits.

GDV assessment also makes it possible to demonstrate the effects of physical exercise, meditation, prayer musical performance, acupuncture and any other intervention. For example, in Figure 12.3 above to the left, note the relatively uniform appearance of the human energy field in a maestro prior to conducting a symphony orchestra. This is in sharp contrast to the very irregular and jagged image following the

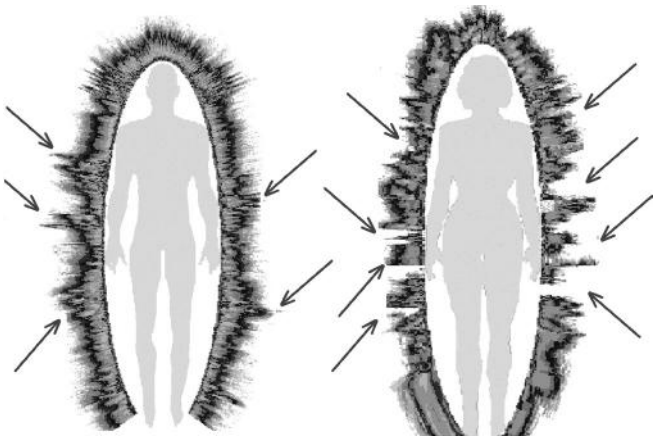

FIGURE 12.2 (See color insert.) Human energy field of an apparently healthy person with problems. Areas indicate the areas of attention.

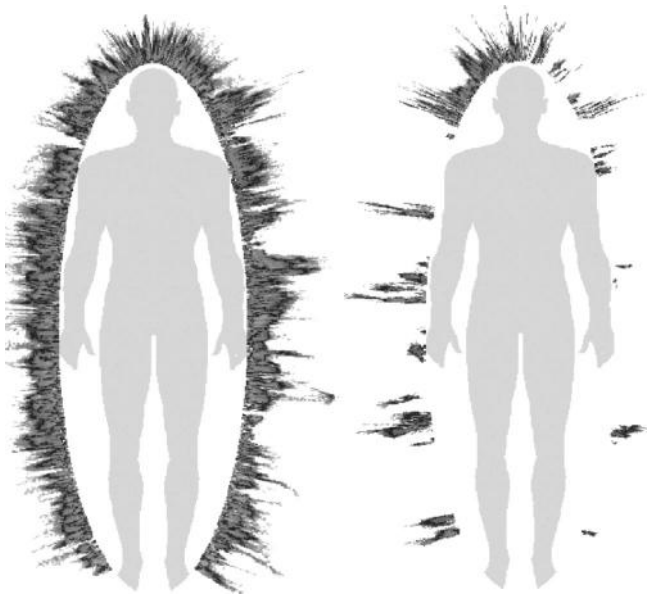

FIGURE 12.3 (See color insert.) Energy field of an orchestra conductor before and after symphony performance.

performance, with multiple gaps reflecting the large amount of emotional and physical energy that had been expended. One can also demonstrate the benefits of a therapeutic intervention, as illustrated in Figure 12.4 above to the right. Although the changes may not be immediate, one can see the marked improvement in the human energy field following a course of acupuncture. The goal of therapy should be to achieve this type of uniform and balanced image.

It should also be emphasized that a very large energy field is not always indicative of good health and there is an upper as well as lower range of normalcy. As this may vary with different individuals, an internet based assessment is being

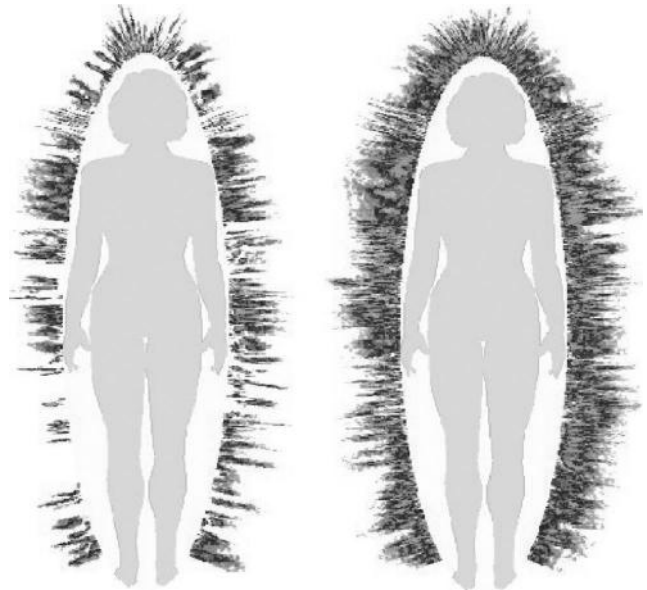

FIGURE 12.4 (See color insert.) Energy field of a person before and after the course of acupuncture.

developed to assist in evaluation, which would otherwise require consulting a qualified expert.

Stress Level Evaluation

Stress is a complex factor that has both an emotional component, such as anxiety, and a somatic component that results from prolonged exposure to anxiety or any stressor. Stress has a very strong impact on the energy field, but by using special GDV software, it, it is possible to make a quantitative assessment of the effects of anxiety index on a 10-point scale.

Altered State of Consciousness

This is a very specific condition that can result from diverse situations ranging from deep meditation, intensive prayer, artistic creativity, and hypnosis, to sleep or oxygen deprivation, trauma, severe infection, psychedelic drugs, and temporal lobe epilepsy. In most cases, an altered state of consciousness will have a specific influence on the energy field, as shown to the left in Figure 12.5. This image was obtained during an Ajurvasco ritual involving a homemade alcoholic drink and rhythmic music that induces a trance like state. As can be seen, the image is much distorted, the left and right sides are not balanced, and there are large gaps. This condition is of particular interest to neurologists, psychiatrists, and researchers who are actively involved in investigating the nature of consciousness.

Chakra Measurement

According to Eastern metaphysical theories and principles of Ayurvedic medicine, there are seven "Chakras" or integrated energy centers that affect physical, mental, emotional, and spiritual well-being. These energy "disks" are positioned or embedded into the spinal column at various locations starting at the coccyx and rising to the crown of the head. Each Chakra is thought to resonate at a different frequency level.

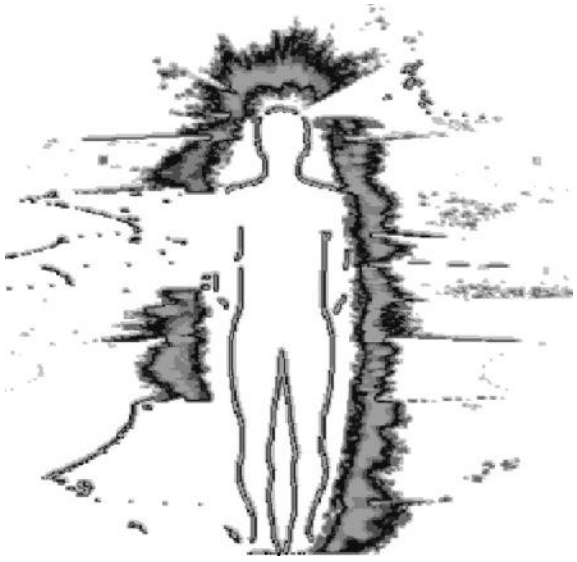

FIGURE 12.5 (See color insert.) Energy field of a person in an altered state of consciousness in the process of an Ajurvasco ceremony.

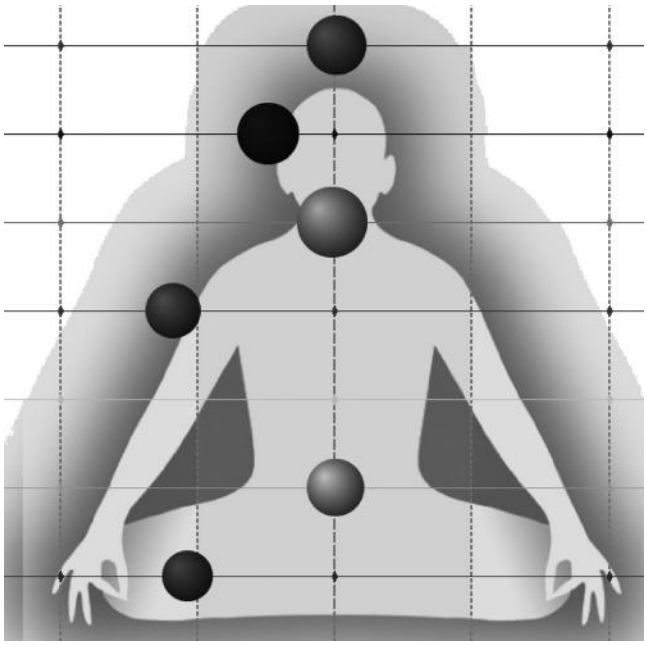

FIGURE 12.6 (See color insert.) Ideal chakras distribution.

GDV software now makes it possible to quantitatively estimate the energy of Chakras, display their level of activation, and indicate whether this level of activation is above or below the average values found in a large number of healthy controls.

The distribution of the Chakras is most important. Ideally, they should be aligned along Sushumna—the central line of the spinal cord, as shown in Figure 12.6. Such optimal states are uncommon and it is more likely to find misaligned chakras that have shifted from this central position and are smaller. This is particularly true when individuals are under stress or emotionally disturbed, as seen in Figure 12.7, where the subject is not well grounded (Chakra N1 is not centered), has some problems (heart Chaka N4 is out of order), but has high spiritual development (upper Chakra N7 is well positioned). Such Chakra abnormalities are usually related more to psychological and spiritual rather than physical factors and are described in detail in Ayurvedic texts.

Monitoring Energy Status to Predict Responses

As previously demonstrated, the GDV device can evaluate the efficacy of an intervention such as acupuncture, as well as responses to stress. When it is used in the "Monitoring Energy State" mode, it can also predict how you will respond to different environmental stimuli, as shown in Figure 12.8.

In the above experiment, the subject sat before a computer with her finger on the GDV device electrode as different

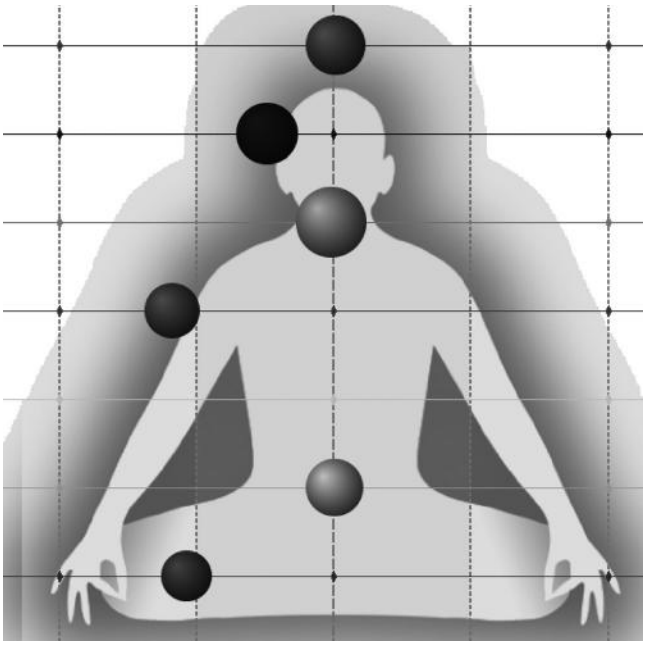

FIGURE 12.7 **(See color insert.)** Chakras distribution of a person.

sounds and images were displayed on the screen. A neutral blue screen was inserted between images of different content to minimize any carry over effect. As can be seen, the signal dropped after beautiful classical music, but then stabilized and slowly increased with rock music with which she was familiar. It fell again following negative images (spider and war scenes) and then increased with a happy wedding scene. The highest reactions were to the Psalms and Prayers at the end of the experiment and the nadir occurred during horrific war pictures.

The "Monitoring Energy State" mode can also be used to predict responses to drugs, foods, allergens, and any item by holding it in your right hand and noting the response on the graph. If the line goes down, the reaction of your energy field is negative; but if it goes up, this signifies it is a medication, food, or something else that will increase your energy.

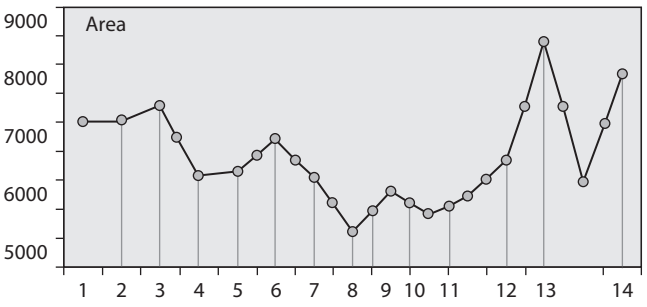

FIGURE 12.8 Change of energy field of a person in an experiment. Stimulations: 1—background; 2,3—classical music; 4,5,6—rock music; 7—image of a spider; 8,9—images of war; 10,11—images of aggression; 12—image of a landscape; 13—image of a wedding; 14—prayer.

This technique can also be used to select gemstones, jewelry, and fragrances that are beneficial, or products that may cause problems because they are allergens. Costly and sophisticated blood tests done in special laboratories can supply this information, but the GDV device allows you to do it for yourself, your friends, and relatives at home.

Monitoring the Environment

The GDV device with a specially designed sensor called the "Sputnik antenna" is used to monitor the energy of the environment and its effects on emotional status. The "Sputnik antenna" is a specialized Bio-Well device that measures the energy of the environment in a room that enables you to see how it varies when people meditate, pray, or listen to a presentation (see http://gdvcamera.com/gdvcamera-bio-well). The physical principle it is based on is measuring the electrical capacitance of a space by using two connected resonance contours.[24] This may be useful for the following purposes:

1. Testing different places in a search for locations that are calm or contain turbulent energy
2. Testing the energy status of different sites that are significantly affected by the position of the sun, moon, season, or time of the year, etc.
3. Measuring the energy in the places of power—both natural and man-made, such as temples and other houses of worship, sacred places, ancient cities, etc.
4. Testing geoactive zones, in particular, geopathic stress zones[19]
5. Detecting the influence of emotions and focused attention on the environment

It has long been observed that people feel differently depending on environmental factors that may include temperature, humidity, atmospheric pressure, and geographic location. There are some places where you sleep like a baby, have wonderful dreams and wake up full of energy. But there are others where sleeping is disrupted, fatigue is frequent, and there is increased susceptibility to illness. Western science has no explanation for this other than it represents a confluence of geomagnetic influences, subterranean anomalies, hollows, water streams, natural and industrial atmospheric gases, electromagnetic fields, and especially solar and cosmic emanations. It has been practically impossible to distinguish between all these factors or to determine what each contributes, so our ability to measure the cumulative effect at any particular place can best be described as primitive and rudimentary.

The GDV device may provide an exciting breakthrough. Many years of research, including expeditions to Peru, Colombia, Ecuador, India, Myanmar, Siberia, and other locations have demonstrated the sensitivity of this device to assess local environmental conditions and idiosyncrasies. There are geoactive zone variations in energy during sunrise and sunset

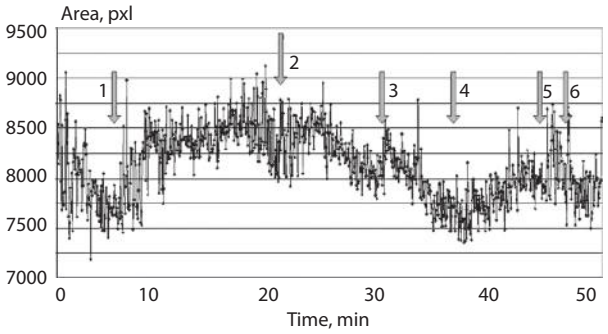

FIGURE 12.9 Time dynamics of the electrophotonic sensor area parameter during the Dr. Emoto ceremony. 1—beginning of ceremony; 2—beginning of the first meditation; 3—presentation of Dr. Emoto; 4—collective meditation; 5—singing a song; 6—end of the event.

or just prior to a thunderstorm. Measurements conducted during religious ceremonies, yoga exercises, group meditation, public lectures, and musical performances also show statistically significant changes in the signal of the Sensor during these activities that correlate with the duration of the event, as shown in Figure 12.9.

On August 3, 2008, Dr. Masaro Emoto conducted the ceremony of blessing the water at Olkhon Island on Lake Baikal in southeast Siberia. Figure 12.9 demonstrates the time dynamics of signal amplitude and intensity recorded from the antenna in the power units that characterize signal strength. Arrows mark different stages of the ceremony. As can be seen, each significant moment in the ceremony was followed by a corresponding change in GDV activity. The gradual decrease between points 2 and 4 might be explained by the group's slow but progressive loss of its initial intense concentration. Nevertheless, group meditation and singing showed consistent positive responses.

A similar set of measurements was made during the first day of a September 12, 2008 Reconnection Healing Workshop in Los Angeles conducted by Dr. Erick Pearl and Doug DeVito, as illustrated in Figure 12.10.[27]

As can be seen, the signal fell during the hour or two of the session, which consisted of introductory comments about the program that most participants had heard many times before and generated little interest. However, when Dr. Pearl started his stimulating presentation, it began to rise (red arrow) and continued to increase over the next 2 h when it reached a sustained peak. At the same time, researchers measured changes in energy using a special pH electrode sensor developed by William Tiller, Professor Emeritus of Materials Science and Engineering at Stanford University. These showed signal changes during Dr. Pearl's presentation that correlated with the GDV results.

We have also demonstrated that the GDV "Electrophotonic Sensor" is sensitive to geophysical environmental changes by field testing in various locations in northern Russia, Venezuela, Cambodia, Colombia, Ecuador, and England. For example, in Novosibirsk, Russia, during an August 1, 2008 solar eclipse, six "Electrophotonic Sensor" devices positioned in different locations of the region recorded statistically significant differences ($p < 0.00001$) in signal strength during different phases of the eclipse. Figure 12.11 shows the signal from one of the devices, with the arrow signifying the moment of a complete eclipse of the sun. As can be seen, there is a marked difference in energy parameters prior to and following the eclipse.

In August 2007, our group participated in two shamanic ceremonies during a trip to Peru. One was held on the Amantani Island of Lake Titikaka, the largest lake in South America. It is situated high in the Andes Mountains and is the highest navigable lake in the world, with an elevation of over 12,500 feet. Amantini Island is considered a sacred place because it has two mountain peaks called Pachatata (Father Earth) and Pachamama (Mother Earth), both of which have ancient ruins and artifacts at the very top. The island has no electricity, cars or heavy machinery, and the 4000 residents who are engaged in agricultural activities work by hand and rely on batteries and candles for light. The ceremony was held at a clearing near the top of one of these mountains but when we turned the monitoring equipment on,

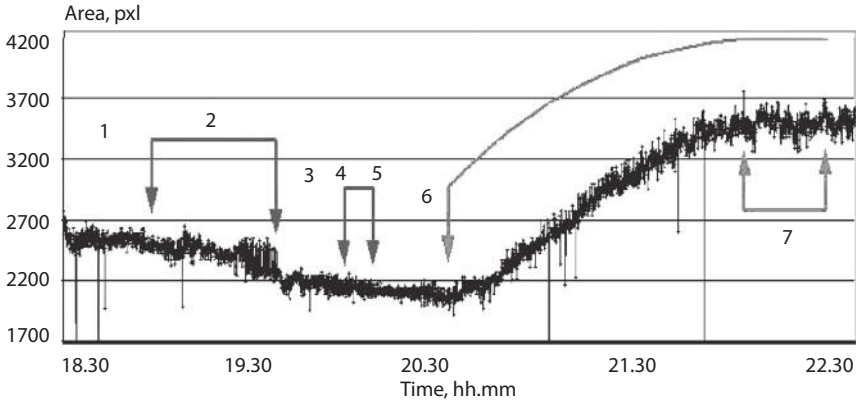

FIGURE 12.10 Time dynamics of the electrophotonic sensor area parameter for the first day of the workshop (September 12, 2008) with marked moments of interest: 1—empty room; 2—beginning of the workshop; 3—break; 4—second part of the workshop; 5—discussion; 6—Eric Pearl presentation; 7—group discussion.

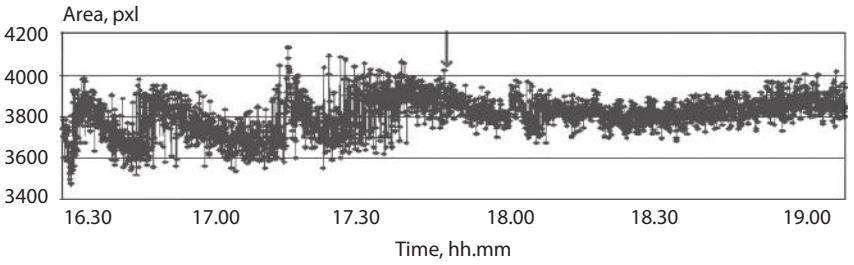

FIGURE 12.11 Time dynamics of the electrophotonic sensor area parameter before and after the eclipse of the sun in Novosibirsk, August 1, 2008.

there was no response. Further testing revealed that all the batteries were dead. This was difficult to understand, as they had all been replaced with fresh ones, were working perfectly the previous night, and the equipment had been turned off. Nevertheless, the charge had completely disappeared after we had climbed to the site where the healing ceremony was traditionally conducted.

The second shamanic ceremony was held near the Inca capital of Cusco and the ancient city of Machu Picchu on a bank of the Urubamba River, known as the *sacred river.* The Urubamba Valley through which it flows is called the "Sacred Valley of the Incas" because of its special geographical and climatic qualities and it still contains numerous archaeological remains. There was no problem with the batteries at this location but there was a dramatic and unexplained change during the ceremony, as shown in Figure 12.12.[28]

As can be seen, there was a very abrupt and sharp drop in energy 55 min after the ceremony started, which gradually returned to previous levels over the next 30 min. It is difficult to attribute these changes either to the emotions of the group or to a change in observable environmental conditions. The ceremony was held about 50 m away from the river, the weather was mild, with a slight wind was blowing, and the participants were standing at some distance from the sensor. We did not have an opportunity to replicate this phenomenon.

A similar unusual and inexplicable recording was obtained when we were investigating a curious crop circle in England. Some people believe that crop circles are formed by natural geomagnetic or electromagnetic forces that interact to form certain geometrical patterns. It is also thought that being inside a crop circle can have healing properties because they provide a source of this energy.

As noted in Figure 12.13, the energy level outside the crop circle was quite stable. In contrast, once the subject was inside the crop circle, it steadily increased throughout the entire measurement period of well over an hour.

DISCUSSION

There is widespread acknowledgment that environmental conditions can affect health, especially changes in weather. The Foehn is a dry southerly wind that blows from the Alps across Switzerland and southern Germany that is associated with a statistically significant increase in accidents, emergency room admissions for heart attacks, asthma and respiratory problems, as well as a spike in suicides. Some hospitals routinely postpone elective surgery until these "winds of depression" subside. Similar responses may accompany the Sirocco in Italy, the Mistral in southern France and the Middle East's Sharav, which the Arabs call Hamsin (the fifty days wind). Western Canada and the U.S., have the Chinook, a Foehn-like wind that raised the temperature in one Montana town by 96 degrees in less than 24 h (–48°F to 48°F). The strong, dry Santa Ana winds of California, called "The Bitter Winds" in Indian lore, have also been blamed for an increase in suicides and homicides. Some studies suggest that these effects may be due to electrical changes in the air that increase positive ions or decrease negative ions. GDV technology has the potential to confirm these observations.

All the energy on earth is derived from the sun, which continually emits a stream of charged particles. The ability of solar magnetic storms to cause mental aberrations was noted by Alexander Chizhevsky almost 100 years ago[29] and subsequent researchers have confirmed this and other effects on health.[30] The earth itself is a giant magnet that is constantly in motion. As life evolved under these influences, it should not be surprising that biological systems have developed to take advantage of electromagnetic forces, or that they can

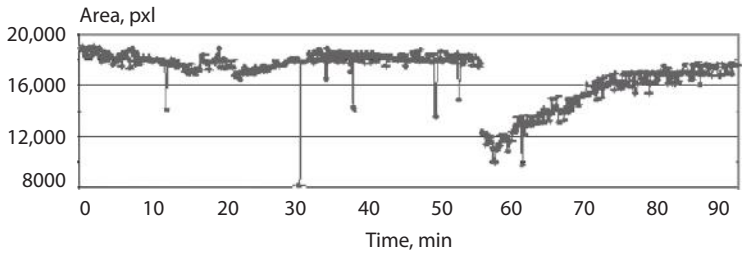

FIGURE 12.12 Time dynamics of the electrophotonic sensor area parameter during the shamanic ceremony in Peru, August 24, 2007.

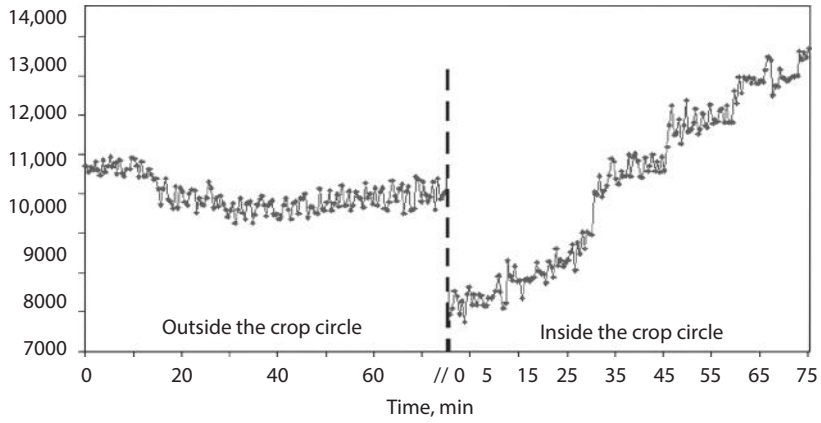

FIGURE 12.13 Time dynamics of the electrophotonic sensor area parameter outside and inside the crop circle in England.

significantly influence physiology and behavior. This can be vividly demonstrated in lower forms of life such as bacteria and planaria, but is also evident in homing pigeons and birds that use geomagnetic information to guide curious migrational habits that have persisted for centuries.

The Chinese used certain animals to predict earthquakes over 6000 years ago and there is abundant evidence that all animals can anticipate other natural disasters like storms, hurricanes and volcanic eruptions. Flamingos, elephants, wild boars, snakes, reptiles, and other animals all fled their usual habitats shortly before the 2004 Indian Ocean tsunami hit. Sharks, dolphins, and fish can also sense an approaching earthquake or hurricane well in advance. Domesticated pets may retain this ability as it has been observed that advertisements for missing cats and dogs consistently increased in volume a few days before an earthquake struck.

Some individuals also seem to be unusually sensitive to natural as well as man-made electromagnetic influences. In addition, there is increasing evidence that living things emit their own energy fields or signals that interact with these environmental forces, as well as with other forms of life. Verifying this has been difficult, because skeptics correctly demand objective proof rather than anecdotal reports. As indicated above, attempts to provide this by electrographic visualization of energy fields date back to 1777. Significant progress was made in the last century due to the efforts of the Kirlians and others, but techniques varied, results could not be consistently reproduced nor were mechanisms of action delineated. The advent of GDV technology and its sophisticated software, has now removed these impediments, and will withstand scientific scrutiny.

CONCLUSIONS

GDV technology bridges the gap between logical Western science and the intuitive science of the East. It makes it possible to present the same phenomenon in different languages, in different systems, and to look at the same phenomena from different perspectives. Experiments can be conducted in a theater, concert hall, church, auditorium, or during sporting events to record individual as well as collective emotional responses. The GDV camera and other equipment is very user friendly and, as protocols are standardized, only minimal training or experience is required to conduct a study that will provide meaningful results, because it can be compared with others. Different models can be developed to explain observations, ranging from those based on chemical and physical criteria to quantum physics and more esoteric principles, but it would be premature to attempt this now. Our top priority must be to amass a very large database of observations in different situations by researchers with diverse interests.

To facilitate this, we recently developed an inexpensive, compact GDV Bio-Well camera that will immediately display your energy level. It does not require an energy source as it is powered via a cable that connects to the USB port of a computer, therefore, it can be used anywhere by friends or family to assess energy levels and how they are affected by stress, emotions, medication, etc.[31]

Collating this information could provide important insights into mechanisms of action and/or the need for further studies in certain areas. We have only scratched the surface of GDV's vast potential, such as investigating the nature of biological (EZ) water that acts like a battery to supply energy to all cells. There is evidence that this or something very similar is present in waters from Lourdes, the Ganges river, and Hunza valley, which have long been associated with curative properties and longevity.

It should be evident from all of the above that this is still a work in progress, as there are many more questions than answers. Finding solutions will require a concerted multidisciplinary approach, and such collaborative efforts are well under way.

ACKNOWLEDGMENTS

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13 Subtle Electromagnetic Interactions in Living Things

*Abraham R. Liboff**

CONTENTS

INTRODUCTION

The meaning of the term *subtle* as in energy medicine is not quite the same as that of the adjective *weak* as used in physics. Both describe events that are difficult to explain. In one sense, weak effects can be subsumed under the more general heading of subtle energies. In another meaning, they are different, although with some overlap. One view holds that weak interactions result in effects that are not easily explained, whereas subtle effects can go unnoticed, or be quietly active. Certainly, this use of the term subtle fits Ross Adey's description[1] of interactions between cells as "whispering together." In Adey's work, one finds an attempt to explain things in established scientific ways, in terms of as-yet undiscovered science. He devoted much effort to arguing that these whispers were transmitted by soliton waves, low-energy frictionless signals that, even today, are at the forefront of theoretical physics.

Weak effects are always regarded as having some sort of scientific basis, despite the fact that this basis may be obscure. Subtle effects can be much more open-ended, allowing for explanations that perhaps are outside our ken or difficult to probe in the laboratory. The large and varied nature of thinking, stretching across the many cultures that contribute to the concept of subtle energies, ranging from Ayurvedic medicine to *Qigong* healers, is a tribute to the powers of human rationalism, the notion that everything is connected. In sharp contrast, explanations of weak interactions are severely constrained to what is scientifically credible. The greatest similarity in these two areas, that which also provides the basis for most of the criticism, is that extraordinarily small energies are obviously at play.

WEAK ELECTRIC AND MAGNETIC EFFECTS IN BIOLOGY

In the present work, we accept the view that there must exist a reasonable scientific explanation for subtle energy observations, no less than one anticipates answers to the questions underlying weak low-frequency electromagnetic biological interactions.

It is now accepted (i.e., Food and Drug Administration-approved) medical practice to employ weak electric and magnetic fields in the repair of bony nonunions, an orthopedic problem where bone fractures resist normal self-repair.[2] The current levels employed in this process are remarkably small. In the very first successful attempt to save a 14-year-old's tibia, we[3] used a simple 1.5 V dry cell to deliver between 1 and 2 μA to the defect. Although this current seems incredibly small, the remarkable fact is that even smaller currents, on the order of tens of nA, were successfully used by Yasuda[4] in exploring such effects in living bone. It is important to realize that even today, many decades later, that there is no credible physical explanation for the positive therapeutic effects obtained using this procedure. It is a fact that these clinical procedures on bone make use of electrical currents so small that they appear to be in violation of existing physical law.

Even 40 years ago while working in this area, it was rather clear that the energies employed to achieve profound biological changes were miniscule, far below any reasonable estimate of what might be expected to interact with tissue. We were fortunate enough to take part in a similar realization in the 1980s when laboratory after laboratory reported that very small magnetic fields, in the order of a few μT, were capable of affecting biological systems. Again, as in the case of bone, it was not difficult to show that these results were energetically impossible, that they violated existing physical law. Incredibly, these observations were later underscored by Zhadin[5] who gave convincing evidence, extensively replicated, that fields as low as 40 nT were also interactive, even though these were fully 100 times less than the earlier values which had already been labeled as impossibly interactive by theoreticians. Because magnetic energies scale as the square, this 100-fold reduction in field amounted to a 10,000-fold reduction in energy.

This impossibility in the form of an energy deficit created a climate of disbelief that led many to simply dismiss out of

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hand relevant laboratory observations. However, the careful scientist will always consider that which is different, no matter how outlandish and bizarre. Only those lacking imagination or historical perspective will reject without thinking that which he or she finds unfamiliar. The exercise of science is, by definition, equivalent to the exploration of new ideas.

Many theoretical attempts have been made to explain these "unreasonable results" showing that very weak electromagnetic fields do interact with living things. To date, the best approach has been that of Emilio Del Giudice[6] utilizing the techniques of quantum electrodynamics (QED). One of the most interesting things about this theoretical work is that it directly involves the physical properties of water. Independently, there is abundant evidence showing that biological contained water,[7] ubiquitous in living things, is structurally distinct from the water we learn about in college chemistry. Many now agree that this structural difference may carry great significance biologically.

The enormous output of materials given over to the idea of energy medicine has as many opinions as writers, making it sometimes difficult to properly parse this area. Interestingly, even though many different cultures are involved, the conceptual explanation is always based on energy to some degree. Ill-defined or not, whether called chi, *Qi, ki*, or even Bergson's *elan vitale*, this energy is felt to accompany the living state in much the same way. Certainly, as evidenced by its ubiquity and historical longevity this is a powerful concept, followed no less today than it has been for thousands of years.

One of the more difficult aspects of energy medicine is trying to bridge the transition between what many think of as spiritual and what may be physical. This sort of transition was examined by the eighteenth century philosopher August Comte, who argued that humans produce science by rationalizing the unknown. In a more general way, we maintain that there is a historical sequence that over time proceeds from magic to religion to science. In energy medicine, one finds elements that are contained in all these stages. Our opinion is that wide scale acceptance of subtle energy medicine is predicated on suppressing the spiritual and instead finding its scientific basis. The mystery of life may require a very special explanation, but this is not necessarily something above scientific categorization.

Our thinking is that electricity and magnetism is fundamental to our understanding of the living state. This follows the approach taken at the University of Bologna in the years following the famous experiments involving frog by Volta and Galvani. In the early nineteenth century, Carlos Matteucci discovered what was later referred to as "currents of injury," wherein he found that injured tissues created an electrical current that disappeared with the healing process. More than a 100 years later, Robert O. Becker followed up on these experiments, discovering that one could mimic nature by application of external electrical applications, specifically obtaining regrowth of amputated tissues by means of applied electric fields.[8] Between Matteucci and Becker there was a train of investigators that explored this fascinating area: Lund, Brown, Burr, Athenstaedt, Jaffe, and others. This author attempted to synthesize this work that began with Matteucci. We hypothesized the existence of a special electromagnetic function Π to represent the living state[9] that evolves parallel with the biological characteristics that are normally considered. Most important this function is a measure of the state of the system, and thus its wellbeing, which, viewed electromagnetically, can be thought of as its optimal state.

We suggested that this function had to depend on just three things, G. the genome of the individual, **P**, the electrical polarization of the components of the organism, and a generalized but elusive function of **P**, such that $\Pi = G[\alpha(\mathbf{P}, t)]$. In this expression there is one function, α, that plays the role of the life force. In our way of thinking, this arbitrary function conceptually represents something that closely resembles chi.

In this view we see the entire organism as one electromagnetic entity, with all of its components contributing to the overall defining function Π, which itself is a product of both its genetic as well as its somatic past. Most pertinent to the present discussion, this electromagnetic view anticipates the nervous system being made more complete through its utilization of magnetic fields.

MAGNETIC CONSCIOUSNESS AND SHARED BEING

Consciousness has been described in many ways: as self-awareness, as the exercise of free will, or, by some, as that part of our thinking that is not "neuralistic," that is, explained in terms of the purely physical attributes of neurons and synapses. We define consciousness as the ability to both recognize and prescribe order, where our understanding of order encompasses a host of human attributes: thoughtfulness, mathematics, symmetry, beauty, causality, and even love.

Johnjoe McFadden,[10] looking at the question of consciousness, remarked on something that after the fact seems almost obvious. If, within the brain, a group of neuronal elements are enabled to act in synchrony, such that they all fire together, the magnetic field thereby generated may be great enough to provide a heretofore unrecognized physical basis for consciousness.

This is a fascinating suggestion. It may not be generally realized that any passage of current occurs in neurons carries with it the intrinsic generation of a magnetic field. As this current increases or as the number of adjacent currents increase, the magnetic field increases proportionally. Therefore, what was suggested was that there may be meaningful magnetic fields produced within the brain, meaningful in the sense that this field might constitute an extra physical attribute for the nervous system, one that can possibly serve as the basis for consciousness. This argument ties in very nicely with the discovery by Zhadin[5] that vanishingly small magnetic fields have biological significance. Furthermore, it happens that consideration of this idea shows that it may have potential significance for *Homo sapiens* beyond simply providing an explanation for consciousness. In the following, we speculate on two such consequences.

First, there may be a strong link between this hypothetical basis for consciousness and subtle energy medicine. The potential connection is found in two separate observations, both requiring further replication and therefore subject to possible future nullification. In the one case, it has been observed that certain resonance magnetic fields are apparently capable of reducing the pH in water (S. Grimaldi, personal communication) and in body fluids (V. Dallago, personal communication). In the other case, we note that a similar lowering of pH was reported during studies on Tiller's model of intentionalism in which a small group of observers was successful in attempting, mentally, to reduce the pH in a nearby container of water. This result should be now reconsidered and perhaps studied independently in view of these more recent claims regarding the effects of weak magnetic fields on water.

The point is that if meaningful magnetic fields are indeed produced by the brain, and if laboratory fields of comparable strength are found capable of influencing the physical properties of water, this not only provides a strong argument for intentionalism, but also goes much further, suggesting a potential basis for many of the observations reported in Eastern medicine.

The key connection between these seemingly disparate areas is found in the properties of water, not only because of its remarkable susceptibility to weak magnetic fields, but also because of the generalized, holistic role that biological water likely plays in maintaining wellness. One very interesting conclusion, therefore, is that this provides a reasonable explanation for many of the apparent "mysteries" of subtle energy medicine. The implication is that the mind, through directed external application of endogenously created magnetic fields, can influence the state of wellbeing in individuals nearby, whether implemented by healing with hands or the transmission of chi or any of the other techniques used in the practice of Eastern medicine. Thus, what has been derided by some as seemingly unscientific is lifted into the realm of scientific possibility.

There is a second consequence of having consciousness based on an endogenous generation of magnetic fields. Consider the possibilities given over to a group of nearby individuals, where each member of the group is capable of both emitting and sensing weak magnetic fields. Just as we can use our other senses to communicate, say through touch or sound, it would prove inevitable that this additional sense, this putative sense of field, would also be capable of being sensed by others. Why? Because nature would never miss such an opportunity!

Of course, merely having this shared sense is not the same as having the ability to communicate information. There is a wide gap between merely making a sound and having a language. We therefore extrapolate our hypothetical sense of magnetic field to a more inclusive use, an attribute that can be shared among nearby individuals, and one that paints a radically new property of our nervous system. We are familiar with our individual ability to hear, taste, see, and touch. We also have to recognize that the nervous system may operate on another level, acting as a single unit for a group of individuals with commonly shared magnetic efferents and afferents.

There are instances of unexplained shared behavior in animals. Certain animals may not be ordinarily social, but nevertheless will act together for their mutual benefit at certain times. One example is the phenomenon attached to birds while flocking, where hundreds, sometimes thousands of birds appear to act in unison, flying en masse to perform maneuvers that are clearly more than the sum of the parts. Coherent swarming activities are similarly observed in schools of fish.

One possible explanation for such coupled gymnastics lies in the mutual sharing of magnetic fields. Unlike all of our other sense-related abilities at communication, one based on field will allow nearly instantaneous reception. One can imagine a sort of signal locking taking place, similar to processes already purposively employed by the nervous system in individuals, for example in connection with the electroencephalogram.

What might be thought of as the human equivalent of animal swarming? Our social activities are less concerned with physical realization, as in the seasonal *zugenruhe* and flocking in birds, and much more in the verbalization of concepts and ideas. We see this in the way we adhere to certain shared precepts, whether love of country and family, religious beliefs, or political views. Shared behavior is found in mob hysteria, sadly exemplified in lynchings and in gang activities. It is clear that mutual magnetic interactions among people would put the understanding of some of our most important cultural and sociological imperatives at risk. If the rational underpinnings of human thought, as individuals, are distributed and shared by a field mechanism, many of our most intimate human interactions have to be reexamined. Our communication may not simply proceed solely by transmitting the spoken word, but more by means of the unspoken thought. In this view, the shared electromagnetic field becomes the prime cultural expression.

SUMMARY

Our central thesis is that, because ultra-weak magnetic fields are capable of increasing the concentrations of biologically contained water, it is likely that this type of interaction helps explain many, if not all, of those positive therapeutic results obtained when using either subtle energy techniques or electromagnetic medicine.

Limiting our discussion to explaining the basis for subtle energy medicine, we find that much of this work may be consistent with observations implicating biologically contained water. If we consider claims, for example, of healing that depend on the use of hands, one can imagine that the healer's hands serve as a conduit for the application of magnetic fields to the biological water in the patient's afflicted region, enhancing its local concentration, and thereby changing the local medical state.

We see that given this one assumption about our brain, that it is capable of generating magnetic fields sufficiently

large to be detected by other humans, results in implications that extend well beyond the immediate question of subtle energy medicine. There are possibilities here that are quite literally mind-boggling. We refer to this radical view of how advanced living systems interact as *Shared Being*, deliberately choosing "shared being" to describe this new concept, as opposed to "shared mind." This choice reflects our personal opinion that mind is merely an expression of being.

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14 The Energetic Heart
Biomagnetic Communication within and between People

*Rollin McCraty**

CONTENTS

INTRODUCTION

Biological Patterns Encode Information

Every cell in our body is bathed in an external and internal environment of fluctuating invisible magnetic forces.[1] It has become increasingly apparent that fluctuations in magnetic fields can affect virtually every circuit in biological systems to a greater or lesser degree, depending on the particular biological system and the properties of the magnetic fluctuations.[1,2] One of the primary ways that signals and messages are encoded and transmitted in physiological systems is in the language of patterns. In the nervous system it is well established that information is encoded in the time intervals between action potentials or patterns of electrical activity. This also applies to humoral communications. Several studies have revealed that biologically relevant information is encoded in the time interval between hormonal pulses.[3–5] As the heart secretes a number of different hormones with each contraction, there is a hormonal pulse pattern that correlates with heart rhythms. In addition to the encoding of information in the space between nerve impulses and in the intervals between hormonal pulses, it is likely that information is also encoded in the inter beat intervals of the *pressure* and *electromagnetic* waves produced by the heart. This supports Karl Pribram's proposal that low-frequency oscillations generated by the heart and body in the form of afferent neural, hormonal, and electrical patterns are the carriers of emotional information and that the higher frequency oscillations found

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in the electroencephalogram (EEG) reflect the conscious perception and labeling of feelings and emotions.[6] It is quite possible that these same rhythmic patterns can also transmit emotional information via the electromagnetic field into the environment, which can be detected by others and processed in the same manner as internally generated signals.

Detecting Bioelectromagnetic Patterns Using Signal Averaging

A useful technique for detecting synchronized activity between systems in biological systems and investigating a number of bioelectromagnetic phenomena is signal averaging. This is accomplished by superimposing any number of equal-length epochs, each of which contains a repeating periodic signal. This emphasizes and distinguishes any signal that is time-locked to the periodic signal while eliminating variations that are not time-locked to the periodic signal. This procedure is commonly used to detect and record cerebral cortical responses to sensory stimulation.[7] When signal averaging is used to detect activity in the EEG that is time-locked to the electrocardiogram (ECG), the resultant waveform is called the *heartbeat evoked potential* (Figure 14.1).

The Heartbeat Evoked Potential

In looking at heartbeat evoked potential data, it can be seen that the electromagnetic signal arrives at the brain instantaneously, while a host of different neural signals reach the brain starting about 8 ms later and continue arriving throughout the cardiac cycle. Although the precise timing varies with each cycle, the blood pressure wave arrives at the brain around 240 ms and acts to synchronize neural activity, especially the alpha rhythm. It is also possible that information is encoded in the shape (modulation) of the ECG wave itself. For example, if one examines consecutive ECG cycles, it can be seen that each wave is slightly varied in a complex manner (Figure 14.2).

The heart generates a pressure wave that travels rapidly throughout the arteries, much faster than the actual flow of blood that we feel as our pulse. These pressure waves force the blood cells through the capillaries to provide oxygen and nutrients to cells and expand the arteries, causing them to generate a relatively large electrical voltage. These pressure waves also apply pressure to the cells in a rhythmic fashion that can cause some of their proteins to generate an electrical current in response to this "squeeze." Experiments conducted in our laboratory have shown that a change in the brain's electrical activity can be seen when the blood pressure wave reaches the brain around 240 ms after systole.

There is a replicable and complex distribution of heartbeat evoked potentials across the scalp. Changes in these evoked potentials associated with the heart's afferent neurological input to the brain are detectable between 50 and 550 ms after the heartbeat.[8] Gary Schwartz and his colleagues at the University of Arizona believe the earlier components in this complex distribution cannot be explained by simple

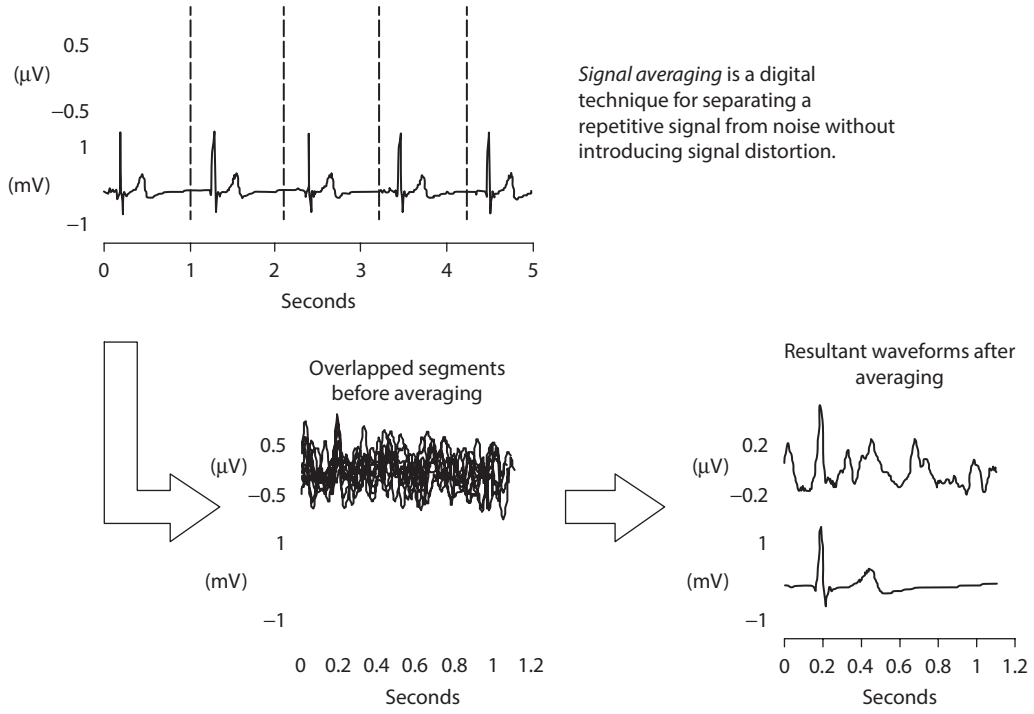

FIGURE 14.1 Signal averaging. The sequence of the signal averaging procedure is shown above. First, the signals recorded from the EEG and ECG are digitized and stored in a computer. The R-wave (peak) of the ECG is used as the time reference for cutting the EEG and ECG signals into individual segments. The individual segments are then averaged together to produce the resultant waveforms. Only signals that are repeatedly synchronous with the ECG are present in the resulting waveform. Signals not related to the signal source (ECG) are eliminated through this process.

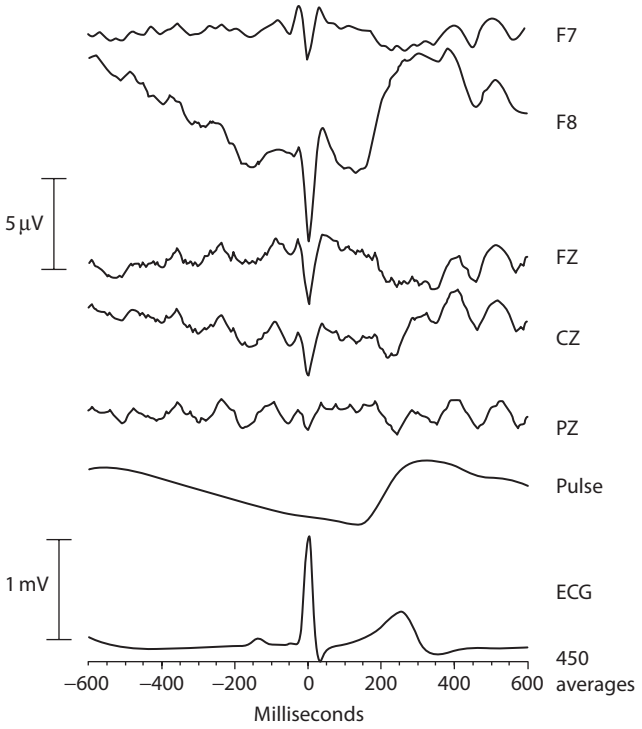

FIGURE 14.2 Heartbeat evoked potentials. This figure shows an example of typical heartbeat evoked potentials. In this example, 450 averages were used. The pulse wave is also shown, indicating the timing relationship of the blood pressure wave reaching the brain. In this example, there is less synchronized alpha activity immediately after the R-wave. The time range between 10 and 250 ms is when afferent signals from the heart are impinging upon the brain, and the alpha desynchronization indicates the processing of this information. Increased alpha activity can be clearly seen later in the waveforms, starting at around the time the blood pressure wave reaches the brain.

physiological mechanisms alone and suggest that an energetic interaction between the heart and brain also occurs.[9] They have confirmed our findings that heart-focused attention is associated with increased heart-brain synchrony, providing further support for energetic heart-brain communications.[2] Schwartz and his colleagues also demonstrated that when subjects focused their attention on the perception of their heartbeat, the synchrony in the preventricular region of the heartbeat evoked potential increased. From this they concluded that preventricular synchrony may reflect an energetic mechanism of heart-brain communication, while postventricular synchrony most likely reflects direct physiological mechanisms.

THE HEART'S ROLE IN EMOTION

Throughout the 1990s, the view that the brain and body work in conjunction in order for perceptions, thoughts, and emotions to emerge, gained momentum and is now widely accepted. The brain is an analog processor that relates whole concepts (patterns) to one another and looks for similarities, differences, or relationships between them, in contrast to a digital computer that assembles thoughts and feelings from bits of data. While some have suggested that emotions originated only in the brain, we now recognize that emotions can be more accurately described as a product of the brain and body acting in concert. Moreover, evidence suggests that of the bodily organs, the heart may play a particularly important role in emotional experience. Research in the relatively new discipline of neurocardiology has confirmed that the heart is a sensory organ and acts as a sophisticated information encoding and processing center that enables it to learn, remember and make independent functional decisions that do not involve the cerebral cortex.[10] Additionally, numerous experiments have demonstrated that patterns of cardiac afferent neurological input to the brain not only affect autonomic regulatory centers, but also influence higher brain centers involved in perception and emotional processing.[11–14]

Heart Rate Variability Patterns

Heart rate variability (HRV), derived from the ECG, is a measure of the naturally occurring beat-to-beat changes in heart rate that has proven to be invaluable in studying the physiology of emotions. The analysis of HRV, or *heart rhythms*, provides a powerful, noninvasive measure of neurocardiac function that reflects heart-brain interactions and autonomic nervous system dynamics, which are particularly sensitive to changes in emotional states.[2,15] Our research, along with that of others, suggests that there is an important link between emotions and changes in the patterns of both efferent (descending) and afferent (ascending) autonomic activity.[12,15–17] These changes in autonomic activity are associated with dramatic changes in the *pattern* of the heart's rhythm that often occur without any change in the *amount* of heart rate variability. Specifically, we have found that during the experience of negative emotions such as anger, frustration or anxiety, heart rhythms become more erratic and disordered, indicating less synchronization in the reciprocal action that ensues between the parasympathetic and sympathetic branches of the autonomic nervous system (ANS).[17] In contrast, sustained positive emotions, such as appreciation, love or compassion, are associated with highly ordered or *coherent* patterns in the heart rhythms, reflecting greater synchronization between the two branches of the ANS and a shift in autonomic balance toward increased parasympathetic activity[15–19] (Figure 14.3).

COHERENCE

The various concepts and measurements embraced under the term coherence have become central to fields as diverse as quantum physics, cosmology, physiology, and brain and consciousness research. Coherence has several related definitions, all of which are applicable to the study of human physiology, social interactions, and global affairs.

Physiological Coherence

We introduced the term *physiological coherence* to describe a number of related physiological phenomena associated

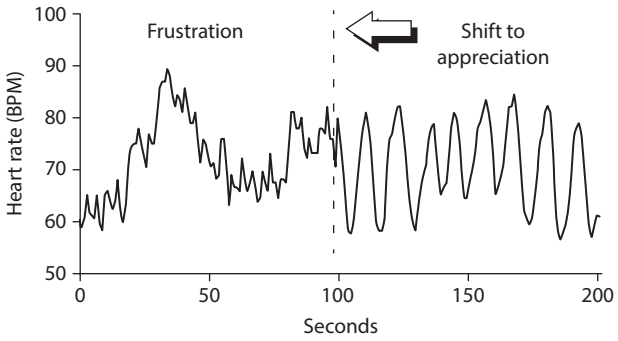

FIGURE 14.3 Emotions are reflected in heart rhythm patterns. Heart rate variability (heart rhythm) pattern of an individual making an intentional shift from a state of frustration to a genuine feeling of appreciation by using a positive emotion refocusing exercise known as the Freeze-Frame technique. It is of note that when the recording is analyzed statistically, the *amount* of heart rate variability is found to remain virtually the same during the two different emotional states; however, the *pattern* of the heart rhythm changes distinctly. Note the immediate shift from an erratic, disordered heart rhythm pattern associated with frustration to a smooth, harmonious, sine wave-like (coherent) pattern.

with more ordered and harmonious interactions among the body's systems.[20] The term *coherence* has several related definitions. A common definition of the term is "the quality of being logically integrated, consistent, and intelligible," as in a coherent argument. In this context, thoughts and emotional states can be considered "coherent" or "incoherent" as different emotions are clearly associated with different degrees of coherence in the oscillatory rhythms generated by the body's various systems. Thus, we use the term *physiological coherence* to describe the degree of order, harmony, and stability in the various rhythmic activities within living systems over any given time period. This harmonious order signifies a coherent system whose efficient or optimal function is directly related to the ease and flow in life processes. By contrast, an erratic, discordant pattern of activity denotes an incoherent system whose function reflects stress and inefficient utilization of energy in life processes.

The term "coherence" is used in physics to describe the ordered or constructive distribution of power within a waveform. The more stable the frequency and shape of the waveform, the higher the coherence. An example of a coherent wave is the sine wave. The term *autocoherence* is used to denote this kind of coherence. In physiological systems, this type of coherence describes the degree of order and stability in the rhythmic activity generated by a single oscillatory system. Methodology for computing coherence has been published elsewhere.[15]

Coherence is also used to describe the coupling and degree of synchronization between different oscillating systems. In some cases, where two or more oscillatory systems operate at the same basic frequency, they can become either phase or frequency-locked as occurs between the photons in a laser. This type of coherence is called cross-coherence and is the type of coherence that most scientists think of when they use the term. In physiology, cross-coherence occurs when two or more of the body's oscillatory systems, such as respiration, heart rhythms and blood pressure rhythms, become entrained and operate at the same frequency.

Global Coherence

There are also many examples in physiology where synchronized activity occurs across different time scales, which is characteristic of a globally coherent system. The brain rhythms operate over a wide range of frequencies, yet most of these exhibit various degrees of synchronized activity with the heart, which has much slower rhythms than the brain. Global coherence does not mean that all the parts are doing the same thing simultaneously. In complex globally coherent systems, such as human beings, there is an incredible amount of activity at every level of magnification or scale that spans more than two thirds of the 73 known octaves of the electromagnetic spectrum. It can appear at one level of scale that a given system is operating autonomously, yet it is perfectly coordinated within the whole. If this were not the case, it would be a free-for-all among the body's independent systems, rather than a coordinated federation of interdependent systems and functions. Biologist Mae-Won Ho has suggested that coherence is the defining quality of living systems and accounts for their most characteristic properties, such as long range order and coordination, rapid and efficient energy transfer, and extreme sensitivity to specific signals.[21]

All the above definitions apply to the study of bioelectromagnetism's role in physiology, energetic level interconnectivity in social settings and between people and the earth's electromagnetic field environment. We have found that positive emotions are associated with a higher degree of coherence *within* the heart's rhythmic activity (autocoherence) as well as increased coherence *between* different oscillatory systems (cross-coherence/entrainment).[2,15] Typically, entrainment is observed between heart rhythms, respiratory rhythms, and blood pressure oscillations. However, other biological oscillators, including very low frequency brain rhythms, craniosacral rhythms, electrical potentials measured across the skin, and, most likely, rhythms in the digestive system, can also become entrained.[2]

We have also demonstrated that physiological coherence is associated with increased synchronization between the heartbeat (ECG) and alpha rhythms in the EEG. In experiments measuring heartbeat evoked potentials, we found that the brain's alpha activity (8–12 Hertz frequency range) is naturally synchronized to the cardiac cycle. However, when subjects used a positive emotion refocusing technique to consciously self-generate feelings of appreciation, their heart rhythm coherence significantly increased as did the ratio of the alpha rhythm that was synchronized to the heart.[2,22]

Resonance

Another related phenomenon associated with physiological coherence is *resonance*. In physics, resonance refers to

a phenomenon whereby an unusually large vibration is produced in a system in response to a stimulus whose frequency is identical or nearly identical to the natural vibratory frequency of the system. The frequency of the vibration produced in such a state is said to be the *resonant frequency* of the system. When the human system is operating in the coherent mode, increased synchronization occurs between the sympathetic and parasympathetic branches of the ANS, and entrainment between the heart rhythms, respiration and blood pressure oscillations is observed. This occurs because these oscillatory subsystems are all vibrating at the resonant frequency of the system. Most models show that the resonant frequency of the human cardiovascular system is determined by the feedback loops between the heart and brain.[23,24]

Heart rhythm coherence and resonance are reflected in the HRV power spectrum as a large increase in power in the low frequency (LF) band (typically around 0.1 Hz, which is equivalent to a 10 s rhythm) and a decrease in power in the very low frequency (VLF) and high frequency (HF) bands. A coherent heart rhythm can therefore be defined as a relatively harmonic (sine-wave-like) signal with a very narrow, high-amplitude peak in the LF region of the HRV power spectrum with no major peaks in the VLF or HF regions.

Coherence at the Social and Global Levels

Social coherence relates to pairs, family units, groups or larger organizations in which a network of relationships exists among individuals who share common interests and objectives. Social coherence is reflected as a stable, harmonious alignment of relationships which allows for the efficient flow and utilization of energy and communication required for optimal collective cohesion and action. There are of course cycles and variations in the quality of family, team or group coherence, similar to variations in an individual's coherence level. Coherence requires that group members are attuned and emotionally aligned, and that the group's energy is globally organized and regulated by the group as a whole. Group coherence involves the same principles of global coherence described in the introduction to this paper, but in this context it refers to the synchronized and harmonious order in the relationships between and among the individuals rather than the systems within the body. The principles, however, remain the same; in a coherent team there is freedom for the individual members to do their part and thrive while maintaining cohesion and resonance within the group's intent and goals. Anyone who has watched a championship sports team or experienced an exceptional concert knows that something special can happen in groups that transcends their normal performance. It seems as though the players are in sync and communicating on an unseen energetic level. A growing body of evidence suggests that an energetic field is formed between individuals in groups through which communication among all the group members occurs simultaneously. In other words, there is a literal group "field" that connects all the members. Sociologist Raymond Bradley in collaboration with neuroscientist Karl Pribram, developed a general theory of social communication to explain the patterns of social organization common to most groups, independent of size, culture, degree of formal organization, length of existence, or member characteristics. They found that most groups have a global organization and a coherent network of emotional energetic relations interconnecting virtually all members into a single multi-level hierarchy.[25] We have found that there is a direct relationship between the heart rhythm patterns and the spectral information encoded in the frequency spectra of the magnetic field radiated by the heart. Thus, information about a person's emotional state is encoded in the heart's magnetic field that is communicated throughout the body and into the external environment. In essence, it appears that a bioenergetic communication system may indeed exist that serves to inform function and behavior in highly coherent groups.[26]

Humans are embedded within social networks that exist on the earth, which is part of the solar system. Therefore, it should not be surprising that human physiological rhythms and global behaviors are synchronized with solar and geomagnetic activity.[27,28] Energetic influxes from solar and geomagnetic fields have been associated with numerous aspects of human health and wellness, both positively and negatively. The Global Coherence Initiative (GCI), which is discussed in a separate chapter in this book, is focused on examining the interactions between humans and the earth's energetic fields.

In summary, we use coherence as an umbrella term to describe a physiological mode that encompasses entrainment, resonance, synchronization, social cohesion, and globally connected complex systems. Correlates of physiological coherence include increased synchronization between the two branches of the ANS, a shift in autonomic balance toward increased parasympathetic activity, increased heart-brain synchronization, increased vascular resonance, and entrainment between diverse physiological oscillatory systems.

Benefits of Coherence

Coherence confers a number of benefits to the system in terms of both physiological and psychological functioning. Practicing certain techniques that increase physiological coherence is associated with both short-term and long-term improvement in several objective health-related measures, including enhanced humoral immunity[29,30] and an increased DHEA/cortisol ratio.[19]

Increased physiological coherence is similarly associated with psychological benefits, including improvements in cognitive performance and mental clarity as well as increased emotional stability and well-being.[2,31] Studies conducted in diverse populations have documented significant reductions in stress and negative affect and increases in positive mood and attitudes in individuals using coherence-building techniques.[18,19,30–32]

Improvements in clinical status, emotional well-being and quality of life have also been demonstrated in various medical patient populations in intervention programs using coherence-building approaches. For example, significant blood pressure reductions have been demonstrated

in individuals with hypertension[33–35], improved functional capacity and reduced depression in congestive heart failure patients,[36] improved psychological health and quality of life in patients with diabetes,[37] and improvements in asthma.[38] Another study reported reductions in pathological symptoms and anxiety and significant improvements in positive affect, physical vitality, and general well-being in individuals with HIV infection and AIDS.[34,35,39,40]

Increasing Coherence

Although physiological coherence is a natural state that can occur spontaneously during sleep and deep relaxation, sustained episodes during normal daily activities are generally rare. While specific rhythmic breathing methods can induce coherence for brief periods, paced breathing is difficult for many people to maintain. Conversely, our findings indicate that individuals can produce extended periods of physiological coherence by actively generating and sustaining a feeling of appreciation or other positive emotions. Sincere positive feelings appear to excite the system at its resonant frequency, allowing the coherent mode to emerge naturally. This typically makes it easier for people to sustain a positive emotion for much longer periods, thus facilitating the process of establishing and reinforcing coherent patterns in the neural architecture as the familiar reference. Once a new pattern is established, the brain strives to maintain a match with the new program, thus increasing the probability of maintaining coherence and reducing stress, even during challenging situations.[12]

Doc Childre, founder of the Institute of HeartMath, has developed a number of practical positive emotion refocusing and emotional restructuring techniques that allow people to quickly self-generate coherence at will.[41,42] Known as the HeartMath system, these techniques utilize the heart as a point of entry into the psychophysiological networks that connect the physiological, mental, and emotional systems. In essence, because the heart is a primary generator of rhythmic neural and energetic patterns in the body, it influences brain processes that control the ANS, cognitive function and emotion. It also provides an access point from which system-wide dynamics can be quickly and profoundly affected. Research studies and the experience of numerous health care professionals indicate that HeartMath coherence-building techniques are easily learned. They have a high rate of compliance, and are highly adaptable to a wide range of demographic groups.[43,44]

Heart Rhythm Coherence Feedback

Used in conjunction with positive emotion-based coherence-building techniques, heart rhythm feedback training can be a powerful tool to assist people in learning how to self-generate increased physiological coherence.[45] We have developed a portable heart rhythm monitoring and feedback system that enables physiological coherence to be objectively monitored and quantified. Known as the emWave Pro, emWave2, and Inner Balance Trainer (HeartMath LLC, Boulder Creek, CA, USA), these interactive systems monitor and display individuals' heart rate variability patterns in real time as they practice the self-regulation techniques. Using an ear or fingertip sensor to record the pulse wave, the emWave plots changes in heart rate on a beat-to-beat basis. As people practice the coherence-building techniques, they can readily see and experience the changes in their heart rhythm patterns, which generally become more ordered, smoother, and more sine wave-like as they experience positive emotions. This process reinforces the natural association between the physiological coherence mode and positive feelings. The real-time physiological feedback essentially takes the guesswork and randomness out of the process of self-inducing a coherent state, resulting in greater consistency, focus, and effectiveness in shifting to a beneficial psychophysiological mode.

Heart rhythm coherence feedback training has been successfully used in clinical settings by physicians, and mental health professionals to facilitate health improvements in patients with numerous physical and psychological disorders.[46,47] It is also increasingly being utilized in corporate, military, law enforcement, and educational settings to enhance physical and emotional health and improve performance.[34,48,49]

BIOMAGNETIC COMMUNICATION

The first biomagnetic signal was demonstrated in 1963 by Gerhard Baule and Richard McFee in a magnetocardiogram (MCG) that used magnetic induction coils to detect fields generated by the human heart.[50] A remarkable increase in the sensitivity of biomagnetic measurements was achieved with the introduction of the Superconducting Quantum Interference Device (SQUID) in the early 1970s, and the ECG and MCG have since been shown to closely parallel one another.[51]

Biomagnetic Information Patterns

The heart generates a series of electromagnetic pulses in which the time interval between each beat varies in a complex manner. These pulsing waves of electromagnetic energy give rise to interference patterns when they interact with magnetically polarizable tissues and substances.

Figure 14.4 shows two different power spectra derived from an average of 12 individual 10 s epochs of ECG data recorded during differing psychophysiological modes. The plot on the left was produced while the subject was in a state of deep appreciation, whereas the plot on the right was generated while the subject experienced recalled feelings of anger. The difference in the patterns, and thus, the information they contain, can be clearly seen. There is a direct correlation between the patterns in the heart rate variability rhythm and the frequency patterns in the spectrum of the ECG or MCG. Experiments such as these indicate that psychophysiological information can be encoded into the electromagnetic fields produced by the heart.[15,52]

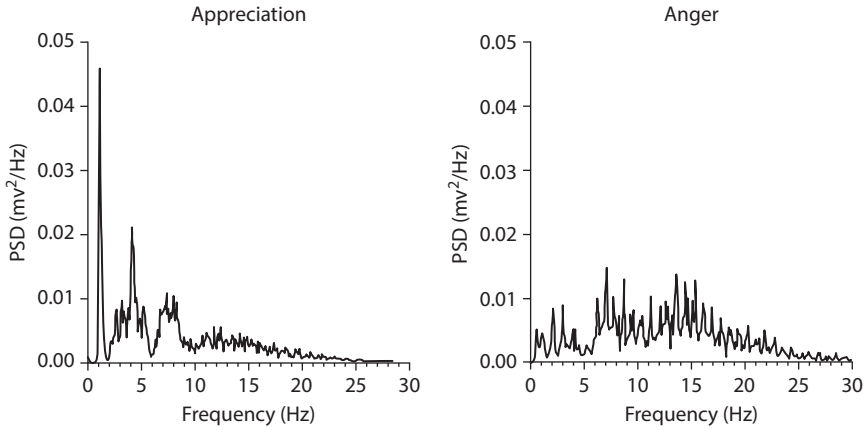

FIGURE 14.4 ECG spectra during different emotional states. The above graphs are the average power spectra of 12 individual 10 s epochs of ECG data, which reflect information patterns contained in the electromagnetic field radiated by the heart. The left-hand graph is an example of a spectrum obtained during a period of high heart rhythm coherence generated during a sustained heartfelt experience of appreciation. The graph on the right depicts a spectrum associated with a disordered heart rhythm generated during feelings of anger.

Biomagnetic Communication between People

The human body is replete with mechanisms for detecting its external environment. Sense organs, the most obvious example, are specifically geared to react to touch, temperature, select ranges of light and sound waves, etc. These organs are acutely sensitive to external stimuli. The nose, for example, can detect one molecule of gas, while a cell in the retina of the eye can detect a single photon of light. If the ear were any more sensitive, it would pick up the sound of the random vibrations of its own molecules.[53]

The interaction between two human beings, for example, the consultation between a patient and her clinician, is a very sophisticated dance that involves many subtle factors. Most people tend to think of communication solely in terms of overt signals expressed through facial movements, voice qualities, gestures and body movements. However, evidence now supports the perspective that a subtle yet influential electromagnetic or "energetic" communication system operates just below our conscious level of awareness. The following section will discuss data suggesting that this energetic system contributes to the "magnetic" attractions or repulsions that occur between individuals. It is also quite plausible that these energetic interactions can affect the therapeutic process.

The concept of energy or information exchange between individuals is central to many of the Eastern healing arts, but its acceptance in Western medicine has been hampered by the lack of a plausible mechanism to explain the nature of this "energy information" or how it is communicated. However, numerous studies investigating the effects of healers, therapeutic touch practitioners, and other individuals have demonstrated a wide range of significant effects including the influence of "energetic" approaches on wound healing rates,[54,55] pain,[56,57] hemoglobin levels,[58] conformational changes of DNA and water structure,[59,60] as well as psychological states.[61] Although these reports show beneficial results, they have been largely ignored because of the lack of any scientific rationale to explain how the effects are achieved.

Physiological Linkage and Empathy

The ability to sense what other people are feeling is an important factor in allowing us to connect or communicate effectively with others. The smoothness or flow in any social interaction depends to a great extent on the establishment of a spontaneous entrainment or linkage between individuals. When people are engaged in deep conversation, they begin to fall into a subtle dance, synchronizing their movements and postures, vocal pitch, speaking rates, and length of pauses between responses,[62] and, as we are now discovering, important aspects of their physiology can also become linked and synchronized.

Several studies have investigated different types of physiological synchronization or entrainment between individuals during empathetic moments or between clinician and patient during therapeutic sessions. One study by Levenson and Gottman at the University of California at Berkeley looked at physiological synchronization in married couples during empathetic interactions. Researchers examined couples' physiological responses during two discussions: a neutral "How was your day?" conversation, to establish a baseline, and a second conversation containing more emotional content in which the couples were asked to spend 15 min discussing something about which they disagreed. After the disagreement, one partner was asked to leave the room while the other stayed to watch a replay of the talk and identify portions of the dialogue where he or she was actually empathizing, but did not express it. Both spouses individually engaged in this procedure. Levenson was then able to identify those segments of the video where empathy occurred and match the empathetic response to physiological responses in both partners. He found that in partners who were adept at empathizing, their physiology mimicked their partner's while they

empathized. If the heart rate of one went up, so did the heart rate of the other; if the heart rate slowed, so did that of the empathic spouse.[63] Other studies observing the psychophysiology of married couples while interacting were able to predict the probability of divorce.[64] A study by Hertenstein and Keltner examined the communication of emotion via touch, and gender related differences that could be observed.[65] In a study on interpersonal effects of nonverbal compassionate communication, measuring psychophysiologic effects, Kemper and Shaltout found significant changes in the receiver's autonomic nervous system.[66]

Although studies that have examined physiological linkages between therapists and patients have suffered from methodological challenges, they do support a tendency to autonomic attunement during periods of empathy between the therapist and patient.[67] Dana Redington, a psychophysiologist at the University of California, San Francisco, analyzed heart rate variability patterns during therapist-patient interactions using a nonlinear dynamics approach. Redington and colleagues used phase space maps to plot changes in the beat-to-beat heart rate of both the therapist and patient during psychotherapy sessions. They found that the trajectories in the therapist's patterns often coincided with the patient's during moments when the therapist experienced strong feelings of empathy for the patient.[68] Carl Marci at Harvard University found evidence of a more direct linkage between patients and therapists using skin conductance measures. During sessions of psychodynamic psychotherapy, Marci observed a quantifiable fluctuation and entrainment in the pattern of physiological linkage within patient-therapist dyads, which was related to the patient's perception of the therapist's empathy. In addition, the preliminary results of his studies indicate that during low physiological linkage there are fewer empathetic comments, more incidents of incorrect interpretations, less shared affect, and fewer shared behavioral responses when compared to episodes of high physiological linkage.[69]

Energetic Communication

An important step in testing our hypothesis that the heart's electromagnetic field could transmit signals between people was to determine if the field and the information modulated within it could be detected by other individuals.

In conducting these experiments, the question being asked was straightforward. Namely, can the electromagnetic field generated by the heart of one individual be detected in physiologically relevant ways in another person, and if so, does it have any discernible biological effects? To investigate these possibilities, we used signal-averaging techniques to detect signals that were synchronous with the peak of the R-wave of one subject's ECG in recordings of another subject's EEG or brain waves. My colleagues and I have performed numerous experiments in our laboratory over a period of several years using these techniques,[70] and several examples are included below to illustrate some of these findings. In the majority of these experiments, subjects were seated in comfortable, high-back chairs to minimize postural changes with the positive ECG electrode located on the side at the left sixth rib and referenced to the right supraclavicular fossa according to the International 10–20 system. The ECG and EEG were recorded from both subjects simultaneously so that the data (typically sampled at 256 Hz or higher) could be analyzed for simultaneous signal detection in both.

To clarify the direction in which the signal flow was analyzed, the subject whose ECG R-wave was used as the time reference for the signal averaging procedure is referred to as the "signal source," or simply "source." The subject whose EEG was analyzed for the registration of the source's ECG signal is referred to as the "signal receiver," or simply "receiver." The number of averages used in the majority of the experiments was 250 ECG cycles (~4 min). The subjects did not consciously intend to send or receive a signal and, in most cases, were unaware of the true purpose of the experiments. The results of these experiments have led us to conclude that the nervous system acts as an antenna, which is tuned to and responds to the magnetic fields produced by the hearts of other individuals. My colleagues and I call this energetic information exchange *energetic communication* and believe it to be an innate ability that heightens awareness and mediates important aspects of true empathy and sensitivity to others. Furthermore, we have observed that this energetic communication ability can be enhanced, resulting in a much deeper level of nonverbal communication, understanding, and connection between people. We also propose that this type of energetic communication between individuals may play a role in therapeutic interactions between clinicians and patients that has the potential to promote the healing process.

From an electrophysiological perspective, it appears that sensitivity to this form of energetic communication between individuals is related to the ability to be emotionally and physiologically coherent. The data indicate that when individuals are in the coherent mode, they are more sensitive to receiving information contained in the fields generated by others. In addition, during physiological coherence, internal systems are more stable, function more efficiently, and radiate electromagnetic fields containing a more coherent structure.[15]

The Electricity of Touch

The first step was to determine if the ECG signal of one person could be detected in another individual's EEG during physical contact. For these experiments we seated pairs of subjects 4 feet apart, during which time they were simultaneously monitored. Figure 14.5 shows a typical example of the results.

While in most pairs a clear signal transfer between the two subjects was measurable in one direction, it was only observed in both directions simultaneously in about 30% of the pairs (i.e., Subject 2's ECG could be detected in Subject 1's EEG at the same time that Subject 1's ECG was detectable in Subject 2's EEG). As shown later, an important variable appears to be the degree of physiological coherence maintained.

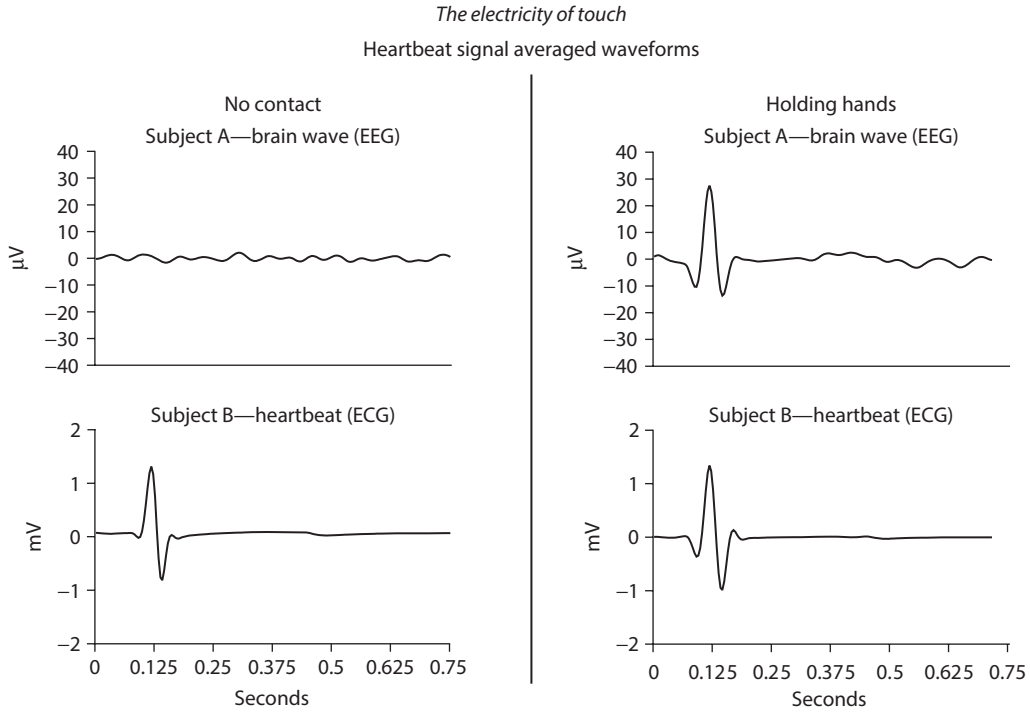

FIGURE 14.5 Signal averaged waveforms showing the detection of electromagnetic energy generated by the source's heart in the receiving subject's EEG. The baseline recording (left side) is from a 10 min period during which time the subjects were seated 5 feet apart without physical contact. The right column shows the recording from the 5 min period during which the subjects held hands. The EEG data shown here were recorded from the C3 site of the EEG.

After demonstrating that the heart's activity could be detected in another's EEG during physical contact, we completed a series of experiments to determine if the signal was transferred via electrical conduction alone or if it was also energetically transferred via magnetic fields. The results suggest that a significant degree of signal transfer occurs through skin conduction, however is also radiated between individuals.[71]

The possibility exists that in some cases the signal appearing in the receiving subject's recordings could be the receiver's own ECG rather than that of the other subject. Given the signal averaging procedure employed, this could only occur if the source's ECG was continually and precisely synchronized with the receiver's ECG. To definitively rule this out, the data in all experiments were checked for this possibility.

Simultaneously and independently, Russek and Schwartz at the University of Arizona conducted similar experiments in which they were also able to demonstrate the detection of an individual's cardiac signal in another's EEG recording in two people sitting quietly, without physical contact.[72]

Heart-Brain Synchronization during Nonphysical Contact

As the magnetic component of the field produced by the heartbeat is radiated outside the body and can be detected several feet away with SQUID-based magnetometers,[73,74] we further tested the transference of signals between subjects who were not in physical contact. In these experiments, the subjects were either seated side by side or facing each other at varying distances. In some cases, we were able to detect a clear QRS-shaped signal in the receiver's EEG, but not in others. Although the ability to obtain a clear registration of the ECG in the other person's EEG declined as the distance between subjects was increased, the phenomenon appears to be nonlinear. For instance, a clear signal could be detected at a distance of 18 inches in one session, but was undetectable in the very next trial at a distance of only 6 inches. Although transmission of a clear QRS-shaped signal is uncommon at distances over 6 inches in our experience, physiologically relevant information is clearly communicated between people at much further distances, and is reflected in synchronized activity.

Figure 14.6 shows the data from two subjects seated facing one another at a distance of 5 feet, with no physical contact. The subjects were asked to use the Heart Lock-In technique,[41] that has clearly been shown to produce sustained states of physiological coherence.[19] There was no intention to "send energy" and participants were not aware of the purpose of the experiment. The top three traces show the signal-averaged waveforms derived from the EEG locations along the medial line of the head.

Note that in this example, the signal averaged waveforms do not contain any semblance of the QRS complex shape as seen in the physical contact experiments; rather they reveal the occurrence of an alpha wave synchronization in the EEG of one subject that is precisely timed to the R-wave of the other subject's ECG. Power spectrum analysis of the signal

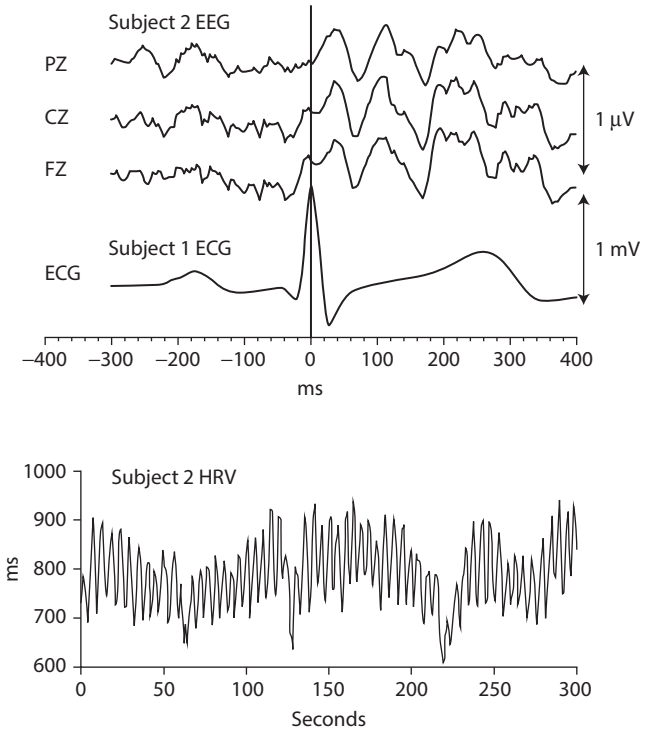

FIGURE 14.6 Heart-brain synchronization between two people. The top three traces are Subject 2's signal averaged EEG waveforms, which are synchronized to the R-wave of Subject 1's ECG. The lower plot shows Subject 2's heart rate variability pattern, which was coherent throughout the majority of the record. The two subjects were seated at a conversational distance without physical contact.

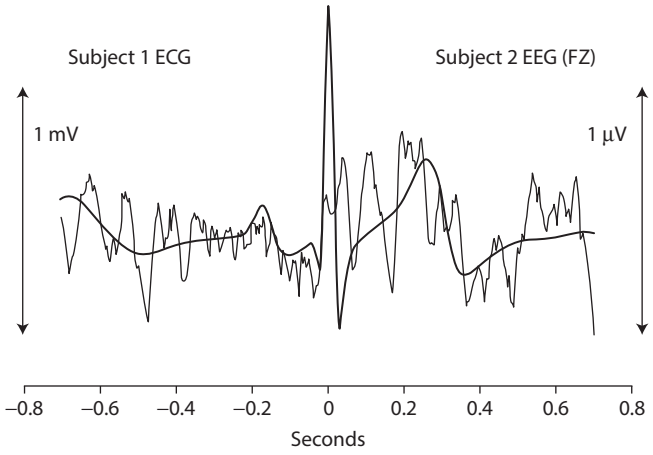

FIGURE 14.7 Overlay of signal averaged EEG and ECG. This graph is an overlay plot of the same EEG and ECG data shown in Figure 14.6. Note the similarity of the wave shapes, indicating a high degree of synchronization.

averaged EEG waveforms showed that the alpha rhythm was synchronized to the other person's heart. This alpha synchronization does not imply that there is increased alpha activity, but it does show that the existing alpha rhythm is able to synchronize to extremely weak external electromagnetic fields such as those produced by another person's heart. It is well known that the alpha rhythm can synchronize to an external stimulus such as sound or light flashes, but the ability to synchronize to such a subtle electromagnetic signal is surprising. As mentioned, there is also a significant ratio of alpha activity that is synchronized to one's own heartbeat, and the amount of this synchronized alpha activity is significantly increased during periods of physiological coherence.[2,22]

Figure 14.6 shows an overlay plot of one of Subject 2's signal averaged EEG traces and Subject 1's signal averaged ECG. This view shows an amazing degree of synchronization between the EEG of Subject 2 and Subject 1's heart. These data show that it is possible for the magnetic signals radiated by the heart of one individual to influence the brain rhythms of another. In addition, this phenomenon can occur at conversational distances (Figure 14.7).

Energetic Sensitivity and Empathy

Figure 14.8 shows the data from the same two subjects during the same time period, only it is analyzed for alpha synchronization in the opposite direction (Subject 1's EEG and Subject 2's ECG). In this case, we see that there is no observable synchronization between Subject 1's EEG and Subject 2's ECG. The key difference between the data shown in Figure 14.6 and Figure 14.8 is the high degree of physiological coherence maintained by Subject 2. In other words, the degree of coherence in the *receiver's* heart rhythms

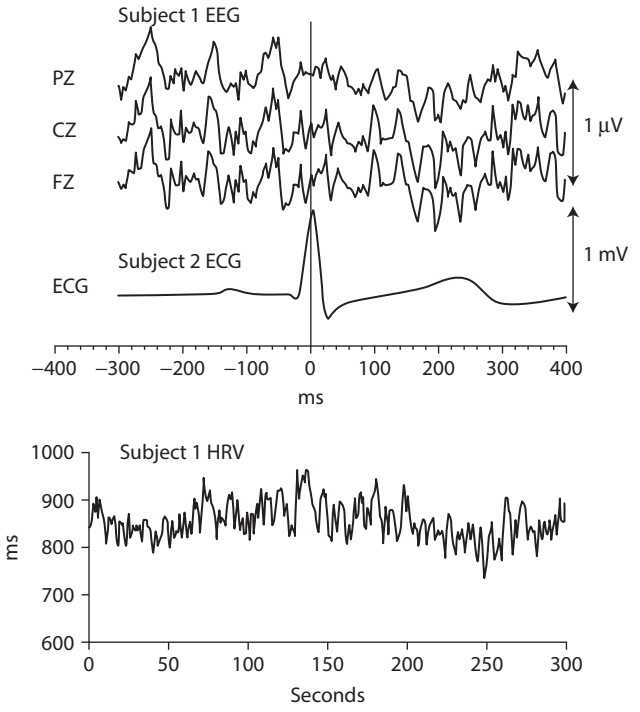

FIGURE 14.8 The top three traces are the signal averaged EEG waveforms for Subject 1. There is no apparent synchronization of Subject 1's alpha rhythm to Subject 2's ECG. The bottom plot is a sample of Subject 1's heart rate variability pattern, which was incoherent throughout the majority of the record.

appears to determine whether his/her brainwaves synchronize to the other person's heart.

This suggests that when one is in a physiologically coherent mode, one exhibits greater sensitivity in registering the electromagnetic signals and information patterns encoded in the fields radiated by the hearts of other people. At first glance the data may be interpreted that we are more vulnerable to the potential negative influence of incoherent patterns radiated by those around us. In fact, the opposite is true. When people are able to maintain the physiological coherence mode, they are more internally stable and thus less vulnerable to being negatively affected by the fields emanating from others. It appears that it is the increased internal stability and coherence that allows for the increased sensitivity to emerge.

This fits quite well with our experience in training thousands of individuals in how to self-generate and maintain coherence while they are communicating with others. Once individuals learn this skill, it is a common experience that they become much more attuned to other people and are able to detect and understand the deeper meaning behind spoken words. They are often able to sense what someone else really wishes to communicate even when the other person may not be clear about that which he is attempting to say. This technique, called Coherent Communication, helps people to feel fully heard and promotes greater rapport and empathy between people.[75]

Our data are also relevant to Russek and Schwartz's findings that people, who are more accustomed to experiencing positive emotions, such as love and care, are better receivers of energetic signals from others.[76] In their follow-up study of 20 college students, those who had rated themselves as having been raised by loving parents exhibited significantly greater registration of an experimenter's ECG in their EEG than others who had perceived their parents as less loving. Our findings, which show that positive emotions such as love, care, and appreciation are associated with increased physiological coherence, suggest the possibility that the subjects in Russek and Schwartz's study had higher ratios of physiological coherence, which could explain the greater registration of cardiac signals.

Heart Rhythm Synchronization between People

When heart rhythms are more coherent, the electromagnetic field that is radiated outside the body correspondingly becomes more organized, as shown in Figure 14.4. The data presented thus far indicate that signals and information can be communicated energetically between individuals, but so far have not implied a literal synchronization of two individuals' heart rhythm patterns. We have found that synchronization of heart rhythm patterns between individuals is possible, but usually occurs only under very specific conditions. In our experience, true heart rhythm synchronization between individuals is very rare during normal waking states. We have found that individuals who have a close working or living relationship are the best candidates for exhibiting this type of synchronization. Figure 14.9 shows an example of heart rhythm synchronization between two women who have a close working relationship and practice coherence-building techniques regularly. For this experiment, they were seated 4 feet apart, and, although blind to the data, were consciously focused on generating feelings of appreciation for each other.

A more complex type of synchronization can also occur during sleep. Although we have only looked at couples who are in long-term stable and loving relationships, we have been surprised at the high degree of heart rhythm synchrony observed in these couples while they sleep. Figure 14.10 shows an example of a small segment of data from one couple. These data were recorded using an ambulatory ECG recorder with a modified cable harness that allowed the concurrent recording of two individuals on the same recording.

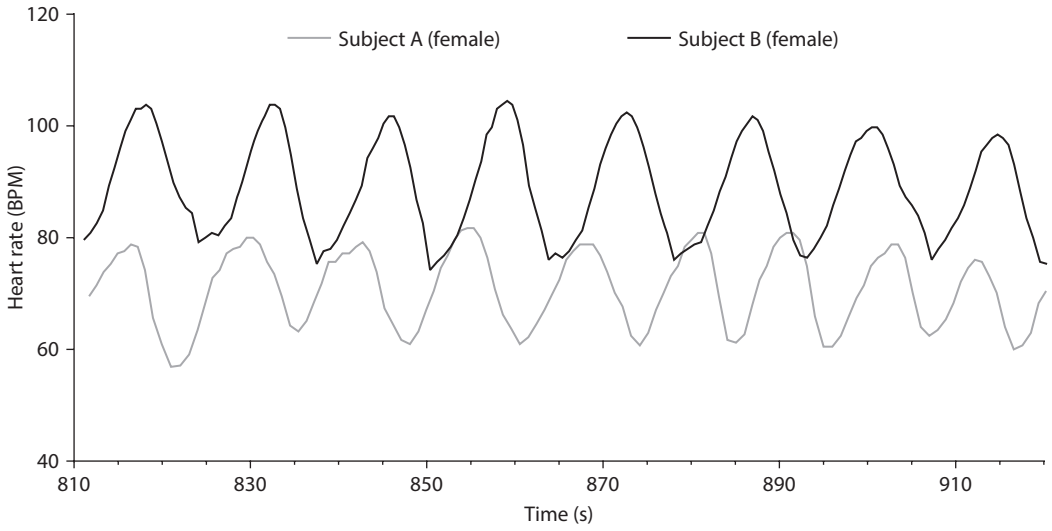

FIGURE 14.9 Heart rhythm entrainment between two people. These data were recorded while both subjects were practicing the Heart Lock-In technique and consciously feeling appreciation for each other. It should be emphasized that in typical waking states, entrainment between people such as in this example is rare.

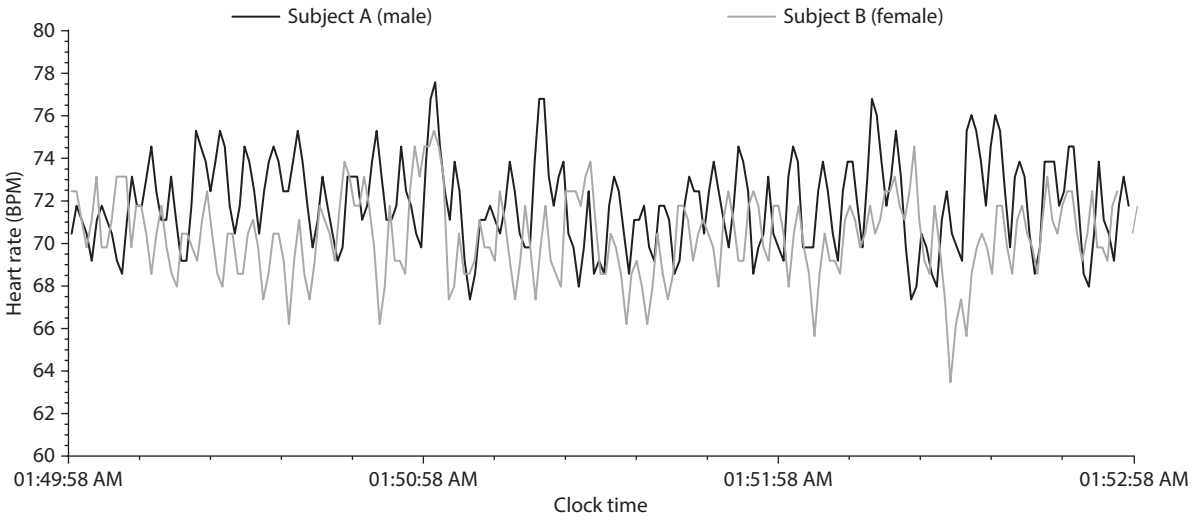

FIGURE 14.10 Heart rhythm entrainment between husband and wife during sleep.

Note how the heart rhythms simultaneously change in the same direction and how heart rates converge. Throughout the recording, clear transition periods are evident in which the heart rhythms move into greater synchronicity for some time, and then drift out again. This implies that unlike in most wakeful states, synchronization between the heart rhythms of individuals can and does occur during sleep.

Another line of research that has shown physiological synchronization between people was in a study of a 30-min long Spanish fire-walking ritual. Heart rate data was obtained from 38 participants and synchronized activity was compared between fire-walkers and spectators. They showed fine-grained commonalities of arousal during the ritual between firewalkers and related spectators but not unrelated spectators. The authors concluded that their findings demonstrated that a collective ritual can evoke synchronized arousal over time between active participants and relatives or close friends. They also suggest that the study links field observations to a physiological basis and offers a unique approach for the quantification of social effects on human physiology during real-world interactions and that mediating mechanism may be informational.[77]

Morris[26] studied the effect of heart coherence in a group setting with 15 participants who were trained in HeartMath's Quick Coherence® Technique. He conducted 148 10-minute trials in which three trained participants were seated around a table with one untrained participant. During each trial, three of the trained participants were placed with one of 25 untrained volunteers to determine whether the three could collectively facilitate higher levels of HRV in the untrained individual. The coherence of the HRV of the untrained subject was found to be higher in approximately half of all matched comparisons when the trained participants focused on achieving increased coherence. In addition, evidence of heart rhythm synchronization between group participants was revealed through several evaluation methods and higher levels of coherence correlated to higher levels of synchronization between participants and there was a statistical relationship between this synchronization and relational measures (bonding) among the participants. The authors concluded that "evidence of heart-to-heart synchronization across subjects was found which lends credence to the possibility of heart-to-heart bio-communications."

Using signal averaging techniques, we were also able to detect synchronization between a mother's brainwaves (EEG-CZ) and her baby's heartbeats (ECG). The pair was not in physical contact, but when the mother focused her attention on the baby, her brainwaves synchronized to the baby's heartbeats. We were not able to detect that the infants EEG synchronized to the mother's heartbeats (Figure 14.11).

Biomagnetic Communication between People and Animals

Farmers and attentive observers know that most cattle and sheep, when grazing, face the same way. It has been demonstrated by means of satellite images, field observations, and

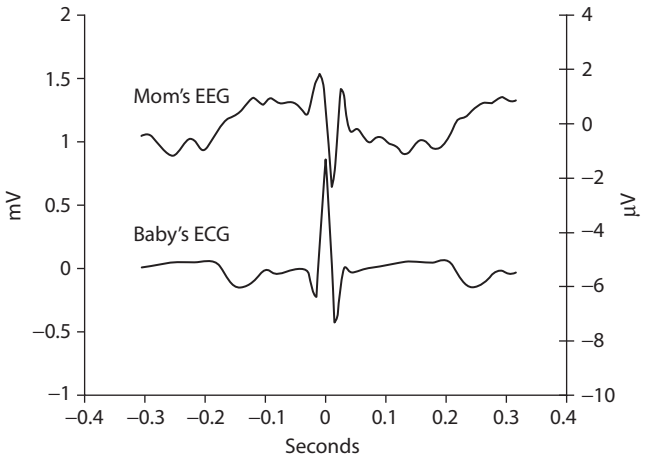

FIGURE 14.11 ECG and EEG synchronization between mother and baby.

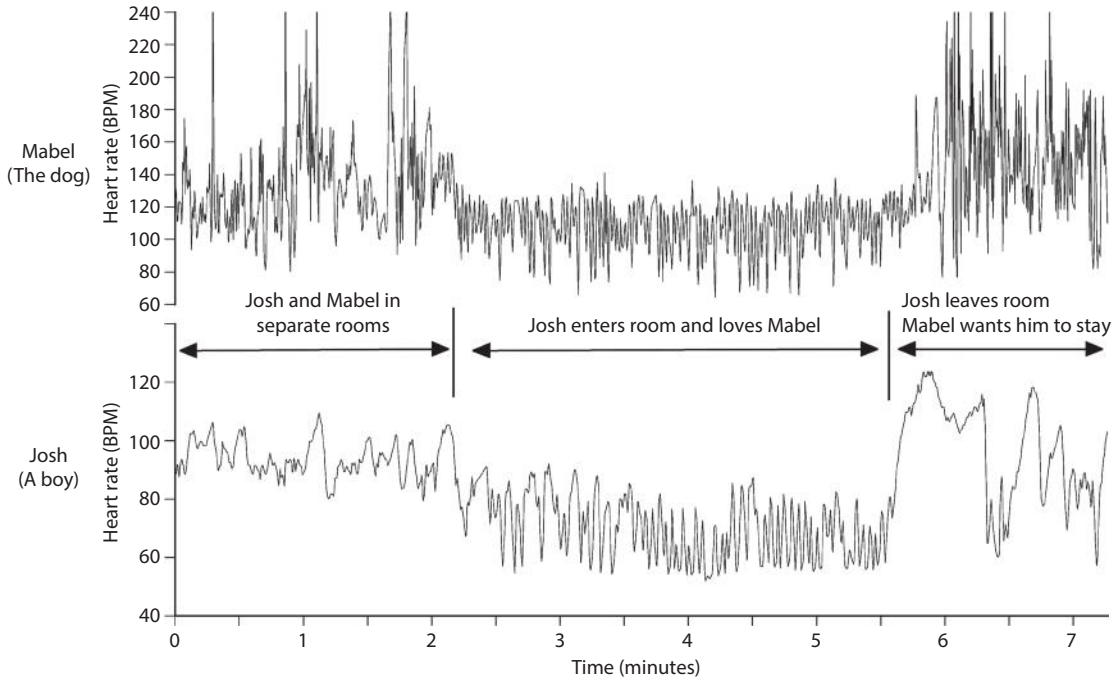

FIGURE 14.12 Heart rhythm patterns of a boy and his dog. These data were obtained using ambulatory ECG recorders fitted on both Josh, a young boy, and Mabel, his pet dog. When Josh entered the room where Mabel was waiting and consciously felt feelings of love and care towards his pet, his heart rhythms became more coherent and this change appears to have influenced Mabel heart rhythms, which clearly shifted to a more coherent rhythm. When Josh left the room, Mabel's heart rhythms became much more chaotic and incoherent, suggesting separation anxiety!

measuring "deer beds" in snow that domestic cattle across the globe, and grazing and resting red and roe deer, align their body axes in roughly a north–south direction and orient their heads northward when grazing or resting. Wind and light conditions were excluded as a common determining factor and magnetic alignment with the earth's geomagnetic field was determined to be best explanation. Magnetic north was a better predictor than geographic north suggesting large mammals have magnetoreception capability.[78]

We have also found that a type of heart rhythm synchronization can occur in interactions between people and their pets. Figure 14.10 shows the results of an experiment looking at the heart rhythms of my son Josh (12 years old at the time of the recording) and his dog, Mabel. Here we used two Holter recorders, one fitted on Mabel and the other on Josh. We synchronized the recorders and placed Mabel in one of our labs. Josh then entered the room and sat down and proceeded to do a Heart Lock-In and consciously radiate feelings of love towards Mabel. There was no physical contact nor did he make any attempts to obtain the dog's attention. Note the synchronous shift to increased coherence in the heart rhythms of both Josh and Mabel as Josh consciously feels love for his pet (Figure 14.12).

Another example of an animal's heart rhythm pattern shifting in response to a human's shift of emotional states is shown in Figure 14.13. This was a collaborative study with Ellen Gehrke, who consciously shifted into a coherent state, as she sat in a corral with her horse, without touching or petting it. When she shifted into a coherent state, the horse's heart rhythm pattern also shifted to a more ordered pattern. Very similar shifts in the horses HRV patterns were seen in three out of four horses' heart rhythms. The one horse that

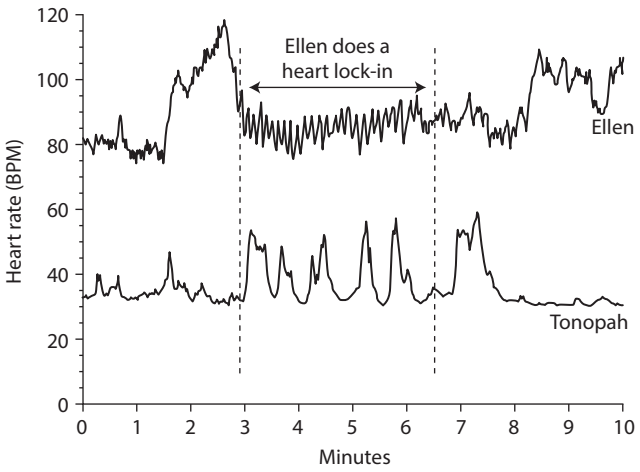

FIGURE 14.13 Heart rhythm patterns of woman and horse. These data were obtained using ambulatory ECG recorders fitted on both Ellen and Tonopah, her horse. When she did a Heart lock-In, her heart rhythms became more coherent and this change appears to have influenced the horse's heart rhythms.

did not show any response was well known for not relating well to humans or to other horses.

CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE

Bioelectromagnetic communication is a real phenomenon that has numerous implications for physical, mental, and emotional health. This chapter has focused on the proposition that increasing the coherence within and between the body's endogenous bioelectromagnetic systems can increase physiological and metabolic energy efficiency, promote mental and emotional stability, and provide a variety of health and social harmony benefits. It is further proposed that many of the benefits of increased physiological coherence will ultimately prove to be mediated by processes and interactions occurring at the electromagnetic or energetic level of the organism.

With the many physiological and psychological benefits that increased coherence appears to offer, helping patients learn to self-generate and sustain this psychophysiological mode with increased consistency in their day-to-day lives provides a new strategy for clinicians to assist their patients on multiple levels. There are several straightforward ways to help patients increase their physiological coherence. Teaching and guiding them in the practice of positive emotion refocusing and emotional restructuring techniques in conjunction with heart rhythm feedback has proved to be a simple and cost-effective approach to improving patient outcomes.[44] These coherence-building methods are not only effective therapeutic tools in and of themselves, but by increasing synchronization and harmony among the body's internal systems, may also help increase a patient's physiological receptivity to the therapeutic effects of other treatments.[35,44,79]

Coherence-building approaches may also help health care practitioners increase their effectiveness in working with patients. In self-generating a state of physiological coherence, the clinician has the potential to facilitate the healing process by establishing a coherent pattern in the subtle electromagnetic environment to which patients are exposed.[80] As even very weak coherent signals have been found to give rise to significant effects in biological systems,[81,82] it is possible that such coherent heart fields may provide unsuspected therapeutic benefits. Furthermore, by increasing coherence, clinicians may not only enhance their own mental acuity and emotional stability, but may also develop increased sensitivity to subtle electromagnetic information in their environment. This, in turn, could potentially enable a deeper intuitive connection and communication between practitioner and patient, which can be a crucial component of the healing process.

In conclusion, I believe that the electromagnetic energy generated by the heart acts as a synchronizing force within the body, a key carrier of emotional information, and a mediator of bioelectromagnetic communication between people. As such, the cardiac bioelectromagnetic field is an innate untapped resource that requires further investigation to explore its clinical applications. Such exploration is likely to provide further insight into the dynamics of health and disease that are strongly influenced by emotions and by interactions with others.

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15 Basic Science and Evidence-Based Support for Acupuncture

The Crucial Importance and Biology of Acupuncture Points

*Richard C. Niemtzow**

CONTENTS

INTRODUCTION

Acupuncture is a psychobiological therapeutic modality focusing on supplementing existing care in the interrelated areas of disease, both psychologically and physically. Developed by the Chinese over 5000 years ago, acupuncture still forms the basis of medical care in China and it is integrated into many of its hospitals employing Western medicine. Auriculotherapy is credited as a French development by Dr. Paul Nogier.

Classically, acupuncture consists of energy called *Qi* that moves in a rhythmic fashion in a network consisting of meridians and specific acupuncture points. This movement or oscillation of energy flows in accordance with the conception of *Yin* and *Yang*, as *Yang* increases, *Yin* decreases, and the converse is true. When the movement of *Qi* is blocked, illness is said to manifest. Despite many attempts to prove the existence of meridians, acupuncture points, and energy *Qi*, unfortunately modern day science has not confirmed its existence.[1,2]

Acupuncture points are reported to be low electrical resistance areas; however, the literature takes various views. There are no agreements substantiating the electrical properties of acupuncture points and meridians.[3] Histological analysis of the acupuncture point demonstrates an area consisting of conjunctive tissue supporting miniscule structures: myelinated and unmyelinated nerve fibers, lymphatic trunks, capillaries, veins, and arteriole vessels.[4] Bossy[4] claimed that acupuncture points have a surface area of 1–5 mm^2. Senelar described an acupuncture point as located in a vertical column of loose connective tissue that is surrounded by the thick dense connective tissue of the skin, which itself is not a good electrical conductor.[4] The physiological significance of this complex is not clearly understood. Body acupuncture points are said to be electrically active in permanence, in contrast to auriculopoints that appear to be electrically active when disease is present and disappear when pathology is absent. No histological analysis of ear acupuncture points has been found in the literature by the author.

Despite the inability to prove or disprove the existence of acupuncture meridians and points, acupuncture is employed around the world in either a primary or an adjunctive mode for the treatment of pain and other diseases. It is well known as a low risk and cost modality.

What is the evidence to support acupuncture and substantiate it as a viable modality? Perhaps some readers might suspect that if we drill down far enough with Western science technology or perform a convincing clinical trial, the proof will be evident and the result will be the confirmation that acupuncture is a substantiated medical modality. I truly doubt investigations will satisfy us even at the quantum level. Instead, it will be more profitable to understand that acupuncture is more complex as it relates to Man's relationship to spirit, nature, environment, and the universe. A patient once told me that her headaches manifested prior to an unannounced high-pressure weather front and still others had bone

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aches during rainy weather. One particular patient developed depression and noncardiac chest pain after being exposed to high winds and dampness during mountain climbing at low attitudes. For this patient, acupuncture needles, employed to "unblock" the *Qi*, succeeded when drugs failed. As Editor-in-Chief of the journal *Medical Acupuncture*[5] for over 17 years, I have literally read hundreds of clinical and basic science acupuncture articles; no definitive evidence has been presented, but indeed enough data has been reported that strongly suggests its worthiness as a medical modality. Still for many clinicians, this is not enough proof.

As a Western trained physician, I was very skeptical about acupuncture. In fact, the only reason I became interested in the subject was due to my curiosity that lasers could possibly be employed to stimulate acupuncture points and bring about healing. As a radiation oncologist, I used high-energy photons to treat cancer. I surmised that the best way to understand lasers and acupuncture was to take a physician's course in medical acupuncture by the famous Joseph M. Helms, MD, who is considered to be the father of medical acupuncture in the United States and the founder of the American Academy of Medical Acupuncture.[6] The course provided on-hand instruction and readings at home. When I finish the 300 h accredited course, it sufficed for me to begin practicing medical acupuncture. Medical acupuncture is a term that relates to a physician who integrates acupuncture into his/her specialty.

In the United States, many states have specific requirements to practice acupuncture. For medical doctors the requirement is to complete an acceptable course of acupuncture instruction of 200–300 h.[7] Nonphysicians must complete a 3–4 year program and pass a national examination.[8] Laser instruction should include a course in laser theory, safety, and clinical application. Without formal instruction that meets State Board requirements, acupuncture should not be attempted. In states where acupuncture is permitted for physicians without any evidence of formal training, malpractice insurance may not be obtainable.

I became the first military physician to establish the only full-time acupuncture clinic in the Department of Defense in 2002. My development in 2001 of a technique that I call "Battlefield Acupuncture (BFA)" was highly publicized.[9–11] This technique is credited as leading the way for the promulgation of acupuncture in the entire United States Armed Forces[12] and considered the most popular and useful auriculotherapy technique for pain in the United States military.[11] Hundreds of American military physicians and Special Forces have been trained in BFA.

HISTORY OF BATTLEFIELD ACUPUNCTURE

The majority of cases that acupuncturists deal with are acute and chronic pain.[9] There are many acupuncture techniques and styles that may be employed. Many practices date back for thousands of years. In 2001, I sought a more rapid technique that would yield quick results, be easy to teach, portable and, most important, safe for the patient; "acupuncture American style." At the time of development, I was an active duty Air Force colonel physician. BFA had to be practical for field deployment. We were militarily building up to become engaged in Iraq and later in Afghanistan. Ear acupuncture was my first choice for consideration. An ear is always accessible. Troops do not like to disrobe during combat situations. I chose semi-permanent needles about <2 mm long and designed by Dr. Paul Nogier about 30 years ago. A feature of these needles is that they can constantly stimulate an ear point for about 3–4 days providing pain relief before they dislodge. Even with the absence of the needle, pain reduction may last for hours, days, months, and years.

Ear acupuncture or auriculotherapy is a micro-acupuncture system first described by Dr. Paul Nogier in France in 1950.[13] It appears to work because cells in the ear contain an organized group of pluripotent cells representing different parts of the body which when stimulated appear to reduce pathology.[13,14] BFA employs five points in the ear and are needled in the following sequence: cingulate gyrus, thalamus, omega 2, shen men, and point zero. Although Nogier described the points of BFA, except the Chinese who described shen men, I selected these points out of hundreds of other ear points and developed the correct needling sequence (Figure 15.1).

I chose the cingulate gyrus auriculopoint based on the work of Professor Zang-Hee Cho, formerly at University of California at Irvine and now at the Neuroscience Research Institute at Inchon, Korea. Briefly, he recognized, using functional magnetic resonance imaging (fMRI) techniques, that the cingulate gyrus and thalamus areas of the brain appeared to be "activated" when pain was introduced to a subject by placing a finger in hot water. A needle in the LR 3 area, which is an acupuncture point located on the foot near the large toe and known to be useful for its analgesic effect, decreased both the pain and fMRI activity of the cingulate gyrus and thalamus areas of the brain.[15] It appeared logical to employ the points for the cingulate gyrus and thalamus classically represented on the ear. I have utilized omega 2 for many years because it is an outstanding point for headaches, neck, upper shoulder pain, and upper and lower extremity

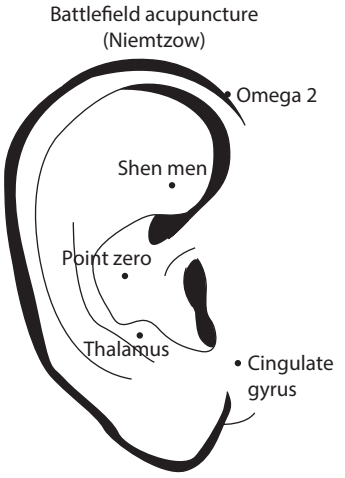

FIGURE 15.1 Battlefield acupuncture.

pain. Shen men, known by the Chinese, is equated in Chinese to the "Spirit or Heavenly Gate." It has a calming effect on the patient. Point zero is interesting from an electrical kinetic point of view. Think of the ear as a battery, which when repeatedly used will eventually run down. My observations over the years have shown that placing an acupuncture needle in this point bilaterally for 30 min or stimulating electronically with microcurrent at about 10 Hz for 2 min recuperates and re-energizes the rest of the ear points. No clinical trial has proven this observation.

A variety of studies support the efficacy of BFA. An article in *Medical Acupuncture* in 2002 tied specific functional MRI changes in the central nervous system to specific ear point stimuli.[16] Later, in a pilot study performed in the Malcolm Grow Medical Center, Joint Base Andrews, Emergency Department, BFA demonstrated a 2.3% reduction in pain for patients randomized only to cingulate gyrus and thalamus points versus a sham acupuncture group.[17] More recently, an observational study, assessing the benefits of acupuncture to control acute and chronic pain in active duty military members, dependents, and retirees seen at the United States Acupuncture Center, Joint Base Andrews, MD, demonstrated significant improvements in pain control and in their scores on standardized quality of life measures such as the SF-81.[18] The majority of patients were treated with BFA. A 2011 study of wounded soldiers being evacuated from Iraq and Afghanistan found an average 30%–46% reduction in their pain one hour after treatment with BFA during flights from Ramstein, Germany to Joint Base Andrews ($p < 000.1$).[19] It has also been widely reported that military flyers who would otherwise be grounded for medication side-effects were able to continue their flying duties after obtaining more rapid relief with BFA. While more studies need to be done, BFA is anecdotally effective in about 85%–90% of pain cases. In a survey of 41 military physicians who completed medical acupuncture training in 2009, 82% of respondents reported that they used BFA more than any other acupuncture modality taught in their Medical Acupuncture (300 h) curriculum.[20] There are other uses for BFA that are emerging: possible oxygen changes in the brain, phantom limb pain, and use of dissimilar metals on BFA points for enhanced pain relief.[10,21]

JOINT INCENTIVE FUNDS

The United States Department of Defense (DoD) and Veterans Administration (VA), Joint Incentive Fund (JIF)[22] recently funded the Army, Air Force and Navy (medical services) and VA $5.4 million for BFA. This proposal obtained funding to establish a uniform training program for BFA across the DoD and VA, funding for training a small cadre of physicians in the DoD and VA in a 300 h medical acupuncture program leading to certification, and funding to initially establish the availability of acupuncture as an option at all levels of care throughout the DoD and VA. It would also allow establishment of uniform credentialing standards and quality assurance processes in order to facilitate integration of acupuncture safely into the mainstream of military and veterans care. This project is just beginning, but represents a significant effort to introduce acupuncture into the DoD-VA health system. I believe this is the largest sum of money spent on acupuncture development in this country. BFA has changed the opinions of many skeptical healthcare providers. Skepticism is healthy as long as it does not inhibit progress.

THE BIOLOGY OF ACUPUNCTURE POINTS

Clinically speaking it has been known for thousands of years that body acupuncture points when stimulated result in specific physiological beneficial effects. Body acupuncture points do not appear to move physically but may shift slightly around their anatomic location when detected electronically. There are many other factors that influence the electrical nature of these points. Acupuncture body points are situated on what appears to be a somewhat steady state network that varies little from human to human. Be what it may be, there is an electrical distinction of the acupuncture physiological complex and the rest of the epidermis away from the acupuncture point; it has a reduced surface resistance. The literature abounds with articles on this subject and it is disputed.[3] The electrical nature of these points may be measured with a device called a "point finder" that has several electronic components: (i) active skin electrode; (ii) a ground electrode serving as the reference electrode that may be held or strapped to the wrist; and (iii) an electronic circuit connected to the two electrodes producing an unbalanced signal when the skin electrode contacts a body acupuncture point. The circuit has a differential amplifier that turns on at preselected levels when detecting + or – acupuncture voltages to produce an amplified signal to drive an audio or visual indicator. Although the use of this instrument may be debatable, practicing acupuncturists incorporated this instrumentation for decades in clinical practice. It appears to find the location of acupuncture points on the body that are useful for pain and other disorders. Detectable electrical ear points appear when pathology manifests in the human body.[13,14]

In effect, the electronic measurement by the point detector of the acupuncture point is actually an area of lower resistance than the surrounding skin. Lower resistance may suggest greater conductance to small electric current flows. What does this low resistance acupuncture area consist of? Is it possible that the physiological complex of the acupuncture point is an increase in electrical conductivity created by the concentration of the structures of the acupuncture point already described and bathed in extracellular fluid that promote mobile electric charges?

Strictly speaking, every living cell as a consequence of molecular spatial arrangements, attachments of neutral and polar molecules, diffusion of organic and nonorganic substances (especially ions), and the resultant chemical diffusion gradients, whether active or passive, has a cellular membrane that is characterized by both an electrical transmembrane potential (TMP) and external surface charge that reflects its proper metabolism.[23] While there has been considerable work on the evaluation of the role of the cell membrane in

the generation and transmission of electrical impulses, such as muscles and neurons, it has only been within the past few decades that the cell membrane has been recognized as an important regulator of many cell functions.[24]

It is important to first understand the origin of the transmembrane potential and then relate this to the physiological complex that forms the acupuncture point. The acupuncture point is not an isolated entity, but forms some connection with the rest of the body, be it the alleged meridian or the interstitial planes of tissues that are bathed in fluids that have the ability to conduct the movements of miniscule electronic currents perhaps in a manner like a semiconductor, which in a biological system, can serve as a conductor or insulator of electrical transmission. The state of biological semiconductors may be influenced by ions, proteins, and other biological molecules.

There are several important models that describe the basis of electrical potentials that are characteristic of living cells. Changes in these potentials reflect normal cellular homeostasis, but large fluctuations might trigger other mechanisms.

The origin of the membrane electrical potential is explained by two models: a physical-chemical approach and an electric model.[25]

Physical-Chemical Model

Liquid Junction Potentials

In this model, the cell interior and the cell exterior are viewed as two chemical phases containing different concentrations of ions separated by the membrane that has specific permeation properties. Note that a membrane is not actually necessary in order to observe a potential between two solutions of different concentrations of ions in contact with one and another.[26] This is a very important concept as the interstitial spaces of the body contain a large portion of body fluids in motion that exist between most of the cells and are formed by filtration through the blood capillaries. They are drained away as lymph. All bodily systems are covered with connective tissues, which form a continuous matrix, connecting every part of the body. The connective tissue has a liquid crystalline form. Mechanical impact (tension, compression, stretching) on connective tissue generates an electrical impulse or a burst of electrons that is characteristic of the type of deformation of this matrix. This is a piezoelectric effect resulting from a structural change of a crystal. Another way that movement generates electricity is by the fluid flow (blood or extracellular) containing ions influenced by electrical properties of local tissue like surface charge. If the connective tissue is deformed, a piezoelectric effect may occur that changes its electric properties that may be transmitted to moving fluid. Conceivably this could be a data exchange that is carried over a long distance to the central nervous system. We have already discussed that two fluids, because of their composition, may have a difference of potential even without a membrane and produce cell signalization, as these potentials oscillate slowly and are influenced by semiconductor effects.

The electrical model of a cell membrane is equivalent to a battery in series with a resistor and a capacitor. The lipid bilayer of the cell membrane acts like a capacitor. The advantage of this model is that methods of physics and electrical engineering can be applied to understand the membrane and the electrophysiological events on the membrane.[26]

Albert Szent-Georgy[27] suggested that certain molecules, such as proteins, are semiconductors. Szent-Georgy[28] also theorized that molecules do not have to touch to interact, but energy can flow through the electromagnetic field and that water can form structures that transmit energy. Every tissue fiber is surrounded by an organized layer of water that can function as a channel of communication and energy flow. As we have already noted, potential differences can exist between two solutions of different concentrations. Solutions that are in contact with cellular membranes offering changes in the outer surface charge of the plasma membrane can serve as a source of information from the cell passing via a weak biological electromagnetic field (EMF) to higher regulating centers in the central nervous system. This may explain why clinicians frequently experience very rapid results with a needle because EMF signals may travel very rapidly as changing weak magnetic fields and electron movements. The same argument may hold for the action of laser stimulation and its effects on the cellular membrane.

In order for a cell to survive, it must communicate with the exterior milieu across the cell membrane. It selectively transfers nutrients inward and waste nutrients outward. Most cells, and in particular those that compose the acupuncture complex, must be capable of responding to photon energy, mechanical stimulation, chemicals, heat, cold, etc. Even more, this complex must respond to chemical messengers: receptor–ligand interactions. All of these reactions are responsible for changes in the transmembrane potential either directly or indirectly. If these cells are deprived of the ability to function as part of a larger network in an afferent or efferent manner, a physiological loss may occur that is detrimental. When this energy is blocked or inhibited by external influences, it may manifest pathological symptoms.

DESTRUCTION OF THE ACUPUNCTURE POINT

When an acupuncture needle(s) is inserted into a distinct area on a meridian known as an acupuncture point, it has the ability to influence the alleged energy flow possibly resolving the pathological situation. Would the inserted needle also serve as an impediment to this alleged energy? We must seek a more modern model congruent to our understanding of human physiology to understand the role of the needle. The needle produces cellular injury that may result in cell signalization. The insertion of a needle into an acupuncture point causes injury to the cells. How does this injury produce a beneficial effect? It seems paradoxical that it does, but after thousands of years of observations, it appears to be true.

A needle placed in an acupuncture point is destructive. Needle insertion requires the protrusion of the needle to penetrate the skin and reach a certain depth where alleged *Qi* is

provoked. The needle may be rotated clockwise or counterclockwise and left in place for at least 20–30 min. Withdrawing the needle also can cause cellular and tissue damage. Often slight bleeding may occur. Most importantly, the cells involved in the acupuncture point are damaged or destroyed. The plasma membrane is ruptured to the extent that normal cellular function is disrupted. For many cells, the intrusion of the needle begins the process of cellular death that is a substantial event and so severe that compensatory mechanisms are insufficient to maintain the biological integrity of the cell. As I have previously reported, a rapid deterioration of the potential signifies cell death as a result of gross destruction of the membrane and extravasation of the cytoplasmic contents.[25] In many instances, a small rising and falling electrical potential is observed in a successive fashion, each peak being lower than the previous, and each dip progressively approaching zero potential.[23] Is it possible that this rapid change in transmembrane potential, which is reflected in the surface charge of the membrane, influences other cells at a distance due to the oscillation of the electrical kinetics of the cell and/or its discharged chemical components impacting on adjacent tissue?

It is the opinion of the author that an "injury" signal from the consequences of the needle damage may possibly trigger a reaction from the central nervous system for homeostasis. This is noted to occur in body and ear points. Low-level lasers may have a different mechanism when stimulating the acupuncture point.

FURTHER INSIGHTS INTO A POSSIBLE NEW ELECTRIC TRANSPORT SYSTEM

In the early 1960s, Dr. Bong-Han Kim claimed to have discovered a novel circulatory system in vertebrates, invertebrates, and plants consisting of vascular thread-like structures (primo-vessels) containing a new fluid (primo-fluid). He named this the primo vascular system (PVS) because he suspected it was more primitive and developed earlier than the vascular and lymphatic systems. Primo-fluid had potent healing properties that he attributed to its high content of microcells that could regenerate any type of damaged tissue, much like pluripotent stem cells. Unfortunately, he did not fully disclose his methods for observing this system, and his claims could not be confirmed despite intensive attempts in China, Japan, and Russia.[29] PVS research began to change in 2002, when, using sophisticated modern technologies, researchers at Seoul National University in Korea reported they had rediscovered primo-vessels in animals at various sites. Their investigations of the morphological and other characteristics of microcells in primo-fluid are consistent with Bong-Han Kim's claims.[29,30]

Other studies support and expanded Kim's theories, and if validated by others, could revolutionize medical care.[29] A brief summary of these advances and their clinical significance may be summarized as follows:[29]

1. Although the PVS is an independent morphological and functional system, the superficial primo-vessels and extravascular primo-vessels are connected with superficial nodes. The deep primo-vessels are connected between them with intravascular primo-vessels, deep primo nodes, and organ nodes composed of many cells. Thin vessels containing multiple subvessels branch out from these nodes.
2. Primo nodes contain different nucleic acids, but the predominant one is DNA.
3. The flow of the transparent liquid containing the microcells as it circulates is slower than the flow of both blood and lymph.
4. The primo-fluid flow follows the direction of blood flow.
5. The flow of this fluid is influenced by heart rate and pressures in blood and lymph vessels.
6. The PVS has unique bioelectric characteristics that differ from those found at acupuncture sites and elsewhere.
7. PVS primo-fluid contains DNA that is outside the cell nucleus.
8. There is increasing evidence that PVS is related to, or corresponds with, the classical system of acupuncture points and their meridians.

CONCLUSION

Research of acupuncture mechanisms continues to generate more insights into how this system may produce beneficial effects. Whether we can definitively prove acupuncture is effective may not be answerable today. The skeptics may say "no" and others may say "yes." Each one can justify their reasoning. In any case, we, the patients, do not care, we just want to get better, whether *Qi*, acupuncture points, or meridians exist or not. As can be seen, research into the mechanisms responsible for the benefits of acupuncture continues to provide insights and clues, but poses many more questions than answers. At present, it may be difficult if not impossible to prove or disprove the benefits of acupuncture. Conversely, theories are not important, only facts are. Some theories are valuable because of their heuristic merit, in that they stimulate others to discover new facts that lead to better theories. In the final analysis, as already mentioned, patients are not completely interested in theories; they just want to know if a therapy is effective and safe. There is little doubt that acupuncture has satisfied those criteria for thousands of years and that its popularity is increasing, despite the fact that scientists have been unable to verify the existence of meridians, acupuncture points, *Yin*, *Yang*, and *Qi*.

Are the forces or energies in magnetic fields, as well as those involved in faith healing, therapeutic touch, consciousness, intentionality, acupuncture the same, or some other manifestation? "And there is no new thing under the sun" the Bible warns in Ecclesiastes. Are the forces or energies in magnetic fields, as well as those involved in faith healing, therapeutic touch, consciousness, intentionality, and bioelectric closed circuits the same, or some manifestation of

chi? Albert Einstein also believed that there was an underlying order to the organization and operation of the universe based on mathematical principles. He proposed not only that electromagnetism and gravity were different aspects of the same force, but that all the four forms of energy were interrelated, and scientists have been trying to prove this Unified Field Theory ever since. Is chi a fifth form of energy that will prove to be the glue that binds all of the others together? The Chinese sage Lao Tsu described chi as follows:

> Look, it cannot be seen—it is beyond form
> Listen, it cannot be heard—it is beyond sound
> Grasp, it cannot be held—it is intangible[31]

Is the human mind capable of comprehending chi, or, like infinity, and the lack of distinction between energy and matter at subatomic levels, is it impossible for us to visualize its composition and mechanism of communication?

DISCLAIMER

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the United States Air Force Medical Corps, the Air Force at large, or the Department of Defense. The author indicates that he does not have any conflicts of interest.

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16 Memory of Water and Law of Similars
Making Sense Out of Homeopathy

*Shahram Shahabi**

CONTENTS

INTRODUCTION

Homeopathy has two important pillars: the first is that there is no molecule of original substance in most homeopathic remedies and the second is the law of similars. The law of similars is the main homeopathic principle that states low doses of a substance that induces a series of symptoms in a healthy person can cure an illness with similar symptoms.[1] Understanding the mechanisms behind both of these pillars would not only help validate the practice of homeopathy but contribute to understanding of physical and chemical influences on biology. The ability of highly diluted homeopathic remedies to have biological activity despite a lack of any molecules of original molecules has been named "memory of water".[2,3] Previous studies suggested scientifically supported, experimentally testable explanations for memory of water.[2,4–18] However, although these studies provide a strong scientific explanation for biological effects of highly diluted homeopathic remedies, they cannot explain the mechanism of the law of similars. Thus, the main purpose of this chapter will be to provide a scientific and testable basis for the law of similars. Detailed information about this model was previously reported elsewhere[19] and we will focus on those aspects that require more detailed explanation based on the feedback to this publication. Furthermore, some details of this supracellular and neuroimmunogical model have been changed, and although some subcellular mechanisms could also be suggested for the law of similars, explaining them is beyond the scope of this chapter and will be discussed in a future publication.

The above mentioned evidence strongly suggested that the effects of highly diluted homeopathic remedies on living systems are electromagnetic in nature. Before an explanation of the model, some of this evidence will be discussed briefly.

EVIDENCE SUGGESTING THE EFFECTS OF HIGHLY DILUTED HOMEOPATHIC REMEDIES ON LIVING SYSTEMS ARE ELECTROMAGNETIC IN NATURE

Living Cells Generate EM Waves

It has been shown in multiple studies that living cells generate electromagnetic (EM) waves of different frequencies, including the extremely low frequency (ELF) segment of the electromagnetic spectrum.[20] ELF-electromagnetic (ELF-EM) waves have frequencies between 3 and 300 Hz, corresponding to photons with extremely low energy levels. Unlike higher frequencies EM waves, ELF-EM waves are rarely used in applications such as radio communications, mainly because of difficulties in detecting these waves.[21]

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Resonance Phenomenon: A Mechanism by Which ELF-EM Waves Affect Living Cells

In addition to producing EM waves, living cells may be "affected" by EM waves, including ELF-EM waves.[22–27] Unlike that of high frequency EM waves, the process of the effect of ELF-EM waves on living cells is fundamentally nonthermal. That means it is not dependent on production of heat due to exposure to ELF-EM waves.[25] Among the mechanisms proposed for the effects of ELF-EM waves on living cells and tissues, the stochastic resonance model has more theoretical and experimental evidence than the other proposed mechanisms.[25,28–32] This model explains the mechanism by which the energy and frequency of weak ELF-EM waves increase to a level more than the threshold needed for affecting adjacent living cells.[25,31,32] According to this model the resonance happens because of the interaction between a noisy background ELF-EM field and the external ELF-EM field. This model describes a "window activity" where, above and below it, the ability of external ELF-EM fields to be in resonance with a noisy background ELF-EM field is attenuated. Therefore, regarding the frequencies that exist in a noisy background ELF-EM field, only some frequencies of external ELF-EM waves are capable of resonating with the noisy background ELF-EM field. The noisy background ELF-EM field may be generated by the adjacent living cells. The resulting cascade of events following the resonance may stimulate or suppress numerous intracellular activities.[25]

Different cells in a variety of tissues may be affected by ELF-EM fields.[22–27,33] ELF-EM fields may affect various physiological activities of the cells, such as cell proliferation, cell cycle regulation, cell differentiation, and metabolism.[34] It has been shown that the sensitivity of sensory neurons is greater than other cells.[21,34–37] Such sensitivity in sensory neurons is anticipated as these cells are highly responsive to electrical signals. Furthermore, both the structure and function of these cells are fundamentally involved in the interaction of an animal with its environment. Transmission of sensory inputs due to stimulation by ELF-EM waves, central processing of this information, and subsequent efferent signals to tissues and organs are the major features of these interactions.[21] Because of the energy threshold needed for affecting the cells, short-term exposure of cells to ELF-EM fields does not necessarily result in an effect unless the activation threshold of the cells is decreased or the duration of exposure lasts sufficiently long to cause accumulation of the effects. This relationship is also true for the sensory neurons that are more sensitive to ELF-EM waves than other cells.[37,38]

Highly Diluted Homeopathic Remedies Contain Aqueous Nanostructures That Are Capable of Producing Detectable EM Waves via Resonance Phenomena

Considering the fact that homeopathic remedies are virtually devoid of any remnants of the initial starting material, numerous *in vitro* and *in vivo* studies have been done to determine if there is any physicochemical signals generated and/or retained in these preparations.[39,40] Barnard was the first who tried to answer this question on how homeopathic remedies work despite the high degree of dilution. He suggested that the process of sequential dilution and succession in preparation of homeopathic remedies results in the formation of polymers of water, and their configurations are dependent on the chemical nature of the original substance.[41,42] George Vithoulkas was the first person to introduce the concept of resonance to explain how homeopathic remedies work. He suggested that resonance occurs when the vibrational frequency of the remedy and that of the patient's defense mechanism match.[43] Jacques Benveniste was the first whose experimental studies showed that the mechanism of biological effects of homeopathic remedies is explainable scientifically. Benveniste's group showed that the highly diluted samples of anti-IgE antibodies were capable of causing degranulations in basophiles.[2,3] Benveniste believed that bioinformation existing in the solvent caused degranulation of basophiles; consequently, he used the notion of "memory of water" to explain the findings. Benveniste pointed to the possibility that EM signals emitted from the solution could be the cause of the reported biological effects.[5,16,44] The efforts of other researchers to reproduce Benveniste's results led to some controversies; while some groups were able to confirm Benveniste's findings,[45,46] others reported that they failed to get the same results.[47] Benveniste also suggested a new mechanism for communication between molecules:

> …The mode of communication between molecules, which is essential to life, is electromagnetic in nature. Molecules communicate like a radio set that receives waveforms carrying specific information from the station to which it is tuned to coresonate and to none other. This communication takes place through water molecules surrounding all biological molecules. Water may have an amplifying role. Some of our data indicate that the signal is indeed emitted by the molecules but is finally conveyed by water, quite similarly to the strings of a violin, which do not create music unless affixed to the resonating wooden box.[4]

According to the model proposed by Benveniste, a receptor can be activated by its ligand when the frequencies of their emitted EM signals are similar.[4,31]

Luc Montagnier was the second scientist whose discoveries had a great impact on revealing what is in homeopathic remedies. Montagnier and colleagues discovered that a particular class of electromagnetic waves exists in high aqueous dilutions of a variety of pathogenic microorganisms.[7,8] Initially they demonstrated that filtrates of human lymphocyte culture supernatants infected with a bacterium named *Mycoplasma pirum*, although apparently sterile due to the filter's pores and the size of the microorganism, could lead to the regeneration of the organism after incubating with *Mycoplasma*-free lymphocyte cultures. The findings were unexpectedly highly reproducible. Interestingly, highly diluted solutions (in the particular range of 10^{-8} to

10^{-12}) derived from the sterile filtrates emitted distinctive low frequency EM waves. Of note, lower dilutions (e.g., 10^{-3}) did not show the emission of detectable EM waves by the instrument. Treatment of diluted filtrates with DNase, RNase, or proteases did not decrease the emission of EM waves. However, heating the samples to temperatures above 70°C for 30 min or freezing them for 1 h at −20°C or −60°C suppressed the emissions. The other aspects of this process were the necessity for vigorous shaking at each dilution step and the requirement for stimulation by low frequency background natural or artificial EM waves.[7] In a separate experiment, Montagnier and colleagues could transfer the ability of emitting EM waves from a tube containing a positive dilution to pure water of another tube that was put in the vicinity of the positive tube at least for 18 h. This procedure required the excitation of both tubes by a 7 Hz magnetic field for the whole duration of the experiment.[6] The experiments of Montagnier and colleagues supported the notion that aqueous nanostructures might be involved in the generation of EM waves. Their findings also suggested that interactions between water molecules through hydrogen bonds are crucial for the existence of the nanostructures. The necessity of the existence of a background magnetic field for emission of EM waves from diluted solutions and also for transfer of the ability of EM wave production from a positive diluted tube to pure water showed that a resonance phenomenon played an important role in these findings. The findings of Montagnier and colleagues corroborated those of Benveniste and colleagues. These findings were considered as a support for homeopathy,[48] especially the important role of water nanostructures and resonance phenomenon in the mechanism of action of homeopathic remedies.

Considering Montagnier, Benveniste, and the other scientists' findings,[2,4–17] it is possible to suggest that highly diluted homeopathic remedies contain aqueous nanostructures. These nanostructures are able to produce EM waves when they are resonated by a natural or artificial ELF-EM background field.

The Resonance Phenomenon May Mediate the Effects of Highly Diluted Homeopathic Remedies on Living Cells

As mentioned above, the aqueous nanostructures that exist in highly diluted homeopathic remedies are able to produce EM waves with noteworthy energy only when they can resonate with a background ELF-EM field. This ELF-EM field may be produced by living cells or tissues. Therefore, before administration, homeopathic remedies do not produce EM waves with noteworthy energy. They may produce ultra-weak EM waves that are not detectable by current instruments.

THE MODEL

As mentioned above, there is much evidence that shows that homeopathic remedies contain aqueous nanostructures capable of producing low frequency EM waves in particular settings. The first part of our model is based on this evidence. However, there is no viable model to explain the mechanism behind the law of similars. Therefore, the second part, which is the major part of our model, is about the suggestion of a scientifically supported and experimentally testable mechanism for the law of similars.

The model suggested here is based on a set of studies performed by our group. Our findings indicated that application of mild local hyperthermia to the peripheral area of burned skin after a burns injury resulted in inhibition of the progression of the burn-induced injury.[49–52]

Our suggested model is also based on generation of low frequency EM waves by the structures of highly diluted homeopathic remedies in particular settings. The different parts of our model are described in the following sections.

Highly Diluted Homeopathic Remedies Affect Living Cells through Resonance Phenomena

According to our suggested model, the EM waves generated by aqueous nanostructures existing in a homeopathic remedy will resonate to generate higher frequency EM waves if their frequencies are in a distinct range that can be resonated by the background ELF-EM field produced by the cells adjacent to the nanostructures. The resonance phenomenon is just a prerequisite for biological effects of homeopathic remedies. The biological effects of the homeopathic remedy will be initiated if the energy of EM waves generated by the resonance phenomenon reaches a level higher than the threshold needed for affecting the adjacent cells. As with the other low frequency EM waves, this will be true unless the needed threshold is decreased or the duration of exposure lasts sufficiently long to cause accumulation of the effects.[37,38]

As mentioned in the section "Highly Diluted Homeopathic Remedies Contain Aqueous Nanostructures that are Capable of Producing Detectable EM Waves via Resonance Phenomena," Montagnier and colleagues could transfer the ability to emit EM waves from a tube containing a positive dilution to another tube of pure water that was placed in the vicinity of the positive tube for at least 18 h. This procedure required the excitation of both tubes by a weak magnetic field for the whole duration of the experiment.[6] This finding brings up the possibility that the nanostructures of a homeopathic remedy after entering a living body may be able to induce the formation of new similar nanostructures in body fluids with the help of excitation by ELF-EM background fields of body cells and tissues. This, in turn, multiplies a whole number of the nanostructures in the body that guarantees the access of these nanostructures to all tissues of the body. After a while, the nanostructures may be broken and disappear from body fluids by the effects of structure breaking or chaotropic agents of the body, which opposite interactions between water molecules.[53] As mentioned previously, the interactions between water molecules are crucial for the existence of aqueous nanostructures.[7]

Proving Phenomena

Homeopathic remedy proving is one the pillars of homeopathy.[54] In homeopathic proving, healthy volunteers consume a substance, usually homeopathically prepared, for the purpose of producing temporary symptoms that are specific to that substance. The arrangement of these symptoms then forms a remedy picture or a symptom pattern specific to the consumed substance.[54] In the other words, "the profile of a remedy can be identified by giving it to the volunteers and then recording all mental, physical, and emotional symptoms experienced."[55]

According to our model, as illustrated in Figure 16.1, when a homeopathic highly diluted remedy is administered to a healthy person, ultra-weak ELF-EM waves of the aqueous nanostructure of the homeopathic remedy will be triggered to generate EM waves with relatively higher levels of energy if ultra-weak ELF-EM waves of the aqueous nanostructures could be resonated by ELF-EM waves generated by the cells adjacent to the aqueous nanostructures (as a background ELF-EM field).[19] According the above mentioned evidence, this means that the two groups of ELF-EM waves, that is, the ultra-weak ELF-EM waves of homeopathic aqueous nanostructures and those of the cells adjacent to the nanostructures, should be in distinct ranges to result in resonance phenomena. This may also be the reason that no tissues would be affected with equal probability by a specific homeopathic remedy, as the background ELF-EM fields of different tissues have different frequency and amplitude characteristics. In other words, the existence of different "target tissues" for different homeopathic remedies may be due to this mechanism. This is in line with the above mentioned evidence for the resonance phenomenon model.[4,25,28–32]

Here a question arises: how does using a highly diluted homeopathic remedy, that is prepared from an original substance, and using low doses of the original substance itself in the proving produce similar symptoms, whereas the original substance contains molecules but the homeopathic remedy contains no molecules and just has aqueous nanostructures? The response to this question will be possible using the mechanism proposed by Benveniste.[4] Benveniste proposed that a ligand activates a receptor if the EM signal emitted by the ligand has a frequency identical to that of the receptor's

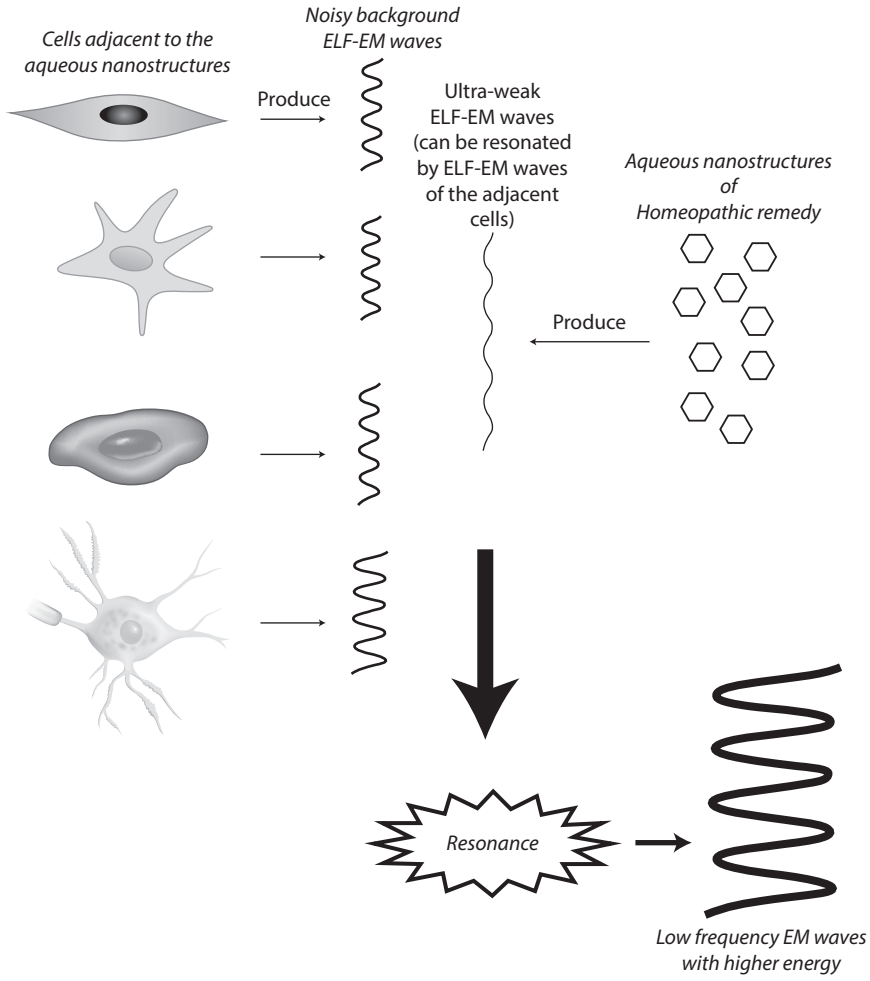

FIGURE 16.1 If ultra-weak extremely low frequency-electromagnetic (ELF-EM) waves of homeopathic aqueous nanostructures could be resonated by ELF-EM waves generated by the adjacent cells, EM waves with relatively higher levels of energy will be produced.

molecule.[4,31] In other words, it could be said if the frequency and amplitude characteristics of EM waves emitted from a molecule are similar to those of the EM waves generated by a receptor, the molecule will bind to that receptor and stimulate it to transduce signals. This is also true for the aqueous nanostructures that exist in the homeopathic remedy produced from this substance. However, because EM waves produced by homeopathic aqueous nanostructures are too weak to be measured by modern instruments, it is probably better to just say if the frequency and amplitude characteristics of EM waves emitted from the aqueous nanostructures are such that they can coresonate with the EM waves generated by a receptor, and if the energy of these resonated EM waves is high enough, the receptor will be stimulated to transduce signals. As the homeopathic remedy is produced from the original substance, it is anticipated that the EM waves emitted from the aqueous nanostructures produced by diluting and shaking (potentiating) the original substance are highly similar to at least a part of EM waves produced by molecules of the original substance. Therefore, the target cells and tissues and target functions of the homeopathic remedy will be among those of the original substance. Furthermore, the EM waves with relatively higher energies that are produced by resonance of ELF-EM waves of different homeopathic remedies and the background ELF-EM field of a cell would contain different frequency and amplitude characteristics. According to Benveniste's theory, it can be suggested that these different homeopathic remedies affect different receptors and signaling molecules in the same cell. This may explain why different homeopathic remedies may have different target functions in the same cell. Therefore, both the target cells and the target functions of a homeopathic remedy indirectly represent the frequency and amplitude characteristics of the homeopathic remedy.

As mentioned for ELF-EM waves, as energy levels of the weak EM waves produced by homeopathic nanostructures, even after resonance with the background ELF-EM field of the living cells, are too low, if the duration of exposure of a healthy person to a homeopathic remedy is too short, this homeopathic remedy will not have any significant biological effect. Therefore, a small number of administrations of a homeopathic remedy to a healthy person usually do not result in any effects. However, repeated administering of the remedy may lead to the accumulation of stimuli of weak EM waves of the nanostructures. When the energy of the accumulated stimuli of ELF-EM waves produced by homeopathic nanostructures reaches a level above the threshold necessary for affecting the adjacent cells, the homeopathic remedy can affect these cells and its biological effects will be initiated (Figure 16.2).[19]

The sensory neurons are the main detectors of electromagnetic waves and their sensitivity to ELF-EM waves are

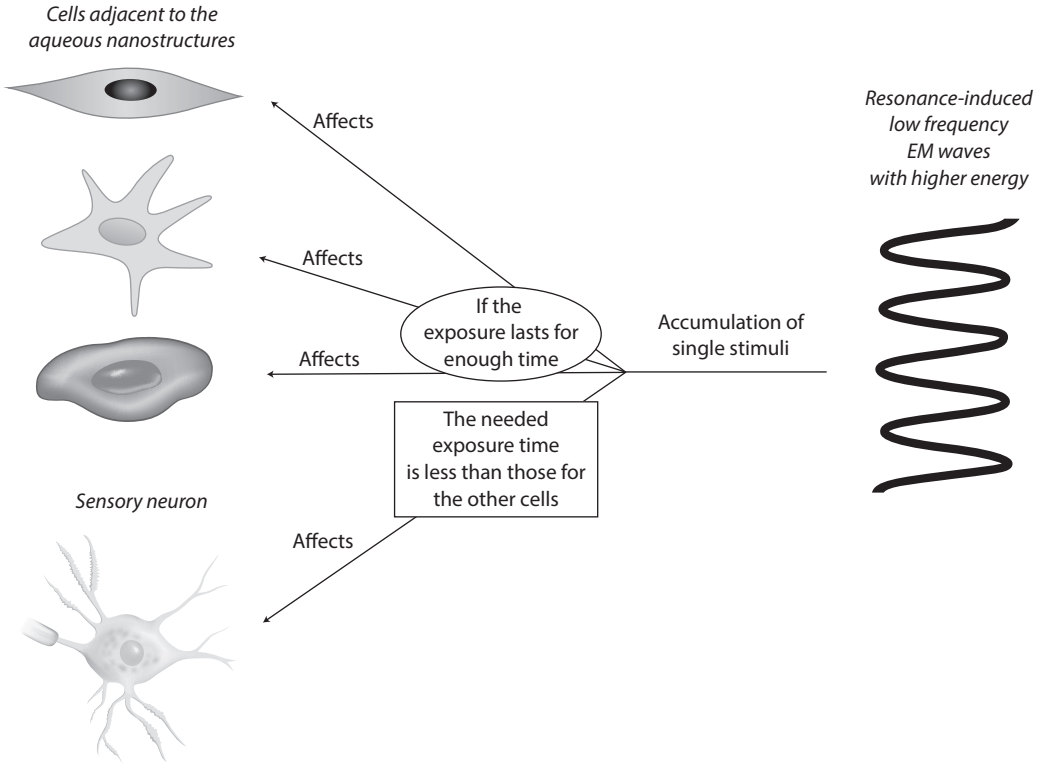

FIGURE 16.2 When the energy of the accumulated stimuli of extremely low frequency-electromagnetic (ELF-EM) waves produced by homeopathic nanostructures reaches a level above the threshold necessary for affecting the adjacent cells, the homeopathic remedy can affect these cells. During the proving by a highly diluted homeopathic remedy, especially in the early phases, the sensory neurons that exist in the tissue and adjacent to the nanostructures are affected with more chance than the other adjacent cells. However, if the proving continues, the other kinds of cells will have an increased chance to be affected by the administered highly diluted homeopathic remedy.

greater than other cells.[21,34–37] Therefore, it can be suggested that during the proving by a highly diluted homeopathic remedy instead of low doses of the original substance, especially in early phases, the sensory neurons that exist in the tissue and adjacent to the nanostructures are more affected than the other adjacent cells. However, if the proving continues, then other kinds of cells will have an increased chance of being affected by the highly diluted homeopathic remedy (Figure 16.2).[19]

It is possible that ELF-EM waves that are produced in a tissue can resonate with the ELF-EM waves of many different homeopathic remedies. However, as mentioned above, depending on the original frequency and amplitude characteristics of ultra-weak ELF-EM waves of the homeopathic aqueous nanostructures, the EM waves with higher energy that are produced by the resonance will have different frequency and amplitude characteristics. They may affect different sensory neurons or the same sensory neurons but with different severity. Therefore, different symptoms may be revealed. For example, symptoms such as pain, itching, and disturbances in hearing, vision, and taste may appear due to the stimulation of the somatic sensory neurons. The stimulation of the autonomic sensory neurons may result in perturbation of the autonomic balance of the target tissues or the whole body. The stimulation of the vagus nerve may lead to mental and emotional symptoms.[56–59] The findings that show that the administration of homeopathic remedies affects heart rate variability, a parameter for evaluation of the autonomic nervous system's activity, support this suggestion that the nervous system is the primary target of the homeopathic remedies in homeopathic proving.[60–62]

As mentioned, cells other than sensory neurons may be affected if the exposure to low frequency EM waves produced by homeopathic nanostructures lasts for enough time. In such a situation, the affected cells, sensory neurons or other types of cells, initially enter the stress state. Longer duration of the exposure may lead to malfunction. Simultaneously, the inflammation may occur due to the stress state or malfunctions of local inflammatory cells, and this in turn may damage the tissue. If the exposure lasts for a long period, then cell death and apoptosis may occur.[22,23] During proving, in addition to stimulation of the vagus nerve, the effect on brain cells may be the cause of the emotional and mental presentations.

The proving often lasts until appearing the primary presentations, including the stimulation of sensory neurons, the stress states, and mild malfunctions. If there is any information about severe malfunctions and tissue injuries in the profile of a homeopathic remedy, it is usually a documented side effect resulting from the abuse or intoxication of the substance that is the origin of the remedy.

As mentioned, exposure of a tissue to two low frequency EM fields with different frequency and amplitude characteristics may result in different symptoms, because different somatic and autonomic sensory neurons and other types of cells may be affected by these two EM fields.[31] Furthermore, in addition to different target cells, affecting different target functions of the same cell by the low frequency EM waves produced by different homeopathic remedies, may play a role in producing different symptoms during proving of different homeopathic remedies. Existence of different target cells and target functions for low frequency EM waves produced by different homeopathic remedies may also explain how similar symptoms with different qualities may be generated during proving with two different homeopathic remedies.[19] For example, one remedy may generate an epigastric pain that is ameliorated by heat application, whereas another remedy may generate an epigastric pain that the heat application makes worse. Other proving-induced physical, emotional, or mental symptoms may have such quality differences.[54,63,64] In this chapter, collection of the symptoms and their qualities that are produced by a homeopathic remedy in a healthy human will be called "symptoms of the homeopathic remedy."[19]

Therapeutic Effects of Homeopathic Remedies

Homeopathic remedies have two types of therapeutic effects. The first one, that is also the most famous one, is based on the law of similars. The law of similars means low doses of a substance that is able to induce a series of symptoms in a healthy person, is capable of curing an illness with similar symptoms.[1] The second type of therapeutic effects does not follow the law of similars.[65]

Therapeutic Effects of Homeopathic Remedies Based on the Law of Similars

This part of our model originates from the experiments that have been done previously by our group.[49–52] Our findings indicated that application of mild local hyperthermia immediately after an acute skin burn injury diminished both burn-induced tissue injuries and inflammation. The local hyperthermia should be applied to the peripheral unburned zone of the burn injury to inhibit progression of the injury. The protective effect of mild post-burn local hyperthermia was inhibited by systemic administration of naloxone, an opioid receptor antagonist, which suggested the possible role of the antinociceptive mechanisms in this effect.[49,52] This experiment can be considered as a simulation for the law of similars: application of a similar mild sublethal stress after a severe lethal stress decreases the severe lethal stress-induced injuries. We hypothesized that mild post-burn local hyperthermia stimulates the sensitized sensory neurons existing in the hyperesthetic area around the burn injury region[52] that, in turn, results in the stimulation of a descending antinociceptive and anti-inflammatory mechanism that inhibits burn injury progression.[49–52] In the other words, while a mild hyperthermia, which may be considered as a minimal dose of heat, does not hurt the cells, it stimulates the descending regulatory mechanisms that are capable of restoring the perturbed homeostasis due to the burn, which may be considered as a disorder due to a high dose of heat. These findings were the source of the hypothesis that it is possible that at least a part of the action of homeopathic remedies may be due to

triggering regulatory responses via a mechanism similar to that of post-burn mild local hyperthermia.

According to our findings, the decrease of the activation threshold of sensory neurons due to noxious stimuli, especially those triggering the descending regulatory mechanisms, played an important role in the beneficial effects of post-burn local mild hyperthermia. Therefore, it is possible that a similar mechanism played a role in therapeutic effects of homeopathic remedies. In addition to noxious stimuli, there are some other candidates that can decrease the activation threshold of the sensory neurons, especially those triggering the descending regulatory mechanisms in nonhomeostatic conditions. Inflammation is the best known consequence of homeostasis perturbation.[66] Inflammatory responses could be triggered by all of the nonphysiologic conditions. Whereas tissue injuries or infections can initiate a reveal inflammatory response, low-grade inflammation can still be triggered by the stress states and malfunctions in the absence of infections and tissue injuries. This low-grade inflammatory response has been named para-inflammation in some texts.[66] This low-grade local inflammation is placed between a classic inflammatory response and a normal homeostatic state.[66] The activation threshold of sensory neurons is decreased by the inflammation; however, they decrease the activation threshold of sensory neurons triggering the descending regulatory mechanisms more than that of the other sensory neurons.[52,67–69] In addition to inflammation and noxious stimuli, the factors that are produced in response to perturbation of the homeostasis (reactive oxygen intermediates, epinephrine, prostaglandin E2, bradykinin, etc.), even before induction of inflammation, acts like inflammation and noxious stimulus in decreasing the activation threshold of sensory neurons.[70–73] Therefore, any perturbation of tissue homeostasis may decrease the activation thresholds of sensory neurons, especially the ones triggering the descending regulatory mechanisms. In the proving phenomenon, administration of minimal doses of a substance may result in the appearance of some symptoms and dysfunctions, especially because of the stimulation of sensory neurons. These sensory neurons are not sensitized because in the proving, the homeopathic remedies are administered to healthy persons. Therefore, administration of a substance during the proving phenomenon does not lead to stimulation of descending regulatory pathways. Furthermore, as a significant part of the patient's symptoms are due to stimulation of the sensory neurons of the target tissues, the patient's symptoms represent which sensory neurons are sensitized by perturbation of the tissue homeostasis. Therefore, if the symptoms produced by a substance during the proving are similar to the patient's symptoms, this means that the sensitized sensory neurons of the patients are similar to the target sensory neurons of the substance. The minimal doses of a substance that are applied based on the law of similars for curing a patient can only stimulate the high sensitized sensory neurons, which are the sensory neurons that trigger descending regulatory pathways, whereas the amount of this substance is too small to efficiently stimulate other sensory neurons or be the source of any injury.

Now the following question arises: how do highly diluted homeopathic remedies, which contain no molecules of the original substance, affect the sensitized sensory neurons? This question will be answered below.

When a highly diluted homeopathic remedy is administered to a patient, if the ultra-weak ELF-EM waves of aqueous nanostructures of the homeopathic remedy could be resonated by ELF-EM waves of the adjacent cells, the resonance occurs and EM waves with higher levels of energy are produced. As mentioned previously, similar to what is true for all low frequency EM waves, sensory neurons are the most sensitive cells to these low frequency EM waves.[21,34–37] Furthermore, as a significant part of the patient's symptoms are due to stimulation of the sensory neurons by perturbation of the tissue homeostasis, if the patient's symptoms are similar to those of the proving of a homeopathic remedy, then it means that the patient's sensitized sensory neurons are the same as those that are stimulated during proving of the homeopathic remedy. Therefore, the resonance-induced EM waves with relatively higher energies preferentially stimulate the sensory neurons triggering regulatory mechanisms because the activation threshold of these neurons in a milieu with perturbed homeostasis is less than the other adjacent sensory neurons.[52,67–73] Therefore, the collection of a patient's symptoms and qualities of the symptoms (which are called patient's symptoms here) could be considered as a guiding map to determine which sensory neurons are sensitized, or, in other words, which sensory neurons should be stimulated to trigger descending regulatory responses. Conversely, the collection of homeopathic remedy-induced symptoms and qualities of the symptoms is a map determining which sensory neurons are stimulated by the homeopathic remedy. If the collection of a patient's symptoms is a subset of the collection of symptoms of a homeopathic remedy, it may be deduced that all the patient's sensitized sensory neurons are stimulated by the homeopathic remedy. As a result, all the needed sensory neuron-induced regulatory responses will be triggered to restore the homeostasis.

When a correctly chosen homeopathic remedy is used to treat a patient according to the law of similars, the needed doses are much lower compared to when the homeopathic remedy is used in the proving. This is because during the proving the sensory neurons are not sensitized, due to the person using the homeopathic remedy being healthy; whereas a patient's sensory neurons are sensitized, and therefore they have lower activation thresholds. So the necessary dose of the correctly chosen homeopathic remedy to stimulate the sensory neurons is much lower than that of the proving. It should be noticed when a patient uses a correctly chosen homeopathic remedy the sensory neuron's descending regulatory responses will be triggered but this event does not happen during the proving.

If the stimulated sensory neurons are somatosensory or viscerosensory, then the triggered descending regulatory mechanisms will be local descending antinociceptive pathways that possess anti-inflammatory characteristics.[74–76] For the activation of the somatosensory or viscerosensory

neurons, it is sufficient that the frequency and amplitude characteristics of the EM waves of the administered homeopathic remedy are similar to those of the target tissue(s) suffering cells. However, as anticipated, the triggered antinociceptive and anti-inflammatory effect is local and is limited to the suffering tissues; it is only able to restore the local homeostasis.

The other regulatory responses that could be triggered by homeopathic remedies are those stimulated by vagal sensory nerves. If the homeopathic EM waves stimulate the vagal sensory nerves, two types of regulatory responses may be triggered. The first one is named the cholinergic anti-inflammatory response. This response can be both humoral and neural in nature.[77–81] The pro-homeostatic roles of the cholinergic anti-inflammatory response can be explained using the cytokine theory of disease. According to the cytokine theory of disease, while low levels of cytokines are necessary to maintain homeostasis, local or systemic overproduction of cytokines cause perturbation of the homeostasis.[81] So stimulation of cholinergic anti-inflammatory response by homeopathic remedies may restore the homeostasis in conditions where over-production of cytokines are the cause of perturbed homeostasis. Conversely, it has been shown that stimulation of the cholinergic anti-inflammatory response normalizes production of pro-inflammatory cytokines and adjusts it in a protective range, but does not abolish it completely and does not cause immunosuppression.[82] Apart from the cholinergic anti-inflammatory response, stimulation of vagal sensory neurons may stimulate other regulatory responses. For example, it has been shown that vagus nerve stimulation can improve epilepsy, mood, and cognitive disorders by affecting brain structures.[83–86] It can also restore homeostasis of the cardiovascular system via anti-inflammatory-independent action.[82,87] This suggested mechanism is in line with homeopathic literature that choosing a remedy for a patient needs special attention to physical symptoms accompanying the patient's emotional and mental symptoms.[55] For example, whether a patient feels his anxiety in their heart or stomach, this is an important discriminative symptom for choosing an appropriate homeopathic remedy.[63] According to our model this is because of the trans-synaptic connections of many vagus, somatosensory, or viscerosensory afferent fibers to areas of the brain pertaining to emotional and mental processes.[85] So when a patient complains of feeling his anxiety in his heart, it means that special vagal sensory neurons in his heart are sensitized and an appropriate homeopathic remedy may stimulate these cardiac vagal sensory neurons, sending signals to the brain region that its perturbed homeostasis is responsible for a feeling of anxiety. These signals, in turn, may improve anxiety feeling through a mechanism similar to that of therapeutic vagus nerve stimulation.[86]

In addition to all the factors that are capable of reducing the activation threshold of somatosensory and viscerosensory nerves (e.g., inflammatory mediators, reactive oxygen intermediates, epinephrine, prostaglandin E2, bradykinin, etc.), deviation of the levels of oxygen, glucose, and other metabolites in the extracellular milieu can decrease the activation threshold of vagal sensory nerves.[82,88] Therefore, it seems the spectrum of perturbed homeostatic conditions that are capable of sensitizing vagal sensory nerves are more than those of somatosensory and viscerosensory nerves. Furthermore, the information transferred by the somatosensory and viscerosensory afferents to the brain may induce autonomic, behavioral, and mental responses,[89] but the stimulation of vagal sensory nerves usually leads to more autonomic, mental, and behavioral changes compared to those of the somatosensory and viscerosensory afferents.[56–59] So autonomic, behavioral, and mental changes induced during the proving of a homeopathic remedy may represent the pattern of vagal sensory nerves that are stimulated by the homeopathic remedy administered during proving. Furthermore, the stimulation of the vagal sensory nerves may play a more important role in the autonomic, behavioral, and mental changes during a disease than those of the somatosensory and viscerosensory afferents.[56–59] Therefore, if autonomic, behavioral, and mental symptoms of a homeopathic remedy are similar to those of a patient, then the frequency and amplitude characteristics of the patient's nonphysiologic EM waves and those of the waves produced by nanostructures of the homeopathic remedy are similar. Furthermore, it is highly possible that the vagal sensory neurons stimulated during proving of the homeopathic remedy are the same ones that are stimulated in the patient. Administration of this homeopathic remedy to this patient results in stimulation of the sensitized vagal sensory neurons that, in turn, activate regulatory humoral and neural cholinergic anti-inflammatory responses. The cholinergic anti-inflammatory response may be either local or systemic. More severe afferent signals are required to trigger the systemic response.[77,79,90,91] Only when the patient's symptoms and those of the homeopathic remedy, especially emotional, mental, and general symptoms, are sufficiently similar; the systemic anti-inflammatory response is stimulated. In such a condition, both local and systemic deviations from homeostasis are restored. A highly matched homeopathic remedy may activate somatosensory and viscerosensory-induced descending regulatory pathways, in addition to cholinergic anti-inflammatory responses.

The regulatory responses that may be triggered by sensory neurons stimulated by homeopathic remedies following the law of similars are not restricted to the above mentioned conditions. For example, conditions with itching and emesis result in sensitization of the sensory neurons transmitting the signals that produce these symptoms. The administration of the correct homeopathic remedy leads to the stimulation of these sensory neurons by amplified EM waves that are produced by the resonance between the EM waves of the homeopathic remedy's nanostructures and those of the adjacent cells.[92,93] This, in turn, may trigger descending anti-itching or anti-emesis pathways through a mechanism similar to the vagal sensory nerves and somatosensory and viscerosensory nerves. Therefore, it is possible to suggest that every perturbation of tissue homeostasis decreases the activation threshold of sensory neurons that innervated the tissue, especially the sensory neurons that trigger the regulatory mechanism to restore the homeostasis.

The other important parameter that determines the rate of the required similarity is acuteness of the homeostatic perturbation. In acute diseases, compared to chronic cases, there is more severe inflammation and noxious stimuli, a more rapid rise in level of factors that are produced in response to perturbation of homeostasis, or a more rapid deviation of the levels of oxygen, glucose, and other metabolites in the extracellular milieu. These, in turn, dramatically decrease the activation threshold of the sensory neurons, especially those triggering regulatory responses. Thus, even the non-high-energy EM waves that are produced by the resonance between partially "similar" EM waves of both the homeopathic remedy's nanostructures and the adjacent cells may stimulate these sensory neurons. This agrees with the homeopathic literature: for the treatment of an acute disease, it does not need all of the symptoms of the patient to match those of the homeopathic remedy.[55] In the case of chronic diseases compared to that of acute diseases, however, the sensory neurons that stimulate regulatory responses are less sensitized. Furthermore, the treatment of chronic diseases, compared to that of acute diseases, needs more systemic regulatory response. These might be the reasons that a strong similarity between symptoms of the homeopathic remedy and those of the patient (especially for emotional, mental, and general symptoms) is required for the treatment of chronic diseases.[55]

However, some of the therapeutic effects of low doses or highly diluted preparations of a substance that follow the law of similars might be due to their effects on cells other than sensory neurons or the nonstimulatory effects on sensory neurons. Explaining such effects is beyond the scope of this chapter and will be discussed in future publications.

The Therapeutic Effects of Homeopathic Remedies That Do Not Follow the Law of Similars

The above mechanism holds only for the therapeutic effects of homeopathic remedies that follow the law of similars. However, some beneficial effects of homeopathic remedies do not follow this principle. These applications of homeopathic remedies are based on clinical experiences instead of proving.[65] In these conditions, the mechanism in the "Therapeutic Effects of Homeopathic Remedies Based on the Law of Similars" section can explain the affinity of the remedy to the specific tissues. One of the possible mechanisms for the therapeutic effects of homeopathic remedies in these conditions may be direct stimulation of the receptors on cells by the amplified EM waves produced through resonance between EM waves of homeopathic nanostructures and those of the adjacent cells.[4] Interaction with intracellular signaling pathways by these EM waves might be among the other possible mechanisms.[44] These suggested mechanisms may also explain some of the biological effects of homeopathic remedies *in vitro*; however, they do not explain the mechanism(s) behind the law of similars.

CONCLUSION

Whereas the resonance between the EM waves produced by living cells and homeopathic aqueous nanostructures is the basis of biological effects of highly diluted homeopathic remedies, this phenomenon by itself cannot explain the mechanism(s) behind the law of similars. According to the model presented here, when the ultra-weak ELF-EM waves produced by aqueous nanostructures of a homeopathic remedy could be resonated by ELF-EM waves of a patient's cells, the resonance occurs. The resonance-induced EM waves stimulate the patient's sensory neurons that are sensitized due to perturbation of homeostasis. This, in turn, stimulates descending regulatory responses that restore the homeostasis.

The model presented here has explained a supra-cellular and neuroimmunological mechanism for the law of similars. There are possible subcellular mechanisms for the law of similars; however, the explanation is beyond the scope of this chapter and will be explained in future publications.

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17 The Need for Quantitative Measurement Tools to Enhance Future Research Efforts on Human Intention and Human Consciousness Effects in Multidimensional Nature

*William A. Tiller**

CONTENTS

INTRODUCTION

In the first edition of this book,[1] this author introduced the topic of "subtle energies" in nature as all those energy fields functioning in nature beyond those generated by the orthodox-science-accepted four fundamental forces of gravity, electromagnetism, the weak nuclear force, and the strong nuclear force.[2] Robust experimental proof was provided for (i) a human's ability to significantly alter, at least in a metastable thermodynamic way, some properties of inorganic and organic plus nonliving and living materials[3] and (ii) the Gauge symmetry state of the experimental space wherein these four target experiments were conducted.[3] This former work illustrated the importance of both human intention, I*, and human consciousness, C*, as significant experimental variables in the investigation of nature's manifold expressions. These experimental results also indicated that our distance-time-only reference frame (RF) was in serious need of expansion to incorporate these new and robust experimental data, some of which have been replicated by others.[4–8]

In the present volume, this author has provided a somewhat detailed expansion of our single spacetime RF to a duplex, reciprocal set of subspaces RF, one of which is spacetime, while the second is a four dimensional frequency domain and all of which are imbedded in three still higher dimensional domains (refer Chapter 40). The "ladder of understanding" metaphor will be introduced in Chapter 40 to provide a specific target for our future research (see Figure 17.1).

The bottom-most rung of Figure 17.1 is allocated to representing the orthodox science research findings of the past ~500 years. The second rung represents the beginning subtle energy research findings involving I* and C* experimental variables. The higher rungs are proposed to represent future research findings associated with the higher dimensional domains of emotion, mind, and spirit via new experimental variables we have yet to discover.

The present volume is devoted to a meaningful discussion of a new experimental tool needed for further exploration of the second rung of "the ladder of understanding."

CONVERTING A pH-MEASUREMENT SYSTEM TO A ROBUST SUBTLE ENERGY MEASUREMENT TOOL

All of today's orthodox science and medicine quantitative measurement tools appear to be, in one way or another, dependent on the use of electromagnetic (EM) energies. However, these are all based on subluminal EM signals ($v < c$) and our companion studies[9] point out that vacuum domain energies are mostly superluminal ($v > c$) in nature. Thus, we cannot count on the use of EM-based instruments to explore rungs two and above in Figure 17.1. This fact presents us with a serious challenge.

In our earlier subtle energy experimental studies,[3,5–8] our general sensor-system devices were temperature (thermistors, thermocouples, and thermometers) measurement, and pH (digital electrode, litmus paper) measurement. In this work, we found that the digital pH-electrode was particularly

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FIGURE 17.1 A metaphorical description of "the ladder of understanding."

useful in replicating our $\Delta pH = +1$ unit and $\Delta pH = -1$ unit changes via specific intentions imprinted into our unique intention-host devices (IHDs). The $\Delta pH = +1$ unit change experiment was replicated at four different IHD treatment sites plus six different control sites in the USA and two control sites in Europe. These particular studies also demonstrated room temperature information entanglement between the macroscopic sized (~10^2 to 10^4 cubic feet volume) IHD sites and non-IHD sites (control sites) separated from each other by as much as 5000–6000 miles. During these studies, we discovered how to gain a quantitative measure of the elevation of the thermodynamic free energy, $\delta G^*_{H^+}$, for the aqueous H^+ ion in these IHD-conditioned spaces relative to our normal, unconditioned, U(1) electromagnetic Gauge symmetry state space.

Let us now develop a quantitative theoretical picture for the determination of $\delta G^*_{H^+}$ from pH-measurements conducted in partially "conditioned" spaces.[9]

Thermodynamics is the master area of scientific inquiry that governs all processes in nature, whether in our conventional U(1) Gauge state or in higher Gauge state symmetries. In the U(1) Gauge state, standard Maxwell equations of EM apply, whereas, in the SU(2) Gauge state, a more complex form of EM applies. For our purposes, here, the appendix provides a background primer.

In thermodynamics, one of the most important quantities is the Gibbs free energy per unit volume, G, of a material that varies in magnitude with pressure (P), temperature (T), and chemical species activity (a_j), as its main intensive variables. Secondary variables are various fields such as electrical, magnetic, gravitational, and stress. A very important derivative quantity for a neutral chemical species in the material is the chemical potential, μ_j, for the jth chemical species ($j = 0,1,2,\ldots, m$) in an alloy. For an electrically charged species in the material, one must use a second important derivative quantity called the electrochemical potential, η_j. This quantity is just the chemical potential, μ_j, plus an electrical energy term, $z_j|e|V$, where z_j is the electrical valence of the particular ion, j, $|e|$ is the absolute value of the electron's charge, and V is the electric voltage existing at the ion's position in the material. Both AC and DC electric and magnetic dipole effects are easily accounted for, as shown in the Appendix. All U(1) state thermodynamic effects can be analyzed and utilized via manipulations of G, μ_j, and η_j.

All pH-considerations, the acid/alkaline balance of water, are defined as

$$pH = -\log_{10}(a_{H^+}) \tag{17.1}$$

for the U(1) state where a_{H^+} is the thermodynamic activity of the hydrogen ion, H^+ (a proton in water). In turn, $a_j = \gamma_j c_j$, where c is the total concentration and γ is the thermodynamic activity coefficient for the solution. pH = 7 is the neutral point between acidity and alkalinity, and is usually determined by the temperature and the carbon dioxide concentration (CO_2) in the air. In fact, if one manufactures ultrapure water (pH = 7) and puts it in physical contact with today's air, the CO_2 concentration absorbed into the water is such as to make the water acidic with a $pH \approx 5.6$ within less than a day. We generally begin our water intention experiments with ultrapure water at pH = 7 in order to have a standard beginning point for all intention experiments of the $\Delta pH = +1$ unit or $\Delta pH = -1$ unit type.

When experimental data indicate that G moves away from the U(1) state, one must expand the list of thermodynamic potentials that need to be taken into account for the SU(2) state. As an example, one serious possibility to consider is that magnetic monopoles *coexist* with electric monopoles (*monopole* = a single isolated charge of the electric or magnetic type as contrasted with a *dipole* of closely opposite sign charges). It was experimentally proven by many worldwide scientists in the 1960s that *magnetic monopoles* were not accessible from a U(1) Gauge state experimental space. Thus, for an SU(2) Gauge state case, we must define a magnetoelectrochemical potential, ψ_j, which is just an expansion of the electrochemical potential, η_j, by the addition of a magnetic energy term, δG^*_j, involving the product of a magnetic charge and a magnetic potential (analogue of $z_j|e|V$ above; see Appendix).

Our present interest, here, is in j = H*, the aqueous hydrogen ion.

In experimental practice, Figure 17.2 provides the schematic setup used at all of our test sites, with the medium of investigation being some type of aqueous solution plus the sensor probes involving a pH-electrode and a temperature sensor. Here, our purpose is directed toward the *detection and measurement* of higher than U(1) Gauge states via pH-measurement.

We will first examine what is involved in the measurement of pH for our standard U(1) EM Gauge state world and then move on to see (i) when the Gauge state begins to change and (ii) when the SU(2) Gauge state world is achieved so that one can compare the differences between these two major EM Gauge states.

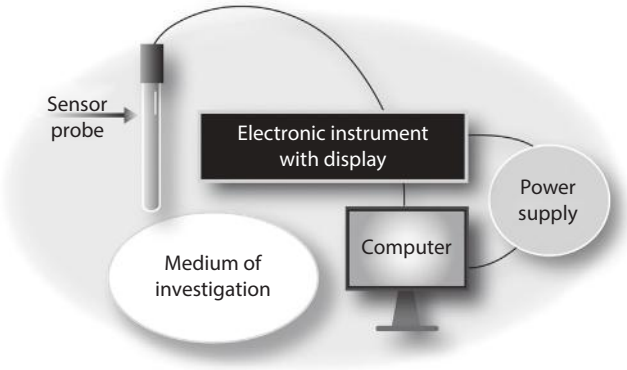

FIGURE 17.2 Diagram of our overall experimental setup.

From our earlier work,[3] we showed experimentally that, for an IHD-conditioned space, *any* material property measurement, Q_M, is given by

$$Q_M = Q_D + \alpha_{eff}\, Q_R \tag{17.2}$$

Here, Q_D is the magnitude that our commercial instruments detect from our spacetime-only aspect of the material; Q_R is the magnitude that is present for our frequency domain aspect (normally undetected) and α_{eff} is the *coupling* coefficient that allows Q_R to be *accessed* by the commercial instruments of our conventional U(1) Gauge state physical reality.

The U(1) Gauge State Reality ($\alpha_{eff} = 0$)

Equation 17.1 provides the standard definition of pH while Figure 17.3 provides qualitative plots of H^+-ion spatial profiles at a pH-electrode cell/aqueous electrolyte interface (n_0 = the background H^+ concentration of the electrode cell and n_∞ = the bulk H^+ concentration of the aqueous solution sample being measured). The mathematical analyses of these n_{H^+} profiles are provided in the Appendix.

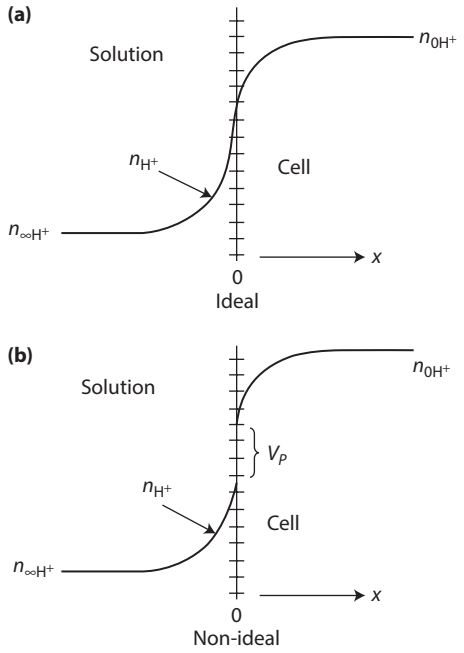

FIGURE 17.3 Plots of H^+ ion density, n_{H^+}, profiles in a pH-electrode for (a) the ideal case and (b) the non-ideal case.

The physical aspect of pH measurement involves a device that connects (i) a standard unit H^+ electrochemical activity cell to (ii) an aqueous solution vessel whose H^+-ion activity is to be measured via (iii) an H^+-permeable membrane located between (i) and (ii).

As the H^+ ion redistributes itself in this system to produce thermodynamic electrochemical potential, η_{H^+}, equilibrium throughout the entire system of Figure 17.3, n_{H^+} changes to the profile illustrated in Figure 17.3a for the ideal case (no membrane adsorption). In this case, one theoretically obtains a simple mathematical relationship connection between the measuring electrode voltage, V, and the bulk solution pH, as

$$V - V_0 = -59.16\ \text{pH (mV)} \tag{17.3a}$$

where V_0 is the unit cell voltage in Figure 17.3. Thus, an experimental measurement of V automatically provides one with a determination of pH for the ideal case.

For the *non-ideal* or *real* electrode case, illustrated in Figure 17.3b, where V_p is the interface polarization factor has a nonzero value, the commercial pH-meter's central processing unit (CPU) incorporates a corrected temperature factor, T_{CORR}, which uses a *parametric* expression to display pH from an internal measurement of V. Here, they set $V_0 = 7$ S, where S is the electrode slope with respect to pH. Thus, they use

$$V = S(pH_{U(1)} - 7)\, T_{CORR} \text{ where } T_{CORR} = \frac{T + 273.15}{298.15} \tag{17.3b}$$

We have taken Equation 17.3b and defined an important new parameter, N, and called it the *Nernst Parameter*, in honor of the great physical chemist of the 1800s, where

$$N = \frac{S}{V}(pH - 7)T_{CORR} \tag{17.4}$$

Of course, N should equal unity for the U(1) Gauge state where $pH = pH_{U(1)}$ as in Equation 17.3b. Experimental data shows that for "unconditioned" spaces, N = 1 is observed.

Back in ~January 2003, in the early *replication* phase of our Minnesota $\Delta pH = +1$ unit IHD studies,[6] Figure 17.4 provides an experimental example of (i) the exponential time-dependent change in measured pH(t) as a function of time compared with the theoretically calculated $pH_{U(1)}$ values plus (ii) the experimental N-values as a function of time determined via Equation 17.4. Here, one sees that N decreases from unity as the pH departs further from the theoretically calculated $pH_{U(1)}$ value. Figure 17.4 experimental data was from Payson Site P_4 while Table 17.1 data provides a range

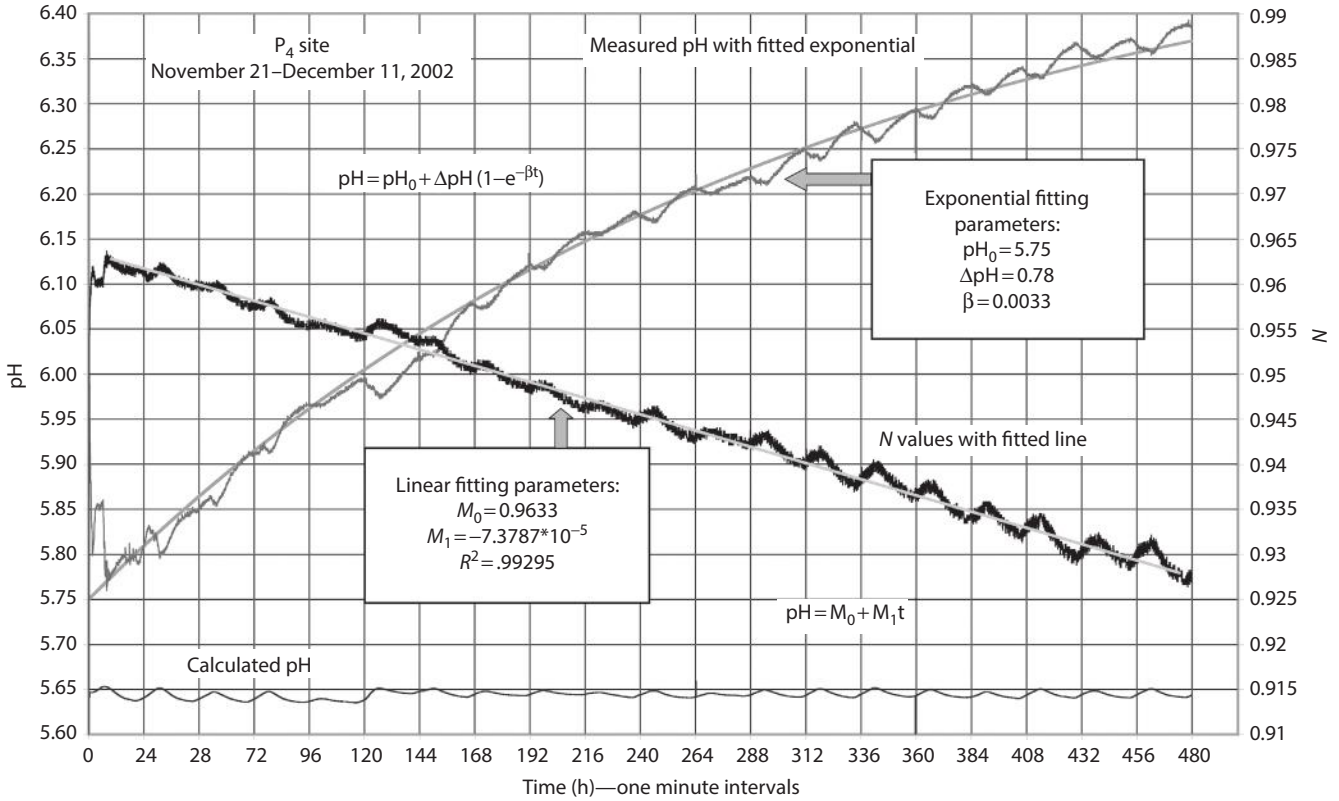

FIGURE 17.4 Showing the time-average exponential variation of pH and N after fresh purified water was introduced into the measurement cell on 11/21/02.

TABLE 17.1
Values of N for All of the Various Sites Operating in Our Overall Experimental System

Site	Recent N-Values	% Departure from 1.00
P_1	0.89	–11
P_2	1.14	14
P_3	0.98	–2
P_4	0.87	–13
M_1	1.3	30
K_1	0.98	–2
B_2	1.23	23
B_1	1.04	4

P = Payson, K = Kansas, M = Missouri, B_1 = Baltimore and B_2 = Bethesda and the subscript numbers stand for particular measurement stations located at these geographic sites (see reference 6) as of ~January 25, 2003.

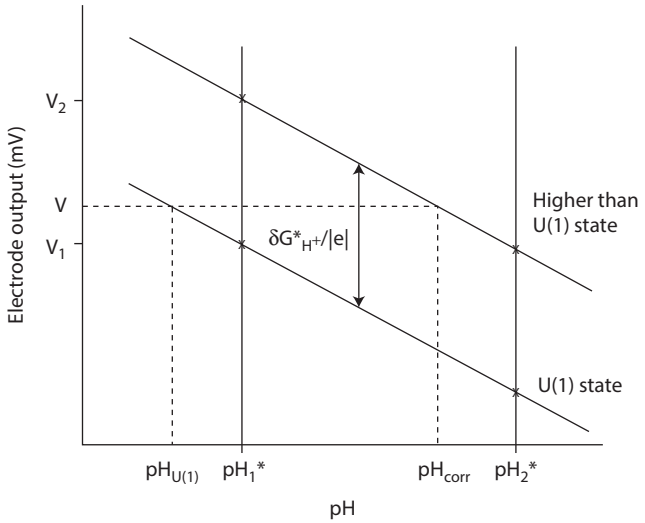

FIGURE 17.5 The electrode electrical output vs. pH plots for both the U(1) state ($\delta G^* = 0$) and a higher than U(1) EM Gauge symmetry state.

of N-values from different sites in our total experimental system.

This Figure 17.4 data is totally consistent with Figure 17.5 where the standard electrode voltage, V, versus pH for the U(1) Gauge state case is experimentally provided. For higher Gauge states, constancy of S is assumed so that, for a background voltage, V_B, shift with $V_B^{SU(2)} > V_B^{U(1)}$, the upper line must be vertically shifted as indicated.

The second obvious change to occur in our analysis is that, for fixed electrode voltage (V), relative to the background voltage (V_B), although the internal CPU of the device will show $pH_{U(1)}$, one must change this to pH_{CORR} from Figure 17.5. Thus, one can expect to see at least two new significant contributions to manifest as a result of "conditioning" the

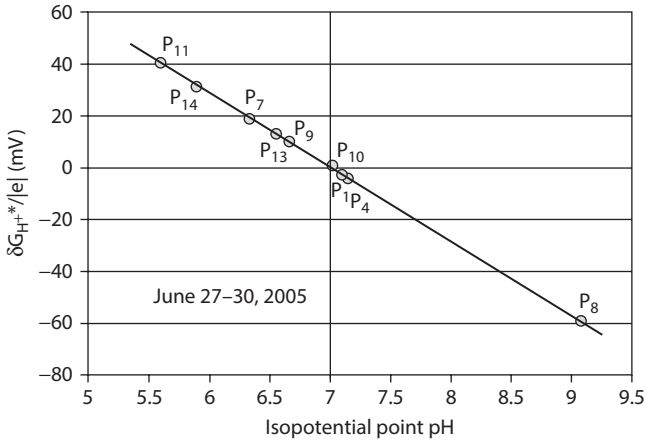

FIGURE 17.6 $\delta G^*_{H^+}$ vs. isopotential point of various electrodes (same type) used at the various P_j stations shown (for the Payson laboratory at calibration). The only difference between electrodes used at these stations is their history. The type of space the electrode is exposed to causes the isopotential point to depart from 7.

experimental space via either an IHD source or the biofield of a human source.

Utilizing Figure 17.5, an analogous parametric expression like Equation 17.3b can be developed to yield

$$V = S(pH_{CORR} - 7)T_{CORR} - \delta G^*_{H^+}/|e| \qquad (17.5a)$$

with

$$pH_{CORR} = pH_{U(1)} - \delta G^*_{H^+}/S|e| \qquad (17.5b)$$

obtained directly from Figure 14.5b. Also, N in Equation 17.4 must change accordingly (even though N is no longer relevant to us).

As the experimental isopotential point for the particular pH-electrode being used (the V = 0 point), we obtain

$$\frac{\delta G^*_{H^+}}{|e|} = \frac{S(pH^o_{U(1)} - 7)T_{CORR}}{1 + T_{CORR}} \qquad (17.6)$$

Experimentally, one can determine the isopotential point, $pH^o_{U(1)}$, via the use of two or three buffer solutions, if a linear relationship between V and $pH_{U(1)}$ is measured (as in Figure 17.5). Using a variety of pH-electrodes of the same commercial type but with different use histories, this experimental procedure (with 2-buffer solutions pH_1^* and pH_2^*) was utilized at nine different experimental stations in the Payson laboratory to obtain Figure 17.6. This is a beautiful linear plot, in complete accord with Equation 17.6 that yields $\delta G^*_{H^+} = 0$ at $pH^o_{U(1)} = 7$, as expected.

As a closing statement to this section, experimentally, we should look more closely at water, which has two chemical forms (i) *ortho* water wherein the two adjacent spins in the HOH molecule point in opposite directions and (ii) *para* water wherein the two adjacent spins in the HOH molecule point in the same direction. Further, in an electrolyte, the H^+-ion is a single proton with spin so that, at some temperature and CO_2 concentration, one might expect to observe spin-spin interactions and magnetic-like properties. Add to this IHD-conditioned space effects, wherein we have already observed some unique magnetic monopole[5–7] type effects and SU(2) Gauge state type of phenomena. Something worth considering in the future!

Although a serious need also exists for a measurement tool for serious studies of human consciousness, C*, because of space limitations, the reader is directed to the last half-dozen pages of Reference 10.

APPENDIX A: PRIMER THEORY FOR Ψ_{H^+} AND $\delta G^*_{H^+}$

In thermodynamics, one of the most important quantities is the Gibbs free energy, $G(P,T,c_j)$, in terms of the intensive variables P (pressure), T (temperature) and c_j (concentration of j-species for j = 0,1,2…m) of the system. An important derivative quantity is the neutral species chemical potential for the j-component defined as

$$\mu_j = \left(\frac{\partial G}{\partial c_j}\right)_{P,T,c_k\,(k\neq j)} = \mu_{0j} + kT\ln a_j \qquad (17.A.1a)$$

Here, $a_j = \gamma_j c_j$ is the thermodynamic activity of the j-species and γ_j is called the activity coefficient of j, k = Boltzmann's constant and μ_{0j} is the standard state chemical potential for the j-species while T is temperature. In this regard, one can incorporate the AC (alternating current) $\underline{E}$ (electric field) and $\underline{H}$ (magnetic field) energy storage, $\Delta\mu_{0j}$, into the μ_{0j} term or the γ_j term where

$$\Delta\mu_{0j} = -\frac{\hat{\upsilon}_j}{2}\frac{d}{dc_j}\left\{\varepsilon\underline{E}^2 + m\underline{H}^2\right\} \qquad (17.A.1b)$$

Here, $\hat{\upsilon}_j$ is the molal volume of j, ε is the electric permittivity of the medium while m is its magnetic permeability. The SI units for E and H are volt/meter and ampere/meter, respectively. For ionic species rather than neutral species, one uses the electrochemical potential, η_j, defined as

$$\eta_j = \mu_j + z_j|e|V \qquad (17.A.1c)$$

where V is the electric potential (voltage), e is the electron charge and z is the ion valence.

The foregoing paragraph applies to our normal, present-day world level wherein the electromagnetic (EM) gauge symmetry state is at the U(1) level. This means that standard Maxwellian EM applies and only one internal space parameter, the phase-angle for the electron wave-function, needs to be defined to satisfy the U(1) requirement. For an IHD-conditioned space,[1–5] the experimental data indicates that the thermodynamic free

energy level moves away from that for the U(1) state given by Equation 17.A.1c and must now be defined by

$$\Psi_j = \eta_j + \delta G_j^* \qquad (17.A.1d)$$

In all probability, δG_j^* is given by

$$\delta G_j^* = q_{m_j} \varnothing_{mj} \qquad (17.A.1e)$$

where q_m is the instrumentally accessed magnetic charge and $\varnothing_{mj}$ is the magnetic potential for the j-species. This new magnetic potential, $\varnothing_m$, is definitely not the vector potential, $\underline{A}$, and provisionally should be considered as a scalar potential or as a tensor potential.

APPENDIX B: pH-ELECTRODE BEHAVIOR ASSOCIATED WITH BOTH U(1) AND SU(2) STATES

Utilizing Figure 17.3, the thermodynamic equilibrium process for the very mobile H^+ ions is given by the general Boltzmann equilibrium equation for H^+

$$\frac{a_{H^+}}{a_{0H^+}} = \exp\left[\frac{-|e|}{kT}\{V - (V_0 + V_P)\}\right] \qquad (17.B.1a)$$

Here, exp is the exponential function, V_0 is the electric voltage of the standard chemical cell in Figure 17.3a, $V_P = 0$ in the ideal case, but is most generally nonzero, and is the interface polarization voltage (see Figure 17.3b) due to the redistribution of all other chemical species in the solution, V is the solution voltage, a_0 is chemical activity for the standard cell while lel/2.303 kT = 59.16 millivolts (lel is the proton charge, T is the absolute temperature and k is Boltzmann's constant). Combining Equations 17.1 and 17.B.1a with $a_{0H^+} = 1$, $V_P = 0$ and $\log_{10}(\exp) = 1/2.303$, one obtains, via taking $\log_{10}$ of both sides in Equation 17.B.1a, the simple relationship connecting the physical measurement, $V–V_0$ to the solution pH as

$$V = V_0 - 59.16\ pH\ (mV) \qquad (17.B.1b)$$

where V_0 is the cell voltage in Figure 17.3.

For the non-ideal or real pH-electrode case (Figure 17.3b) with $V_P \neq 0$, a commercial pH-meter's CPU incorporates a corrected temperature factor and uses the following parametric expression to display the pH from an internal measurement of V,

$$V = S(pH_{U(1)} - 7)\,T_{CORR} \text{ where } T_{CORR} = \frac{T + 273.15}{298.15} \qquad (17.B.1c)$$

Here, S is the electrode slope = $d[V - (V_0 + V_P)]/dpH$ and $pH = pH_{CPU} = pH_{(U(1))}$. In addition, V_0 is taken to be –7S, as the experimental isopotential point (V = 0) is found to occur at pH = 7 for an ideal electrode. In order to make these parametric choices of the commercial pH-electrode suppliers fit the fundamental physics implicit in Equation 17.4, the following is also required for internal self-consistency

$$V_P = (S + 59.16)\ pH_{U(1)}\ T_{corr} \qquad (17.B.1d)$$

From Equation 17.B.1c, we can define a new parameter, N, by rearranging this equation and call it the Nernst Parameter in honor of that great physical chemist of the 1800s where

$$N = \frac{S}{V}(pH - 7)\,T_{CORR} \qquad (17.B.2)$$

For the U(1) state, N must always be unity. When $N \neq 1$, usually because pH in Equation 17.B.2 is different than $pH_{U(1)}$ in Equation 17.B.1c, then we have reached the SU(2) state where our two unique levels of physical reality become coupled and our measuring instrument reveals that Equation 17.2 of the main text applies, where $\propto_{eff}$ is of a significant magnitude and Q_R can be positive or negative. For this SU(2) case, Equation 17.B.1a must be modified to

$$\frac{a_{H^+}}{a_{0H^+}} = \exp\left[\frac{-|e|}{kT}\left\{V - \left(V_0^* + V_P^*\right) + \frac{\delta G_{H^+}^*}{|e|}\right\}\right] \qquad (17.B.3a)$$

Now, because H^+ has a magnetic dipole moment and an R-space magnetic potential, $\varnothing_m$, is also present, the standard cell chemical activity, a_{0H^+}, can no longer be assumed to be unity. In addition, V_0^* and V_P^* must be considered to be different than their U(1) EM gauge state values. Thus, taking $\log_{10}$ of both sides of Equation 17.B.3a, we have

$$pH - \log_{10}(a_{0H^+}) = \frac{-|e|}{2.303kT}\left\{V - \left(V_0^* + V_P^*\right) + \frac{\delta G_{H^+}^*}{|e|}\right\} \qquad (17.B.3b)$$

Rearranging, Equation 17.B.3b becomes

$$V = -59.16\ pH_{corr}\,T_{corr} + \left[V_0^* + V_P^* + 59.16\ \log_{10} a_{0H^+} - \frac{\delta G_{H^+}^*}{|e|}\right] \qquad (17.B.3c)$$

In the main text it was pedagogically useful to use the parametric form of Equation 17.3b to express the connecting relationship between V and pH with S being the slope, V_0 being –7S and V_P being a correction factor, or baseline voltage, V_B, in Figure 17.5 to make everything be mathematically correct in the final form for the U(1) case. Here, for the SU(2) case, it is also pedagogically useful to use this type of parametric form and allow correction factors to adjust for mathematical precision. Our chosen parametric form is

$$V = S(pH_{corr} - 7)T_{corr} - \frac{\delta G_{H^+}^*}{|e|} \qquad (17.B.4a)$$

with

$$V_0^* = V_0 + \Delta V_{0m} = -7S + \Delta V_{0m} \quad (17.B.4b)$$

$$V_P^* = V_P + \Delta V_{pm} = (S + 59.16)pH_{corr} - \Delta V_{0m} - 59.16 \log_{10}(a_{0H^+}) \quad (17.B.4c)$$

and

$$\Delta V_{pm} = (S + 59.16)(pH_{corr} - pH_{U(1)})T_{corr} - \Delta V_{0m} - 59.16 \log_{10}(a_{0H^+}) \quad (17.B.4d)$$

Thus, in Figure 17.5 of the main text

$$V_B^{U(1)} = (S + 59.16)pH_{U(1)}\ T_{corr} \quad (17.B.5a)$$

and

$$V_B^{SU(2)} = V_P^* + \Delta V_{0m} + 59.16 \log_{10} a_{0H^+} \quad (17.B.5b)$$

$$= V_B^{U(1)} + (S + 59.16)[pH_{corr} - pH_{U(1)}]T_{corr} \quad (17.B.5c)$$

Thus, if $V_B^{U(1)}$ is chosen as a constant baseline through the transition of $\propto_{eff}$ from ~0 to ~1 due to space "conditioning," then the upper line in Figure 17.5 must be shifted upwards by an additional segment of magnitude $[V_B{}^{SU(2)} - V_B{}^{U(1)}]$. Such a choice would produce an altered value of pH_{corr}. The bottom line here is that there are, at least, two main space conditioning factors to deal with: (i) the instrumentally accessed magnitude of $\delta G^*_{H^+}$ and (ii) a pH-electrode "conditioning" effect.

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Section IV

Brain, Nerve, and Bone Stimulation

18 Repetitive Transcranial Magnetic Stimulation for Depression and Other Indications

Mark S. George, E. Baron Short, Suzanne Kerns, Xingbao Li, Colleen Hanlon, Christopher Pelic, Joseph J. Taylor, Bashar W. Badran, Jeffrey J. Borckardt, Nolan Williams, and James Fox*

CONTENTS

INTRODUCTION

Transcranial magnetic stimulation (TMS) can noninvasively, and relatively painlessly, focally stimulate the brain of awake individuals.[1] When TMS pulses are delivered in a periodic repeating pattern, it is referred to as repetitive TMS, or rTMS. rTMS is sometimes modified by the adjectives "fast," to describe stimulation frequencies greater than 1 Hz, or "slow," for frequencies of 1 Hz or less.[2] Fast rTMS is currently limited to very brief runs of about 25–30 Hz, although some machines can now reach 50 Hz for brief bursts. Stimulation frequencies faster than this have an increased seizure risk and most modern capacitors cannot keep delivering the needed energy before depleting.[3]

TMS is able to focally stimulate the cortex by creating a dynamic magnetic field generated by brief but powerful electrical currents passed through an electromagnetic coil.[4] This localized pulsed magnetic field over the surface of the head depolarizes underlying superficial neurons,[5,6] which then induces electrical currents in the brain.[7] High-intensity current is rapidly turned on and off in the electromagnetic coil through the discharge of capacitors. Thus, the end result

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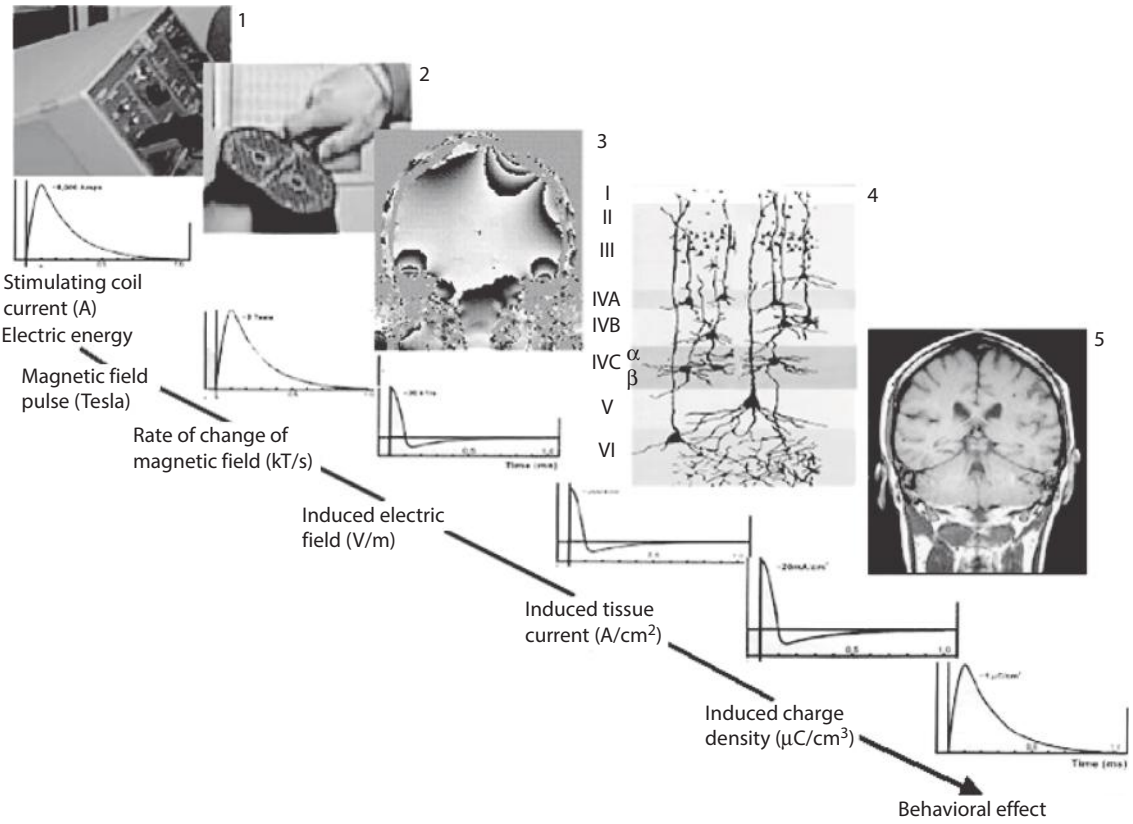

FIGURE 18.1 **(See color insert.)** This diagram shows the cascade of events that occur following a transcranial magnetic stimulation pulse. It was initially thought that almost all of the biological effects of TMS come from the electrical induced current in the brain, at the end of the cascade. The studies and discussion of the rest of this book, however, reveal that there may be biological effects of the magnetic field itself, or any of the other steps in the TMS cascade.

of TMS is electrical stimulation of the brain, explaining why some refer to TMS as "electrodeless electrical stimulation" (see Figure 18.1). The magnetic fields produced by TMS are thus integral in transmitting energy across the skull. Figure 18.1 shows how the electrical energy stored in a capacitor discharges and creates about 3000 amps. Through Maxwell's equations and Faraday's law, this creates a powerful magnetic field, on the order of 2 Tesla. This rapidly changing magnetic field (~30 kT/s) then travels across the scalp and skull and induces an electric field within the brain (~30 V/m). This induces current to flow in the brain by creating a transmembrane potential (for a thorough discussion see Reference 8).

Conventional TMS or rTMS, which produces powerful but brief magnetic fields that in turn induce electrical currents in the brain, therefore differs from most of the techniques discussed elsewhere in this book where direct electrical or magnetic energy is applied to the brain or body. TMS also radically differs from the currently popular use of low-level static magnetic fields as alternative therapies. The chapters in the rest of this book describe how constant exposure to static magnetic fields can have biological effects.[9] However, conventional TMS generates brief temporal dynamic magnetic fields on the scale of microseconds, and they are relatively weak except directly under the TMS coil. It is thus assumed, by most TMS researchers, that TMS produces its behavioral effects solely through the induction of electrical currents in the cortex of the brain. This assumption, however, has not been proven and the pulsed magnetic field generated by the TMS coil likely has some biological effect apart from the ability to induce neuronal depolarizations. Although direct transcutaneous applications of electricity can influence brain function, this is extremely painful.[10] Moreover, the skull acts as a large resistor in direct electrical current applications that increases the difficulty to focus the electricity to specific brain regions.

Most recently, one manufacturer (Neosync, Boston, MA, USA) has produced a form of TMS called synchronized TMS, or sTMS.[11] In this version of TMS, static magnets placed across the vertex rotate at a set frequency. These static magnets are not powerful enough to move the thumb. However, their synchronized rotation generates a fluctuating magnetic field, which can influence the brain's magnetic field, especially if the rotation or rhythm is synchronized with the patient's brain. This form of TMS, called sTMS, may be interacting with the brain in a way that is very different from other forms of more powerful TMS.[12,13]

The magnetic field induced by TMS diminishes rapidly as distance increases away from the coil. Thus, with current technology, TMS coils are only able to directly electrically

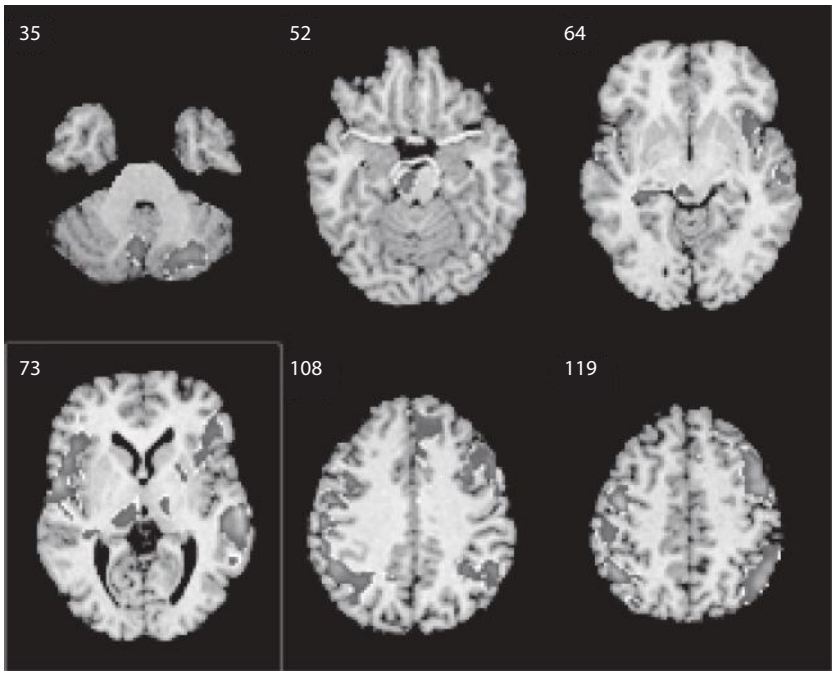

FIGURE 18.2 (See color insert.) fMRI demonstrates the secondary brain effects of prefrontal transcranial magnetic stimulation (TMS). Shown in color are the brain regions that are significantly activated compared to rest ($p < 0.01$, extent $p < 0.05$) in six adults with clinical depression during left prefrontal TMS at 1 s. The differences are projected on a common brain (Talairach). The arrow depicts the TMS coil position, which follows the algorithm developed in 1994 for probabilistically finding the prefrontal cortex based on relative distance from the motor cortex. TMS was originally used over the prefrontal cortex to treat depression because of the potential for activating cortical-limbic loops. Imaging studies such as this one show that this assumption was likely correct and that the prefrontal cortex is a window to stimulating subcortical and limbic sites. Future work is needed to determine the optimum cortical sites for maximal clinical effectiveness, and whether there are general rules for finding this across individuals or should be individually guided based on structural or functional imaging.[209] (From MUSC Brain Stimulation Laboratory and Center for Advanced Imaging Research, Dr. Li.)

stimulate the superficial cortex, and are not able to produce direct electrical stimulation deep in the brain. Although this limited depth of penetration is a limitation of present technology, deeper brain structures can be influenced by cortical TMS, due to the cortex's massive interconnections, and redundant cortical-subcortical loops[14] (see Figure 18.2). Moreover, several groups (Brainsway, Jerusalem, Israel; Cervel, San Jose, CA, USA) have developed novel TMS coil designs that reach deeper into the brain without overwhelming superficial cortical structures.[15–20] The studies combining TMS with functional imaging (PET, SPECT, fMRI), have now convincingly shown that TMS applied to the cortex can activate cortical-limbic loops.[21–24] Whether these secondarily transmitted TMS signals are involved in therapeutic mechanisms of action remains unclear, although the evidence is mounting that TMS causes changes in effective connectivity and plasticity within circuits.

The amount of electricity needed to cause changes in the cortex varies from person to person, and from one brain region to the next.[25] One commonly used method for standardizing and adjusting the amount of electricity delivered and induced by TMS across different individuals is to determine each person's motor threshold (MT). The MT is commonly defined as the minimum amount of electricity needed to produce movement in the contralateral thumb, when the coil is placed optimally over the primary motor cortex. MT can be determined either by using EMG recordings,[26] or, with less precision, by using visible movement.[27]

TMS MECHANISMS OF ACTION

The mechanisms of the action of TMS can be grouped according to the time course of their effects—immediate (seconds), intermediate (minutes) and long-term (days). TMS has been shown to produce *immediate effects (within seconds)*, such as the movement of the thumb, or direct inhibition of another TMS pulse followed shortly in time. These immediate effects are thought to result from direct excitation of inhibitory or excitatory neurons. There is some evidence to suggest that TMS at different intensities, frequencies, and coil angles, can excite different elements (cell bodies, axons) of different neuronal groups (interneurons, neurons projecting to other parts of the cortex, U fibers).[3,28,29] This is further complicated by the 6-layer arrangement of human neocortex, along with the varying gyral folds, which place some aspects of the brain very close to the surface, and others far away in sulcal folds.[24]

A quick jerky movement or a flash of light are about the only easily observable short term effects that have been produced with TMS. This is somewhat disappointing given the rich literature of complex smells, sounds, and memories produced in epilepsy patients with direct electrical stimulation.[30] Why does TMS not produce the same immediate behavioral effects as direct electrical stimulation? A full discussion of this most interesting question is beyond this chapter.[31,32] An important method for studying immediate TMS effects is through a process called *paired-pulse TMS (ppTMS)*. This technique involves delivering two consecutive TMS pulses to the same region with varying interpulse intervals (usually milliseconds long) and intensities.[26] Depending on the relative strength of the first pulse to the second, and the interpulse interval, the first pulse can either inhibit or enhance the second pulse. Paired pulse TMS (ppTMS) over the motor area can be used to assess natural brain inhibitory and excitatory systems, both at rest in individuals with different disorders,[33] and following the administration of different centrally-active compounds, or other treatments.[34] Because it uses a motor evoked potential (MEP) as the endpoint variable, paired pulse TMS can only make statements about the motor cortex.[35]

One of the most easily demonstrated immediate effects of TMS is *speech arrest*, where high frequency TMS, placed precisely over the Broca's area, can immediately and transiently block fluent speech.[36] TMS, used in studies like this, can produce what are sometimes referred to as "virtual lesions." Importantly, none of these temporary lesion effects has been demonstrated to persist beyond the time of active TMS administration. Thus, the "lesions" are truly "virtual" and temporary. It is unclear what is happening at a neurobiological level during speech arrest. It is likely that the TMS pulses are interfering with normal brain function, prohibiting that brain region from participating in coordinated circuit behavior. Early theories that the region was "jammed" are not likely true, as speech arrest can be achieved with frequencies as low as 4 Hz. Recent modeling and experimental work with deep brain stimulation (DBS) has shown that even at frequencies of >100 Hz, information is still flowing through a stimulated region,[37] albeit of a highly regular and nonphysiologic nature.

The intermediate effects of TMS (seconds to several minutes) likely arise from transient changes in local pharmacology, such as gamma amino butyric acid (GABA) or glutamate, and changes in local resting "tone" or activity. Much attention has been focused on whether and to what degree different frequencies of TMS might have divergent intermediate-term biological effects. For example, repeated stimulation of a single neuron at low frequency in cell culture produces long-lasting inhibition of cell-cell communications (called long-term depression or LTD).[38,39] Conversely, repeated high frequency stimulation can improve cell-cell communication (called long-term potentiation or LTP).[40] Scientists have wondered whether TMS, exciting hundreds or thousands of neurons in a pulse, can produce sustained inhibitory or excitatory effects in a way analogous to single cell electrical stimulation.[41] Supporting this concept, many studies have now shown that chronic low frequency stimulation of the motor cortex can produce inhibitory *intermediate term effects* (lasting for several minutes) following stimulation.[42] There is also evidence that high frequency stimulation can produce intermediate term excitatory effects.[43]

Many investigators have used TMS to influence brain functions at this immediate or intermediate time domain to explore how the brain works. These studies have investigated movement,[44] visual perception,[45] memory,[46] attention, speech,[47] and mood.[48] A full review is beyond the scope of this chapter.[6,49]

Longer-term effects of TMS are those that occur over days to weeks. The antidepressant and likely other therapeutic effects of TMS fit under this category. Less is known about the neurobiological mechanisms involved in this class of effects, although new studies are being published monthly. As discussed below, TMS causes changes in cortical-limbic loops, and function in these circuits is changing over time. There is also some evidence that TMS might have long-term anticonvulsant effects.

Animal Models

Numerous animal studies have been important in trying to understand the modes of action of TMS. TMS studies with intracranial electrodes in rhesus monkeys have provided information about the nature and spatial extent of the rTMS-induced electric field.[50] Corticospinal tract development, aspects of motor control, and medication effects on corticospinal excitability have been studied fairly extensively in nonhuman primates using single pulse TMS.[51–57] Such work has yielded information about TMS neurophysiological effects, such as the observation that TMS evoked motor responses result from direct excitation of corticospinal neurons at or close to the axon hillock.[57]

Rodent rTMS studies have reported antidepressant-like behavioral and neurochemical effects. In particular, rTMS enhances apomorphine-induced stereotypy and reduces immobility in the Porsolt swim test.[58] rTMS has been reported to induce electroconvulsive shock (ECS)-like changes in rodent brain monoamines, beta-adrenergic receptor binding, and immediate early gene induction.[59, 60] The effects of rTMS on seizure threshold are variable and may depend upon the parameters and chronicity of stimulation.[61] Even with the attempt at focal rat stimulation, the effects involve an entire hemisphere and cannot readily be extrapolated to what is happening in human TMS using focal coils.

Combining TMS with Functional Imaging

A critically important area is to combine TMS with functional imaging to directly monitor TMS effects on the brain, and to thus understand the varying effects of different TMS use parameters on brain function. As it appears that TMS at different frequencies has divergent effects on brain activity, combining TMS with functional brain imaging will better delineate not only the behavioral neuropsychology of various psychiatric syndromes, but also some of the pathophysiologic circuits in the brain. In contrast to imaging studies with

ECT, which have found that ECT shuts off global and regional activity,[62] most studies using serial scans in depressed patients undergoing TMS have found increased activity in the cingulate and other limbic regions.[63,64] However, two studies have now found divergent effects of TMS on regional activity in depressed patients, determined both by the frequency of stimulation and the baseline state of the patient.[65,66] That is, for patients with global or focal hypometabolism, high frequency prefrontal stimulation has been found to increase brain activity over time, with the opposite happening as well. Conversely, patients with focal hyperactivity have been shown to have reduced activity over time following chronic daily low frequency stimulation. However, these two small sample studies have numerous flaws. They simultaneously show the potential, and the complexity, surrounding the issue of how to use TMS to change activity in defined circuits. They also point out an obvious difference with ECT, where the net effect of the ECT seizure is to decrease prefrontal and global activity.[62]

Several recent studies combining TMS with other neurophysiological and neuroimaging techniques have helped to elucidate how TMS achieves its effects. Our group at MUSC has pioneered and perfected the technique of interleaving TMS with blood oxygen level dependent (BOLD) fMRI, allowing for direct imaging of TMS effects with high spatial (1–2 mm) and temporal (2–3 s) resolution.[67–72] Other groups in Germany, London, and at Stanford, have now succeeded in interleaving TMS and fMRI in this manner, partially replicating the earlier MUSC work.[72] Work with this technology has shown that prefrontal TMS at 80% MT produces much less local and remote blood flow changes than does 120% MT TMS.[73] Strafella et al. used PET to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus[74] and has reciprocal activity with the anterior cingulate gyrus.[75]. Our group at MUSC,[63] as well as groups in Scotland[64] and Australia,[66] have all shown that lateral prefrontal TMS can cause changes in the anterior cingulate gyrus and other limbic regions in depressed patients. It is thus clear that TMS delivered over the prefrontal cortex has immediate effects in important subcortical limbic regions (see Figure 18.2). The initial TMS effect on cortex and the secondary synaptic changes in other regions likely differs as a function of mood state, cortical excitability, and other factors that would change resting brain activity. Combining TMS with functional imaging will likely continue to be an important method for understanding TMS mechanisms of action. Combinational TMS/imaging will likely also evolve to be an important neuroscience tool for researching brain connectivity.[21,22,76,77]

AN UPDATE ON THERAPEUTIC USES OF TMS

Depression

Although there is controversy, and much more work is needed, certain brain regions have consistently been implicated in the pathogenesis of depression and mood regulation.[78–83] These include the medial and dorsolateral prefrontal cortex, the cingulate gyrus, and other regions commonly referred to as limbic (amygdala, hippocampus, parahippocampus, septum, hypothalamus, limbic thalamus, insula) and paralimbic (anterior temporal pole, orbitofrontal cortex). A widely held theory over the last decade has been that depression results from a dyregulation of prefrontal cortical and limbic regions.[81,82,84,85]

The original uses of TMS as an antidepressant were not influenced by this regional neuroanatomic literature, and stimulation was applied over the vertex.[85–87] However, working within the prefrontal cortical limbic dysregulation framework outlined above and realizing that theories of ECT action emphasize the role of prefrontal cortex effects,[88] one of us (MSG) in 1995 performed the first open trial of prefrontal TMS as an antidepressant,[89] followed immediately by a crossover double-blind study.[90] The theory behind this work was that chronic, frequent, subconvulsive stimulation of the prefrontal cortex over several weeks might initiate a therapeutic cascade of events both in the prefrontal cortex as well as in connected limbic regions, thereby alleviating depression symptoms.[91] The imaging evidence previously discussed now shows that this hunch was correct—prefrontal TMS sends direct information to important mood-regulating regions like the cingulate gyrus, orbitofrontal cortex, insula, and hippocampus (see Figure 18.2). Thus, beginning with these prefrontal studies, modern TMS was specifically designed as a focal, nonconvulsive, circuit-based approach to therapy. TMS was conceived of and launched to bridge from functional neuroimaging advances in circuit knowledge to the bedside as a focal, noninvasive treatment.

Since the initial studies, there has been continued high interest in TMS as an antidepressant treatment. Multiple trials have been conducted from researchers around the world. In general, there is not a large industry sponsoring or promoting TMS as an antidepressant (or therapy for other disorders), and the funding for these trials, until just recently, has largely come from foundations and governments. The sample sizes in these antidepressant trials, especially those before 2010, are small (in all, less than 100 per trial) compared to industry-sponsored pharmaceutical trials of antidepressants. A thorough review of all of these trials is beyond the scope of this update. However, the overwhelming majority of approximately 89 studies have found modest antidepressant effects that take several weeks to build.[92] Not all TMS antidepressant treatment studies have been positive.[93]

In 2008, the NeuroStar TMS Therapy system (Neuronetics, Inc., Malvern, PA, USA) received Food and Drug Administration (FDA) clearance for the treatment of adult patients with major depressive disorder (MDD) who have failed to receive satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. FDA clearance was based on a large, multisite, sham-controlled randomized study that showed that daily prefrontal TMS was a safe and effective treatment for certain patients with major depression. The observed effect sizes in both the original study population ($n = 301$),[94] and in the subset of patients who met the FDA

approved indication for use of the NeuroStar TMS Therapy system ($n = 164$)[95] are of similar or greater magnitude than those observed with the majority of currently approved antidepressant medication treatments.

George et al., in a 190 patient NIMH-sponsored multisite, randomized controlled trial (called OPT-TMS) demonstrated that rTMS, as drug-free monotherapy, produced statistically significant antidepressant effects with a remission rate 4 times that of sham patients.[96] This study provided industry independent Class I evidence of safety and efficacy in a well-studied and carefully controlled cohort. Recently two additional publications resulted from this trial. McDonald et al.[97] reported on an open-label extension phase. They found that 43 of 141 (30.5%) patients who enrolled in the open phase study eventually met criteria for remission. Some patients took up to 6 weeks to fully remit.[97] Most recently Mantovani et al. reported on the three-month durability of the TMS antidepressant response in this trial. Of the 50 patients who remitted and agreed to participate in follow-up, at 3 months, 29 of 50 (58%) were classified as in remission (HDRS-24 </ = 10), two of 50 (4%) as partial responders (30% </= HDRS-24 reduction <50% from baseline), and one of 50 (2%) met criteria for relapse.[98]

Zangen and colleagues have completed a large multisite antidepressant trial, which resulted in FDA clearance of their device (Brainsway H Coil) for treating depression in February 2013. This trial has not yet been published but the results have been referred to in the FDA approval notice and have been presented in abstract form at several meetings. At 20 sites, investigators enrolled 212 outpatients with unipolar major depression who had failed 1–4 antidepressant treatments within the current episode. Patients were randomly assigned to undergo deep TMS using an H-coil or sham TMS, applied as a monotherapy after patients had tapered off antidepressant medications. Patients received daily weekday treatments over the prefrontal cortex (18 Hz, 120% intensity related to the individual motor threshold) for 4 weeks acutely, and then biweekly for additional 12 weeks. Patients in the per protocol analysis set receiving active dTMS had a 6.39 point reduction in HDRS-21 scores, compared to a 3.28 point reduction in the sham group ($p = 0.008$), 0.76 effect size (95% confidence interval [CI]: [0.83;5.40]). Response and remission rates were significantly higher with active deep TMS compared to sham treatment (response: 38.4% and 21.4%, respectively, $p = 0.01$; remission: 32.6% and 14.6%, respectively, $p = 0.005$). These differences between active and sham treatment were stable during the 12-week maintenance treatment phase and were also observed in patients with higher degrees of treatment resistance. Though deep TMS did generally show little side effects, one seizure occurred in a patient (who did not obey the protocol) in the active group.

Making things even more interesting, another company, Neosync, has recently completed a 6-week double-blind sham controlled treatment trial that they hope will allow FDA approval of their device. As mentioned above, their form of TMS differs from conventional TMS in that the magnetic field is relatively weak, derived from rotating permanent magnets rather than from a powerful electromagnet. The result is a novel TMS device for treatment of MDD. This device uses three rotating neodymium magnets positioned close to the head to impart subthreshold sinusoidal waveform magnetic stimulation to the brain. The rotation frequency of the magnets was synchronized to the individual's alpha frequency (IAF), determined from a single-channel electroencephalography (EEG) performed prior to the first treatment. The sham device utilized nonmagnetized rotating steel cylinders. One hundred and twenty unmedicated adult subjects (mean age 46) with moderate DSM-IV MDD (mean baseline 17-item Ham-D score of 21.5) completed 6 weeks of treatment per protocol. Antidepressant treatment history scores ranged from 0 to 4. They found that subjects treated with sTMS had a significantly greater mean decrease in Ham-D scores after 6 weeks than those receiving sham treatment (–9.00 versus −6.56, $p = 0.033$). Subjects with a history of treatment resistance or intolerance in the current episode had a significantly higher response rate to sTMS than to sham (34.2% versus 8.3%, $p = 0.017$). When treatment-naïve subjects were included, there was a numerically greater but not significantly different response rate in subjects receiving sTMS (33.9% versus 29.5%, n.s.). There was no difference in adverse events between treatment groups.

Sometimes treatments work in rigorous well conducted trials with carefully selected subjects but then they fail to work in the real world, for a variety of reasons (complexity of delivery, side effects, mitigating effects of comorbid illnesses). Does TMS have an efficacy-effectiveness gap? Surprisingly, TMS actually seems to work better in clinical practice than in the rigorous clinical trials. Several recent studies describe the *effectiveness* of TMS in modern clinical practice. The first was a multisite observational study in 307 real-world patients receiving Neurostar TMS in clinical practice settings.[99] With an acute course of TMS treatments (average 28.3 [standard deviation: 10.1] treatment sessions), symptom severity ratings decreased significantly. With categorical outcomes, 58% of the subjects were responders on the primary outcome measure (CGI-S), and 37% had reached remission, with similar findings on the secondary measures. Given that over half of the subjects met criteria for resistance to two or more antidepressant trials in the current episode, outcomes were stratified by level of treatment resistance (<2 versus ≥2 treatment failures); response and remission rates were similar between groups (e.g., 59.4% versus 56.8% response for low versus high levels of resistance; 39.9% versus 34.9% remission rates).

Connolly et al.[100] reported data from the first 100 patients treated at their university-based TMS clinical service following FDA approval. Their cohort was also treatment resistant, with a mean of 3.4 failed adequate antidepressant trials in the current episode. Thirty-one individuals had received prior lifetime ECT, and 60% had a history of psychiatric hospitalization. The CGI-I response rate was 50.6% and the remission rate was 24.7% at 6 weeks. The HDRS response and remission rates were 41.2% and 35.3%, respectively. Forty-two patients (49%) entered 6 months of maintenance TMS

treatment. Sixty-two percent (26/42 patients) maintained their responder status at the last assessment during the maintenance treatment. These data from care-seeking patients suggest that TMS, unlike many therapies in medicine, does not suffer from an efficacy/effectiveness gap between clinical trials and clinical treatments.

Meta-Analyses of TMS Antidepressant Effect

One way of understanding the state of the art of TMS as an antidepressant is to perform meta-analyses on the published trials. There have now been at least 12 independent meta-analyses of the published or public TMS antidepressant literature, each differing in the articles included and the statistics used.[101–105] Their results are largely the same—daily prefrontal TMS delivered over several weeks has antidepressant effects greater than sham treatment. For example, Burt and colleagues examined 23 published comparisons for controlled TMS prefrontal antidepressant trials, and found that TMS had a combined effect size of 0.67, indicating a moderate to large antidepressant effect.[103] A subanalysis was done on those studies directly comparing TMS to ECT. The effect size for TMS in these studies was greater than in the studies comparing TMS to sham, perhaps reflecting subject selection bias. The authors suggested that perhaps TMS works best in patients who are also clinical candidates for ECT. In summary, meta-analyses of the TMS published literature concur that repeated daily prefrontal TMS for two weeks has antidepressant effects greater than sham.

An interesting clinical issue is whether TMS would be clinically effective in patients referred for ECT. This question has been addressed in a series of studies in which ECT referrals were randomized to receive either ECT or rTMS. In an initial study, Grunhaus et al. compared 40 patients who presented for ECT treatment and were randomized to receive either ECT or TMS.[106] ECT was superior to TMS in patients with psychotic depression, but the two treatments were not statistically different in patients without psychotic depression. This same group recently replicated this finding in a larger and independent cohort with an improved design.[107] Recently, Janicak and colleagues reported a similar small series, finding near equivalence between TMS and ECT.[108] The major differences between these studies and the rest of the controlled studies of TMS efficacy are the patient selection (suitable for ECT), the length of treatment (3–4 weeks), the lack of a blind, and the lack of a sham control. Unfortunately, none of the studies explicitly measured differences in cognitive side effects, although presumably TMS has no measurable cognitive side effects, while ECT has several. In a similar but slightly modified design, Pridmore[109] reported a study comparing the antidepressant effects of standard ECT (3-times/week), and one ECT/week followed by TMS on the other four weekdays.[109] At 3 weeks, they found that both regimens produced similar antidepressant effects. Unfortunately, detailed neuropsychological testing was not performed but one would assume that the TMS and ECT group had less cognitive side effects than the pure ECT group. Finally, an Israeli group recently published that relapse rates in the 6 months following ECT or rTMS were similar.[110] In summary, the studies to date suggest that TMS clinical antidepressant effects are in the range of other antidepressants, and persist as long as or better than the clinical effects following ECT.

Current State of TMS Clinical Practice for Depression

To summarize the acute antidepressant effectiveness data, over 89 individual trials have been conducted and four different large multisite trials have all found statistically and clinically significant effects of TMS compared to sham. Twelve meta-analyses confirm these trials. Two different devices now have FDA approval with several others in some form of FDA pre-review.

Unresolved Issues

Although the literature suggests that prefrontal TMS has an antidepressant effect greater than sham, and that the magnitude of this effect is at least as large as other antidepressants, many issues are not resolved. For example, it is unclear how best to deliver TMS to treat depression. Most, but not all,[111] studies have used focal coils positioned over the left prefrontal cortex. It is still not known whether TMS over one hemisphere is better than another, or whether there are better methods for placing the coil. For the most part, the coil has been positioned using a rule-based algorithm to find the prefrontal cortex, which was adopted in the early studies.[89] However, this method was shown to be imprecise in the particular prefrontal regions stimulated directly underneath the coil, depending largely on the subject's head size.[112] Most studies now employ a positioning system based on EEG coordinates, or move the treating coil at least 6 cm anterior to the thumb motor area.[113] Two retrospective analyses of clinical trials where brain imaging was performed to document the coil location have independently confirmed that a coil position that is anterior and lateral is associated with a better clinical response to active but not sham TMS.[114]

An Australian group has performed a randomized controlled trial examining different prefrontal locations and a more anterior and lateral location did indeed produce superior antidepressant response.[115] These findings suggest that the location of the coil matters, even within broad boundaries of a specific lobe. It is not clear whether individualized location will be needed or used, or whether general algorithms (such as a newly suggested 7 cm anterior, or AF3 positioning[116]) will suffice for a probabilistic positioning for most patients. The 7 cm rule simply places the coil 7 cm anterior to the thumb location. The AF3 system follows a system long used in EEG placements to determine where to place EEG electrodes. AF3 stands for anterior frontal left side. This system takes into account a person's head size and is thus more individually tailored.

Additionally, most studies have stimulated with the intensity needed to cause movement in the thumb (called the motor threshold or MT). There is now increasing recognition that higher intensities of stimulation are needed to reach the prefrontal cortex, especially in elderly patients, where prefrontal atrophy may outpace that of motor cortex, where the motor threshold is measured.[117–120] There is also emerging data that TMS therapeutic effects likely take several weeks to build. Consequently, many of the initial trials, which lasted only 1–2 weeks, were likely too brief to generate maximum clinical antidepressant effects. There is only limited data on using TMS as a maintenance treatment in depression.[121] At MUSC recently, seven treatment resistant bipolar depressed patients who had responded to an acute treatment were entered into a maintenance study. TMS was performed one day per week over the left prefrontal cortex at 110% motor threshold, 5 Hz for 8 s for 40 trains. During this follow-up period, four subjects dropped out of the maintenance study and they were labeled nonresponders (average 25 weeks of treatment). Three subjects completed 1 year of weekly TMS without a depression relapse. These data suggest that TMS might eventually be used as a maintenance tool in depression, and that one treatment per week might be a good first attempt at a maintenance schedule. Several groups have performed maintenance TMS, but there have been no controlled clinical trials, and optimal ways of using TMS to prevent relapse remain to be defined.[122,123] Much more work is needed however.

TMS to Treat Post-Partum Depression

Literature on the use of TMS to treat post-partum and perinatal depression is sparse. This seems unfortunate given that TMS is nonsystemic and confers little risk of side effects to the mother, no risk to the breastfeeding infant and likely little to no risk to a developing fetus. Garcia et al. studied the effects of 20 rTMS treatments over 4 weeks (10 Hz, 120% motor threshold, left dorsolateral prefrontal cortex) in nine women with postpartum depression.[124] Results revealed a significant reduction in depressive symptoms by the end of week 2 of treatment, and analyses yielded a medium effect size (r = 0.68) on the primary outcome variable of Hamilton Rating Scale for Depression – 24 Item (HRSD-24). Eight participants achieved remission of symptoms, defined as a HRSD < 10 and a CGI-S = 1, and a significant improvement in maternal-infant bonding was suggested. At 6-month follow-up, seven of the eight remitters remained in remission without further psychiatric intervention. The authors do note that their results should be interpreted as preliminary data given the small sample size, open-label design and that their participants all had recurrent treatment responsive (not resistant) depression but were unwilling to take medications while breastfeeding. Myczkowski et al. showed slightly less positive findings in a randomized, controlled, double-blind pilot study to evaluate the impact of rTMS on clinical, cognitive, and social performance in women with postpartum depression.[125] Fourteen women were randomized to receive 20 sessions of sham rTMS or active 5 Hz rTMS over the left DLPFC. At 6 weeks (2 weeks post-rTMS) the active rTMS group showed small but significant improvements in HDRS-14, global assessment scale (GAS), and clinical global impression (CGI) when compared to the sham group, and mathematical, but not statistically significant, improvements in social rating scales. Notably, none of the patients from the above trials experienced significant side effects, and all were able to continue breastfeeding through their treatments, again highlighting the promise of noninvasive brain stimulation in the treatment of post-partum depression.

TMS to Treat Mania

Grisaru and colleagues in Israel delivered right or left prefrontal TMS to a series of BPAD patients admitted to their hospital for mania.[126] TMS was given daily in addition to the standard treatment for mania. After 2 weeks, the group receiving right-sided TMS was significantly more improved than the group that had received left sided TMS. The authors concluded that TMS might be useful as an antimanic agent. However, although subjects were assigned to the two groups at random, the left-sided group was more ill than the right-sided group on several measures. Surprisingly there has been little research in this area in the past decade, perhaps because there are many different anti-manic agents, or that it is very difficult to study this population.

Accelerated TMS to Treat Suicidality

Some open-label prefrontal rTMS studies have found rapid reductions in suicidality.[127] At MUSC we recently tested whether a high dose of rTMS to suicidal inpatients is feasible and safe, and also whether this higher dosing might rapidly improve suicidal thinking. At two hospitals, we delivered nine sessions of rTMS over 3 days as adjunctive to usual inpatient suicidality treatment to 41 patients (randomized 1:1, active to sham). Repetitive TMS (rTMS) was delivered to the left prefrontal cortex with a figure-of-eight solid core coil at 120% motor threshold, 10 hertz (Hz), 5 s (s) train duration, 10 s intertrain interval for 30 min (6000 pulses) 3 times daily for 3 days (total nine sessions; 54,000 stimuli). We found that this intense schedule of rTMS with suicidal inpatients was feasible and safe. Minimal side effects occurred, none differing by arm, and the 3-day retention rate was 88%. No one died of suicide within the 6-month follow-up. Suicide rating scores declined rapidly over the 3 days for both groups, with a trend for more rapid decline on the first day with active rTMS (sham change −5.9 [95% CI: −10.1, −1.7], active −13 points [95% CI: −18.7, −7.4]; $p = 0.054$). Subjective ratings of "being bothered by thoughts of suicide" declined significantly as well (sham change −24.9 [95% CI: −34.4, −15.3], active change −43.8 [95% CI: −57.2, −30.3]; $p = 0.028$). This study, currently in peer review, suggests that delivering high doses of left prefrontal rTMS over three days (54,000 stimuli) to suicidal inpatients is possible and safe, with few side effects and no worsening of suicidal thinking.

A Review of Potential Antidepressant Mechanisms

How does TMS act to improve depression? Work done to date has shown clear evidence that prefrontal TMS produces immediate[73–75,128,129] and longer term[63] changes in mood-regulating circuits. Thus, the original hypothesis about its antidepressant mechanism of action is still the most likely explanation. What remains unclear is which specific prefrontal or other brain locations might be the best for treating depression, and whether this can be determined with a group algorithm or needs individual imaging guidance. Much work remains to understand the optimum dosing strategy for the antidepressant effect of TMS. It is unlikely that the initial combinations of intensity, frequency, coil shape, scalp location, number of stimuli or dosing strategy (daily, twice daily), are the most effective for treating depression. Finally, it is not understood how electrical stimulation of these circuits over time results in improvement of depression symptoms. The translational cascade of events remains undefined. It is clear that determining these answers using clinical trials alone would be a slow and expensive process. Work with animal models and functional imaging should streamline this research area.

Some behavioral evidence from treatment trials is consistent with the functional imaging data above showing repeated subtle changes in mood-regulating circuits. Szuba and colleagues initially discovered that there is a very subtle but statistically significant improvement in self-rated mood within each day over the 20 min of a daily TMS session (and that this is greater than with sham TMS).[130,131] We confirmed this in an independent study in bipolar depression.[132] A more recent clinical trial has found this as well,[133] and suggests that these subtle within subject, intra-session effects might predict eventual response. We tested this in the OPT-TMS study using visual analog scales immediately before and then after each session and failed to find an immediate change that predicted eventual clinical response. Thus, some studies suggest that during each treatment session, the mood regulating circuit is being activated and slightly normalized. This gradual daily improvement may then sum over several weeks when genuine clinical antidepressant effects emerge.

There is less data to suggest that TMS works to improve depression through activating normal anticonvulsant regulating systems – a widely held theory about the antidepressant mechanisms of action of ECT.[134] An appealing notion is that the brain "interprets" TMS induced currents as potential seizures, with resultant activation of anticonvulsant cascades, which are tied to antidepressant efficacy. In support of this hypothesis, several animal studies have found that TMS has ECS-like anticonvulsant effects.[135–137] However, there is only scant evidence to suggest that TMS has anticonvulsant effects in depressed patients. An initial open study found that the MT slightly increased over 2 weeks of TMS.[138] However, the MT does not always correlate with seizure threshold, and this was an open study with only small effects. Operator bias can influence MT determination, particularly with respect to coil location and angle. In a recent double-blind study, we examined for, and failed to find, a significant change in MT over the course of a TMS treatment trial.[132, 139] Moreover, if TMS antidepressant efficacy were linked to its ability to initiate anticonvulsant cascades, then the TMS use parameters closest to producing seizures would be predicted to be the most efficacious. However, there is no clear advantage of higher frequency TMS,[140,141] even though it is clearly more likely to provoke seizures. Further work, perhaps using surrogate markers such as MR spectroscopy measured GABA, are needed to explore this hypothesized antidepressant mechanism of action.

TMS AS A TREATMENT FOR OTHER CONDITIONS

TMS has also been investigated as a possible treatment for a variety of neuropsychiatric disorders. In general, the published literature in these conditions is much less extensive than for TMS as an antidepressant, therefore, conclusions about the clinical significance of effects must remain tentative until large sample studies are conducted.

Movement Disorders

Some initial studies found positive effects in Parkinson's Disease (PD);[142] however, one of these early results failed to replicate,[143] and some of the methods described were actually not credible. Moreover, a recent study found that TMS delivered over the supplementary motor area (SMA) actually worsened PD symptoms.[144] However, a recent study,[145] as well as a study from Japan using TMS over the prefrontal cortex, at very low frequencies and doses,[146] reported that TMS may improve effects in PD. Remember that Strafella and colleagues demonstrated in healthy adults that prefrontal TMS can change dopamine activity in the caudate.[74] Thus, it should be noted that only a small portion of the combinations of use parameters, brain regions, and dosing schedules have been tried. Further studies are needed.

There are two small positive studies showing that TMS can benefit writer's cramp, a form of focal dystonia.[147] Following a positive small abstract, two groups have used TMS to investigate and possibly treat Gilles de la Tourette syndrome.[148] Therapeutically, there is one report of potential beneficial effects of slow rTMS in action myoclonus.[149] One study found modest and transient beneficial effects on tics when applied over prefrontal cortex. Another study at MUSC also found positive effects on tics, and OCD symptoms.[148] Others have begun exploring using TMS over the SMA. Further work is needed in this promising area.

The TMS motor threshold is reduced in patients with untreated epilepsy,[150] hinting at widespread problems in cortical excitability. Additionally, TMS has been used to examine cortical excitability and inhibition in Tourette syndrome (GTS), dystonia and obsessive compulsive disorder (OCD).[151] Reduced intracortical inhibition has been reported in all three illnesses.

Schizophrenia

Several studies have used TMS to investigate schizophrenia, without consistent replications of early findings, which were compounded by medication issues.[152] As the neuropathology of schizophrenia involves many brain regions and is not focal, TMS treatment studies in patients with schizophrenia have largely been targeted at patients with specific symptom clusters. The bulk of the studies have been focused on either reducing auditory hallucinations, improving negative symptoms, or improving cognition. With respect to *improving negative symptoms*, a one-day prefrontal TMS challenge study by Nahas and colleagues at MUSC failed to find significant effects on negative symptoms.[153] In terms of treating auditory hallucinations, most research has followed the pioneering lead by Hoffman and colleagues who used low frequency TMS over the temporal lobes to treat hallucinations in patients with schizophrenia.[154–157] Some studies have failed to replicate these results,[158] while others have been positive. Overall, there does appear to be a clinically significant reduction in hallucinations that can last up to 1 month.[159–163] We are not aware of any manufacturer attempting to obtain FDA approval for this treatment approach.

Anxiety Disorders

In a randomized trial of left and right prefrontal and midoccipital 20 Hz stimulation in 12 patients with OCD, Greenberg et al.[164] found that a single session of right prefrontal rTMS decreased compulsive urges for 8 h. Mood was also transiently improved, but there was no effect on anxiety or obsessions. Using TMS probes, the same group reported decreased intracortical inhibition in patients with OCD,[165] which has also been noted in patients with Tourette's disorder.[151] Somewhat surprisingly, OCD patients had a lowered MEP threshold in one study,[166] unrelated to intracortical inhibition, and which appears to replicate (E.M. Wassermann, personal communication). Two studies have examined possible therapeutic effects of prefrontal rTMS in OCD. A double-blind study using right prefrontal slow (1 Hz) rTMS and a less-focal coil failed to find statistically significant effects greater than sham.[167] In contrast, a recent open study in a group of 12 OCD patients, refractory to standard treatments, who were randomly assigned to right or left prefrontal fast rTMS, found that clinically significant and sustained improvement was observed in a third of patients.[168] Mantovani and colleagues stimulated the SMA as a potential treatment for OCD and have found promising results.[169,170] Clearly, further work is warranted testing TMS as a potential treatment for OCD.

There have been a flurry of studies recently using TMS to treat posttraumatic stress disorder (PTSD), often creatively combining the TMS with some form of exposure or talking therapy. McCann et al.[171] reported that two patients with PTSD improved during open treatment with 1 Hz rTMS over the right frontal cortex. Grisaru et al. similarly stimulated ten PTSD patients over motor cortex and found decreased anxiety.[172] Other blinded studies have demonstrated clinically and statistically significant reduction in PTSD symptoms in patients treated with rTMS to either the right or left dorsolateral prefrontal cortex.[173,174] Most recently, an Israeli group has published a study using TMS for PTSD where 30 patients were assigned to a receive rTMS using the Brainsway H-coil at low frequency (1 Hz) or high frequency (10 Hz) or sham rTMS. They found that the ten daily treatments of 10 Hz rTMS at 80% motor threshold over the right dorsolateral prefrontal cortex had therapeutic effects on PTSD patients.[175] Patients were given exposure therapy immediately before the TMS treatment session.

At MUSC, we recently completed a pilot study assessing whether it is possible to actually perform TMS while PTSD patients are listening to a tape about their trauma, while they are also actively participating in a trial of exposure therapy. Eight patients received a full course of protocol-driven exposure therapy and they were randomly assigned to receive either rTMS or sham rTMS. rTMS was delivered to the prefrontal cortex with a figure-of-eight solid core coil at 120% motor threshold, 10 Hz, 5 s train duration, 10 s intertrain interval for 30 min (6000 pulses) weekly for 5 weeks (30,000 stimuli). Patients were able to tolerate the combination and there was a trend for more rapid improvement in the active group. A larger study is needed.

Pain

The neural circuits that modulate mood and attention overlap with the neural circuits that modulate the affective dimension of pain.[176,177] Thus, noninvasive forms of brain stimulation like TMS are currently being explored as alternative or adjunctive therapies for pain conditions. The FDA recently approved a single-pulse TMS device for the acute treatment of migraine with aura based on the results of a double-blind randomized controlled trial.[178] Prefrontal and motor cortex rTMS have been shown to diminish laboratory-induced pain and chronic pain,[179–181] but these interventions need to be further evaluated.[182,183]

Some of the most promising research has focused on rTMS for perioperative pain. In two different postoperative studies, a single 20 min session of left prefrontal rTMS reduced morphine self-administration by 40% when compared to sham rTMS.[184,185] Once again, additional studies are needed to replicate these findings and to reveal antinociceptive mechanisms. There is evidence to suggest that the opioid system is necessary for the analgesic effects of prefrontal rTMS in healthy adults.[186] Naloxone pretreatment, for example, abolishes rTMS-induced analgesia as well as rTMS-induced attenuation of BOLD signal response to painful stimuli.[21] These studies are particularly fascinating given the role of the prefrontal cortex in modulating subcortical responses to pain.[187]

Addictions

The application of TMS to patients with substance abuse disorders has been an area of tremendous growth in the past decade. As in other clinical areas, TMS has been used as

both a research tool as well as a method to manipulate craving.[188,189] In the last few years several investigations that have used TMS to successfully manipulate craving among nicotine smokers, cocaine users, alcohol users, and methamphetamine users. At MUSC, we have been interested in whether a single session of prefrontal TMS can change nicotine craving in nontreatment seeking smokers. Dr. Xingbao Li at MUSC recently studied 16 nontreatment-seeking, nicotine-dependent participants.[190] They were randomized to receive either real high frequency rTMS (10 Hz, 100% resting motor threshold, 5 s on, 10 s off for 15 min; 3000 pulses) or active sham (eSham) TMS over the DLPFC in two visits with 1 week between visits. The participants received cue exposure before and after rTMS and rated their craving after each block of cue presentation. Stimulation of the left DLFPC with real, but not sham, rTMS reduced craving significantly from baseline (64.1 ± 5.9 versus 45.7 ± 6.4, $t = 2.69$, $p = 0.018$). When compared with neutral cue craving, the effect of real TMS on cue craving was significantly greater than the effect of sham TMS (12.5 ± 10.4 versus -9.1 ± 10.4; $t = 2.07$, $p = 0.049$). More decreases in subjective craving induced by TMS correlated positively with higher Fagerstrom Test for Nicotine Dependence score ($r = 0.58$, $p = 0.031$) and more cigarettes smoked per day ($r = 0.57$, $p = 0.035$). We thus concluded that a single session of high-frequency rTMS (10 Hz) of the left DLPFC significantly reduced subjective craving induced by smoking cues in nicotine-dependent participants.

A single challenge study in a lab is exciting, but cannot be considered a treatment. Importantly, Dr. Zangen and colleagues have performed a clinical trial with 115 adult men and women aged 21–70 who smoked at least 20 cigarettes per day. They were motivated to quit smoking and recruited from the general population using advertisements in newspapers and on internet websites. Participants were divided randomly to high frequency, low frequency, and sham stimulation groups. Each group was subdivided randomly into two subgroups, either presented or not presented with smoking cues, just before the daily TMS session. The smoking "cues" were a person lighting up a cigarette directly in front of the subject, followed by three smoking puffs. The rationale for stimulating the LPFC immediately after presentation of nicotine-associated cues is that such stimulation would reactivate the addiction memory traces, causing them to be labile for interference by rTMS. Deep rTMS sessions were administered using a specific version of the H-coil over the prefrontal cortex and insula. The H-coil was designed to generate a magnetic field deeper into the brain than does the standard figure-of-eight coil.

After defining the resting motor threshold (RMT), the coil was then moved forward 6 cm anterior to the motor spot and aligned symmetrically (over the lateral PFC location) and trains of pulses were delivered at 120% of the measured RMT. For those randomized to high frequency TMS, their session consisted of 33 trains of 10 Hz for 3 s, inter-train interval (ITI) of 20 s. The total treatment duration was 760 s (about 13 min) with 990 pulses. Low frequency stimulation was a continuous 1 Hz stimulation, ITI of 970 ms. The total treatment duration was 600 s (10 min) with 600 pulses. Sham was delivered with either high or low frequency, but using a sham coil that mimicked the noise and scalp sensation but does not penetrate the brain. All subjects received 13 daily deep rTMS sessions were applied (over 4 weeks' time), 6 months follow-up was than conducted. Cigarette consumption was evaluated objectively by measuring cotinine levels in urine samples and subjectively by participants' self-reports. Dependence and craving were evaluated by standard questionnaires, the Fagerström Test for Nicotine Dependence (FTND) questionnaire was used to evaluate nicotine dependence. To evaluate general craving for tobacco, the researchers used the short version of the Tobacco Craving Questionnaire (sTCQ). Cue induced craving was evaluated using a visual analogue scale (VAS), ranking participants' response to the question: "how much do you want to smoke right now?" before and after cue presentation and after treatment. Impulsivity was evaluated by a set of neurocognitive tests. This group detected significantly higher reductions in cigarette consumption and nicotine dependence, as well as higher response rates and higher abstinent rates in the high frequency deep rTMS stimulated groups compared to the sham groups and compared to the low frequency groups. The low frequency groups demonstrated results similar to the placebo groups. Presentation of smoking related cue improved the efficacy of the high frequency treatment, with higher reduction in dependence and consumption, and yielded abstinence rate of 44% at the end of the treatment. Abstinence rate at the end of the treatment were 44% and 25% in the high frequency deep rTMS stimulated groups, 13% and 0% in the placebo groups, and 0% and 14% in the low frequency stimulated groups. Furthermore, long-term study results revealed a low relapse rate in the high frequency groups and high abstinent rates persisted after 6 months. Presentation of smoking related cues improved the efficacy of the high frequency treatment, and resulted in a 33% abstinence rate at 6 months follow-up. Abstinence rates 6 months post treatment were 33% and 23% in the high frequency deep rTMS stimulated groups, 9% and 0% in the placebo groups, and 0% and 14% in the low frequency stimulated groups. This initial study involving 115 subjects divided into six subgroups suggests that high frequency deep rTMS treatment over the LPFC and Insula, combined with presentation of smoking cues, reduces cigarette consumption and nicotine dependence. The company is now organizing a pivotal multisite study geared toward potential FDA approval for this indication.

Although the growing interest in this field is evident by the number of new investigations and rising interest from federal funding agencies in the Unites States, there is still a lot of variability with regard to the best site of stimulation, frequency of stimulation, and behavioral task used during stimulation. One common strategy used to decrease craving in these experiments is to apply high frequency repetitive TMS to the left DLPFC (as is done in depression). This presumably increases activity in neural circuits involved in cortical control. It is also possible that low frequency stimulation to neural regions directly responsible for craving (limbic regions such as the

medial prefrontal cortex, anterior cingulate cortex, the insula, and the striatum) may also be fruitful. While it is currently not possible to directly stimulate subcortical areas with a traditional figure-of-eight coil, new developments in coil design such as the H-coil and other multichannel coils may make this possible in the next decade. Additionally, there is evidence to suggest that there is significant interindividual variability in the neural region that is most activated during craving. A recent functional neuroimaging study in nicotine smokers demonstrated that the area of peak functional activity during a cue-induced craving task was located in the medial prefrontal cortex in most individuals. However, the between subjects variability was high enough that these peak areas would not be captured by a standardized location applied to everyone.[191] This suggests that future studies applying TMS to substance dependent populations may want to tailor their stimulation location to that individual's own site of peak activity during craving.

Tinnitus

One of the more recent and interesting areas of TMS treatment applications is for tinnitus, a phantom auditory perception disorder. The origin of the perceived ringing has been highly debated in previous decades and surgical management via destructive procedures does not provide substantial relief.[192] The hypothesis that tinnitus is actually a brain disorder arising from abnormal spontaneous activity in the brain has grown and TMS is a logical method for modulating these hypothesized deregulated neural networks. There currently is no biomarker for tinnitus, which makes treatment targets difficult to determine and efficacy arguable as results are subjective. Bilateral low frequency TMS of the auditory cortex did not prove effective in decreasing tinnitus loudness in 50 patients with chronic tinnitus.[193] Right frontal cortex low frequency stimulation decreased tinnitus loudness by 21% in 11 out of 44 patients, although the total number of pulses in the dose was relatively low at 200.[194–198] High frequency TMS applied to the frontal cortex combined with low frequency TMS over the temporal cortex has also proven to be promising in decreasing intensity of perceived loudness in a study with 32 patients, suggesting multiple networks may be deregulated in chronic tinnitus. Although there are several positive studies, there is much debate in regards to treatment location and stimulation frequency, leaving this area of research with both positive and negative results. For reviews see References 198 and 199.

Stroke Recovery

Yet another clinical area with intense research, but as of yet no proven efficacy, is to use TMS, usually combined with rehabilitation, to try to improve recovery following stroke. One of the key theories has been to determine if it is better to try to stimulate the portion of the brain directly damaged by the stroke, or to try and inhibit or excite the other areas of the brain (contralesional). There is no consensus at the moment but multiple trials are underway.[201,202]

SAFETY ISSUES ASSOCIATED WITH TMS

Despite the initial safety concerns about TMS, it continues to have an excellent safety record. Inadvertent seizures can occur, but they have not happened when researchers have been following the safety guidelines.[203] It is important to realize that the TMS safety table was developed in a small subject sample using a surrogate endpoint for a seizure – spread of TMS induced motor evoked potentials (MEP) beyond the target area of stimulation. Thus, the safety table exists only for stimulation of motor cortex, and it cannot readily be applied to using TMS over other brain regions. Further, although the intensity and frequency of stimulation were examined, the inter-train interval was not. One of the inadvertent seizures was induced with stimulation trains that were within the safety guidelines, but which were administered with an excessively short inter-train interval.[204] A general rule of thumb is that one should have an inter-train interval at least as long as the period of stimulation. A known seizure disorder, history of epilepsy, or intracranial abnormality, such as a prior stroke, can all increase the risk of a TMS induced seizure.[205] Although an inadvertent seizure is the main safety hazard associated with TMS, there have been only 20–30 reported cases since 1985, when cranial TMS began. It is, in fact, not easy to intentionally use TMS to produce a seizure, even in patients with epilepsy.[206] For example, an attempt to use TMS to intentionally produce a seizure in a patient with a focal epilepsy was not successful.[206] In addition, in a study exploring rTMS as a method to induce therapeutic seizures, stimulation parameters far above the published safety thresholds had to be used to reliably induce seizures.[207] There do not appear to be any deleterious cognitive side effects of TMS even when used in high doses for several days.[208] A muscle tension type headache and discomfort at the site of stimulation are less serious but relatively common side effects of TMS. In the USA, fast rTMS is an experimental procedure that requires an investigational device exemption (IDE) from the FDA for research. As mentioned before, modern TMS did not begin until 1985[1] and the total number of subjects or patients to receive TMS is likely still less than 100,000. However, substantial experience to date suggests that at least in the short term (<20 years), TMS at moderate intensity has no other evident lasting adverse effects in adults.

SUMMARY AND CONCLUSIONS

TMS is a powerful new brain stimulation tool, with an extremely interesting body of research including one confirmed and several putative therapeutic potentials. TMS is unique among the new class of brain stimulation techniques because of its noninvasiveness and positive safety and side effect profile. It clearly has the ability to engage subcortical-limbic circuits, and to produce immediate, intermediate, and long-term effects. Further understanding of the ways by which TMS changes neuronal function, especially as a function of its use parameters, will improve its ability both to answer neuroscience questions, as well as to treat diseases.

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19 The Evolution of Cranial Electrotherapy Stimulation for Anxiety, Insomnia, Depression, and Pain and Its Potential for Other Indications

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CONTENTS

NATURAL ELECTRICITY: THE DISCOVERY OF A PECULIAR PROPERTY OF FISH

Ancient writings on papyri inform us that electric catfish in the Nile River were used to relieve pain by the Egyptians 4700 years ago. The ancient Greeks used them to numb the pain of childbirth and surgical procedures.[1] In his 380 B.C. dialogue *Meno*, Plato accused Socrates of "stunning people" with his puzzling questions in a manner similar to the way the torpedo fish stuns or numbs.[2] In fact, the word "narcotic" stems from narke, which is the Greek word for these types of electric ray fish.

Perhaps the first known use of what is now referred to as cranial electrotherapy stimulation (CES) was when electrical fish were applied to the skull to relieve headache by the Greek physician Claudius Galen, who had more of an influence on Western and Arabic Medicine than any other individual. Galen was called "The Medical Pope of the Middle Ages" as his word was considered gospel and his humoral theory of disease lasted well into the nineteenth century. He

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was the first to describe migraine, which is derived from the Greek word hēmikrania (half the head). After investigating the ancient treatment of headache with torpedo fish, Galen wrote:

> The whole torpedo, and I mean the sea-torpedo, is said by some to cure headache and prolapsus ani when applied. I indeed tried both of these things and found neither to be true. Therefore, I thought the torpedo should be applied alive to the person who has the headache, and it could be that this remedy is anodyne and could free the patient from pain as other remedies which numb the senses: This I found to be so. And I think that he who first tried this did so for the above-mentioned reason.[3]

Galen's endorsement made this the treatment of choice for headache and other pains. Books and poems were written about it, and some who used a trident (a three pronged metal spear) for fishing claimed that the shock that traveled up the metal spear relieved their arthritic pains. Recommendations for applying live torpedo fish for headache and joint pain persisted throughout medieval Europe and were advocated by leading Muslim physicians such as Avicenna (Ibn Sina) and Averoës in the tenth and eleventh centuries.[4] In the 1500s, Dawud al-Antaki, the famous Syrian physician and philosopher declared it to be effective in "relieving chronic headache, unilateral headache (migraine), and vertigo, even in desperate cases."[5]

The most powerful source of electricity came from the huge South American eel (*Electrophorus electricus*) which, despite its name, is more closely related to a giant catfish. Adults are typically 6 or 7 feet long and can generate electric shocks of up to 600 volts through 24 feet of water, which allows them to feed on other fish and small mammals. When they were brought to Europe in 1750, people flocked to be treated with its "natural electricity," especially those suffering from arthritis.

THE MODERN ERA

The practice of using electrical fish eventually diminished following the advent of the Leyden jar and Volta's primitive battery. These were much more accessible sources of electricity in dosages that could be controlled.[6]

At the turn of the last century, Edison and Tesla's electrification of New York and beyond replaced candles and gas lighting, ushering in the modern era and bringing previously unimaginable technologies to the patent office and then the market. During this time, many physicians and scientists experimented with a multitude of electromedical devices and their applications. These included the many variations of transcutaneous electrical nerve stimulators (TENS) that continues to evolve today for numerous pain and non-pain related conditions, along with the putative mechanisms to explain such phenomena.

While electricity has historically been used therapeutically on all areas of the body, cranial electrotherapy stimulation, or CES, is a specific term denoting electrical stimulation to the brain. CES involves devices that deliver electrical currents transcranially through electrodes. The brain functions electrochemically and it can readily be modulated by electrical intervention. Unlike peripheral electromedicine, CES has been less frequently cited in older, historic literature. Krueger is perhaps the first person to mention this use, noting in 1743 that the experimental self-application of electric current allowed him to sleep better.[7] Aldini wrote in depth about its use in mental disease in 1802.[8] Marat described the application of strong currents across the head that produced convulsions.[9] These latter studies were a precursor to the development of electroconvulsive shock treatment (ECT) in the 1930s.[10]

Originally referred to as "electrosleep," the intended purpose of early CES devices had been to induce sleep through the application of small amounts of electrical stimulation to the brain as a primary or adjunctive modality of the "sleep cure" widely employed in psychiatry throughout the early part of the twentieth century.

In 1902, the French physiologist Stephen Leduc produced sleep in rabbits by the transcranial delivery of 35 volts, at 110 Hz. He attempted to extend his successes to himself with 100 Hz direct currents (DC) of 3–12 milliamperes (mA) of a 10% duration. While he remained conscious, he could not move or speak, and experienced blunted sensations of pain.

Using himself as a test subject, Leduc attached an electrode to his forehead and another electrode near the base of his spine. His sensations after administering a series of 50-volt pulses in the milliampere range were similar to "…a dream but I was conscious of the absence of power to move and an inability to communicate with my colleagues; I felt the contact, the pinches, striking of pins in my forearm, but the sensations were dulled."[11,12] Despite Leduc's reported success with electroanalgesia, these findings failed to arouse significant interest among clinical practitioners outside of the former Soviet Union and France.

In 1914, Louise Robinovitch distinguished between electrically induced sleep and analgesia, producing electric sleep in patients suffering from insomnia by applying a negative electrode to the forehead and a positive electrode to the hand. She reported that patients fell asleep within the 1 h treatment period and continued to sleep after the current was discontinued.[13]

The work of Gilyarovsky and associates in the former USSR were responsible for advancing the use of electrosleep in clinical settings during the decades of the Cold War. According to declassified government documents containing English translations of the authors' observations:

> In hospitals the procedure is performed in bed. The patient undresses and lies down as though for his night's sleep. Usually electric sleep is administered simultaneously to a group of patients in a separate half-darkened ward. Gradually the sensation of heaviness of the lids, ideas of 'going off' appear, sometimes a mild dizziness occurs, and a drowsy state supervenes, which gradually deepens to the degree of physiological sleep. The patient is in a calm relaxed position, usually on his side; the respiration becomes deeper, slower and more regular; the pulse slows up by several beats a minute.[14]

In its contemporary form, CES is a descendant of the aforementioned investigations. In the electroconvulsive shock paradigm, 120 volts at 60 Hz and 500 mA was applied in 0.2 s bursts. From this electroanesthesia was derived, which used a reduced current level of 2 volts at 700 Hz and 30 mA given for the duration of major surgery. A final derivation to electrosleep was produced by 700 Hz at 1 volt and 5 mA. Today's CES devices typically deliver a range from 0.5 to 15,000 Hz from a 9 volt or 1.5 volt AA or AAA battery source supplying from 50 microamperes (μA) to 4 mA.

CES COMES TO AMERICA

The attention of psychiatrists and experimental psychologists in the United States was heightened by clinical research conducted in Europe involving electrosleep that appeared in English language journals during the late 1960s.[15,16] Professional interest coupled with popular notions of "instant sleep" achieved through techno-wizardry prompted independent consultant and businessman, Arsen Iwanovsky, to market a device he named the Electrosone 50, as America's first portable, battery-operated cranioelectrical sleep generator around 1973.[17] Prior to the device's debut, Iwanovsky published the basic circuit schematics of the unit for the benefit of biomedical researchers and experimenters.[18]

According to promotional materials that accompanied the device,[19] the Electrosone 50 was used for "Assisting in the fields of relaxation and sleep… [A] very weak, pulsating electrical current produced and controlled in this instrument passes through the patient's brain by means of four electrodes: two are placed on the closed eyelids and in the back of the neck (occipital area)." The sleek and compact Electrosone represented a considerable improvement over the bulkiness of Gilyarovsky's original design due to the unit's dependence on vacuum tube technology from the 1950s.[20]

When CES was first utilized in the USA, psychopharmaceutical treatments were less well known than they are today so intense interest was generated by the possibilities that this new method offered for treating difficult psychiatric cases. Studies were conducted in university laboratories to identify the mechanisms of action that putatively were responsible for the clinical responses beginning to be observed. More devices came on the market with names such as Anesthelec, Diastim, Electrodorn, Electroson, Neurometer, Neurotone, Neurotransmitter Modulator, RelaxPak, and Somlec, among others.[15]

The clinical intent was that electrosleep treatment should induce sleep immediately when the current was applied to the patient's head, and that the patient should remain asleep naturally, once the sleep was induced. That did not occur, however, even though many of the earliest clinical studies in the USA focused on discovering the waveform that would successfully induce sleep.[17] Researchers used a variety of frequencies, current levels, and waveforms as well as electrode configurations. Unfortunately, not all reports of CES use included descriptions of the waveform used, and these varied widely. Older devices utilized frequencies ranging from 100 to 4000 hertz (Hz) and current intensity up to 8 milliamperes (mA), while more recent devices utilize frequencies as low as 0.5 Hz and current intensity as low as 100 microamperes (μA).[15] Of course, all these variables meant that the results from different CES devices varied as well, and this remains true with the devices commercially available today.

The evolution of electrode placements was particularly notable. As the treatment arrived in the U.S. from Europe, devices such as the Electrosone used saline saturated gauze pads wrapped around metal plates placed over each closed eyelid connected to electrodes placed over the mastoids. At the time it was thought that the eyes were the best, if not the only, place where electricity could enter the brain. Later, because of the discomfort from the pressure on the eyelids and the side effect of blurred vision lasting approximately 15–45 min immediately following treatment, researchers began to place the frontal electrodes just above each eyebrow while the rear electrodes remained over the mastoids. Subsequently, the frontal electrodes were no longer used, with electrodes only placed on the mastoid processes just behind each ear, so that the current went laterally across the head instead of anterior-posteriorly. This caused vertigo; therefore, the electrodes were next moved to the temples. The typical electrode placement used today employs ear clip electrodes clipped to each ear lobe, although some devices still direct the current across the temples.[15]

EARLY ELECTROENCEPHALOGRAPHY RESEARCH AND THE SUBSEQUENT EXPANSION INTO THE TREATMENT OF MOOD DISORDERS

When a treatment strategy that would reliably induce sleep could not be found, electroencephalography (EEG) studies were initiated to examine the possible neurophysiologic events that occurred when current was applied across the head. The first study was designed to see if there were any changes in the EEG relevant to sleep. The findings were inconclusive as some patients slept when in the treatment condition, some slept in the control condition, while others never slept during any phase of the study.[20]

Another EEG study found that one 30 min electrosleep treatment per day for 5 days produced slower EEG frequencies with increased amplitude in the fronto-temporal areas in all of the patients. Most patients also showed increased quality and quantity of the EEG alpha rhythm with increased amplitude in the occipital-parietal leads.[21]

Weiss conducted an early EEG study in a sleep laboratory, in which patients who had been diagnosed with insomnia were allowed to sleep in their usual way in the university laboratory while having their EEG monitored. Five patients were given subsensory electrosleep treatments 30 min daily for 10 days, and five were given sham treatments. Subsequent monitoring of their EEG sleep patterns showed that patients receiving actual treatment went to sleep faster, spent more time in stage IV sleep during the night, had fewer nocturnal awakenings, went back to sleep sooner when they did

awaken in the night, and reported significantly more restful and restorative sleep upon awakening the next morning than did the sham group.[22] All these changes were maintained at a 2-year follow-up.[23]

Soon thereafter, a growing number of researchers demonstrated that CES not only ensured sound, restful sleep for patients suffering from insomnia, but was an effective treatment for stress-related symptoms as well, as determined through the use of various psychological assessment scales of anxiety and depression (e.g., Hamilton Anxiety Scale, State/Trait Anxiety Inventory, Zung Depression Scale, Profile of Mood States, etc.). More importantly, it was confirmed that numerous psychophysiologic measures, including sleep patterns, improved regardless of whether the patient slept during the treatment or not.[11,20]

As a result, the term "electrosleep" was dropped in the USA although it remains in use in parts of Europe. Instead, American researchers called it by several names, including "transcranial electrostimulation." In 1978, the Neurology Panel of the Food and Drug Administration (FDA) suggested that it be called "cranial electrotherapy." The FDA agreed, but added the word "stimulation" to the phrase, as they were not yet convinced that it was therapeutic. The FDA also determined that CES would be only available by prescription, making the USA the only country in the world in which an order from a licensed health care practitioner must be obtained for its use, a restriction continued through today.

CES now has a foundation of more than 50 years of research and clinical use in the USA from which proof of safety and effectiveness have been well established for the nonbiased reviewer.

Nasrallah commented on psychiatry's future, predicting that "neurostimulation for brain repair" was one of the top six trends in clinical practice.[24] He cited repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS), all of which are invasive and costly medical procedures. CES is also neurostimulation for brain repair and in contrast is a more cost-effective, noninvasive type of device that can be safely used by patients at home. It can be used as an adjunct to medication or psychotherapy or as a stand-alone treatment. The only contraindications to CES are pregnancy and having a pacemaker or other implanted electrical device, and even those are dubious.

The FDA recognizes CES devices for the treatment of anxiety, insomnia and depression.[25] Off-label use in chronic pain is increasing, particularly in the treatment of such difficult management problems as fibromyalgia and spinal cord injuries in war veterans where double-blind studies with significant outcomes have been conducted and replicated.[26–28] There is also increased interest in its use in the treatment of cognitive dysfunctions, such as attention deficit disorder (ADD).[29] Future research on central nervous system mechanisms of CES may well demonstrate its potential utility in a widespread range of neurological and psychological disorders. What is currently known, however, is that CES has been proven to be a safe, efficacious, and inexpensive intervention for a wide variety of disorders of the nervous system.

MECHANISMS OF ACTION

The mechanisms of action of CES have not been clearly identified; however, several mechanisms have been postulated. Most commonly, CES is thought to be derived from a direct mode of action, and thus, under the current paradigm of thought, CES has been described largely from a neurobiological standpoint regarding its effect on electrical brain activity, neurotransmitters, and hormones.

Animal studies indicated that CES might have one of two possible effects: postsynaptic hyperpolarization or alterations in neurotransmitters. In either case, early research revealed a resultant increase in the degree of inhibitory processes resulting in analgesia and sleep.[30,31] Subsequent research in CES focused on the changes in neurotransmitter concentrations. In an early study, psychiatric patients and controls that received 5 days of CES showed increased urinary free catecholamines but no change in 17-ketosteroids.[32] Normal and depressed subjects receiving CES had increased blood concentrations of serotonin and cholinesterase after one 20 min session and following 2 weeks of daily 20 min sessions.[33] Additionally, substance abuse subjects receiving 30 min sessions of CES for 4 weeks had increased blood concentrations of monoamine oxidase-B and gamma amino butyric acid (GABA) that also corresponded with an improvement in symptoms in contrast to the control group. However, no changes were noted in concentrations of serotonin, dopamine, or beta-endorphin in that study.[34]

A small study of volunteers revealed an increase in cerebral spinal fluid concentrations of serotonin and beta-endorphin following 20 min of CES. The average increase for beta-endorphin was 50% from baseline although one subject had a 219% increase.[35] These data should be viewed with caution as the small sample size included executives of a CES manufacturer. However, those possible chemical changes are consistent with clinical findings suggesting that increased neurotransmitter concentrations may be involved in the sedative effects of CES with regard to GABA and beta-endorphins at the GABA and mu opioid receptor sites.[36] Because GABA serves as a major inhibitory neurotransmitter, increased concentrations of GABA may result in anxiolysis. Likewise, sedation is one result of mu opioid receptor stimulation. Several studies report decreased opioid requirements and increased potency of nitrous oxide in surgical patients receiving CES for which increases in beta-endorphin were postulated as the likely mechanism.[37–39] Patients experiencing anxiety from alcohol withdrawal were found to have a concentration of beta-endorphin that was inversely correlated to anxiety.[40]

In a series of five canine studies, Pozos and his group at the University of Tennessee Medical Center examined the effects of CES on central neurotransmitters.[41] Characteristically, most neurons regulate the production, intracellular transport and release of neurotransmitters through a multi-component feedback system. This maintains a relative equilibrium of neurotransmitters produced, released, and reuptake into the presynaptic cell, postsynaptic action. The amount of

neurotransmitter released and available within a synapse also affects the activity and chemistry of proximate neurons in the local environment. As a variety of drugs can affect these mechanisms, they can also be used as research tools that alter brain chemistry and thus behaviors and other psychiatric effects.

Pozos' group increased the amount of dopamine in the brains of experimental dogs by administering the drug reserpine, which induces a robust release of dopamine throughout the brain. Dopamine controls a variety of behaviors, most notably movement and emotional status. Pozos' reserpine-treated dogs developed mild movement abnormalities (e.g., tremor) as a result of dopamine depletion and loss of neural circuits in the motor areas in the brain that are stimulated by the neurotransmitter acetylcholine. The decreased dopamine in the reserpine-treated dogs led to an imbalance of acetylcholine-induced motor stimulation. Interestingly, CES produced the same effect as reserpine, so it was hypothesized that electrical stimulation of the brain was capable of altering the release of neurotransmitters.

To examine further the role of CES on neurotransmitter systems, the researchers discontinued the administration of all drugs and let half of the dogs rest with their usual allotment of food and water. They found that these animals returned to an apparently normal state within 3–5 days. Another group had the drugs discontinued but were given CES treatment. The theory was that if CES stimulated the down-regulated dopamine system, the animals would return to normal more quickly. The dogs given CES returned to normal within 3–7 h, which was comparable to recovery seen following the administration of the dopamine precursor L-dopa. This suggests that CES appears to stimulate the dopamine system, although it is not known if this effect is direct or indirect.

Pozos also studied the biochemical effects of ECT and found them to be similar to CES. He surmised that treatment with CES would accomplish the same effects as ECT, but over the course of several weeks instead of milliseconds. Conversely, none of the negative side effects from ECT should be encountered in the process.

In an attempt to determine a possible cellular mechanism of CES, Siegesmund and his coworkers examined whether electrical stimulation affected the quantity or quality of neurotransmitter release.[42] Neurotransmitters are stored in vesicles, packets of chemicals that upon stimulation are released into synaptic space to exert an action. Sigismund's group found that electrical stimulation of the brain tended to force the pre-synaptic vesicles present to release their contents into the synaptic space, while at the same time causing the development of many more pre-synaptic vesicles. Once the stimulus was terminated, the system tended to return toward normal.

Taken together, these findings strongly suggest that CES is capable of producing both neurotransmitter release and resynthesis, a process known as "turnover." The next step was to find a clinical connection to these studies.

Following Pozos' studies, a human double-blind study was conducted in which narcotic addicts were withdrawn from opiate use and given either alpha methyl dopa (a dopamine and norepinephrine reuptake blocker) or CES.[43] Heroin acts on endogenous opioid receptors in the brain, down-regulating the production of endorphin, and thus, disturbing norepinephrine production in the locus ceruleus. When heroin is discontinued sensitized opioid receptors on norepinephrine neurons evoke an uninhibited release of norepinephrine, which acts at adrenergic receptors of the central and peripheral nervous systems to produce characteristic withdrawal signs and symptoms.

In the study, half the patients received CES while the other half were given alpha methyl dopa to block the postsynaptic norepinephrine receptors. Those patients that had been treated with the norepinephrine reuptake blocker did not show profound withdrawal effects but they all experienced rebound depression. In contrast, CES treatment resulted in patients becoming heroin abstinent without any withdrawal or depressive signs or symptoms. Many more studies were conducted on substance abuse populations and then mood disorders became the focus of modern research.[15]

MORE ELECTROENCEPHALOGRAPHIC STUDIES

About 20 EEG studies have appeared in the CES literature beginning shortly after CES achieved popularity in Eastern Europe during the late early 1960s. Using enhanced EEG technology, U.S. researchers continue this type of investigation to this day.

Research to date has shown that CES treatment evokes a change in the EEG pattern of every person to whom it is applied. CES induces significant changes in the EEG as shown in the brain map in Figure 19.1. It increases alpha (8–12 Hz) relative power, and decreases relative power in the delta (0–3.5 Hz) and beta (12.5–30 Hz) frequencies.[44] Increased alpha correlates with improved relaxation and increased mental alertness or clarity. Decreased delta waves indicate a reduction in fatigue. Beta wave reductions from 20–30 Hz correlate with decreases in anxiety, ruminative thoughts, and obsessive/compulsive-like behaviors.

Low resolution electromagnetic tomography (LORETA) and functional magnetic resonance imaging (fMRI) studies showed that CES reached all cortical and subcortical areas of the brain, producing changes similar to those induced by anxiolytic medications.[45,46] Many symptoms seen in psychiatric conditions, such as anxiety, insomnia, and attention deficit disorders are thought to be exacerbated by excess cortical activation.[47,48] An fMRI study in an anxiety population showed that CES causes cortical brain deactivation in the midline frontal and parietal regions of the brain after just one 20 min treatment.[45] Another fMRI study was conducted as part of a randomly controlled double-blind trial (RCT) in a pain population that revealed greater decreases in average pain levels ($p = 0.023$) than those using a sham device or receiving usual care without CES.[49] The active CES device was shown to decrease activation of pain processing regions of the brain, such as the cingulate gyrus, insula and prefrontal cortex, compared to the sham device.

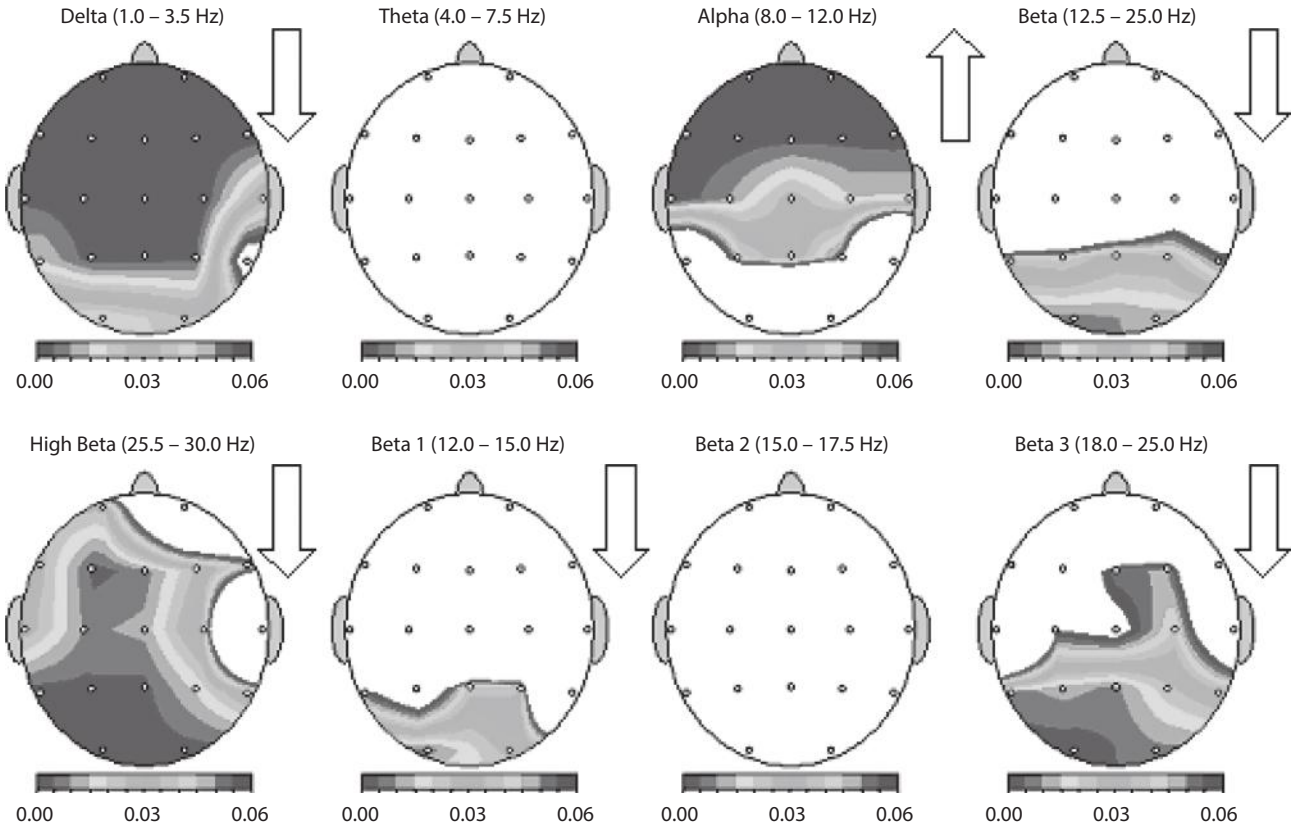

FIGURE 19.1 **(See color insert.)** Relative power *p*-value topographical map for 0.5 Hz cranial electrotherapy stimulation (CES). Statistically significant changes ($p < 0.05$ or better) after a single 0.5 Hz CES session are indicated by color; white indicates no significant change. The arrows indicate the direction of change. Statistically significant decreases were seen in delta and beta with statistically significant increases in alpha.

The above mechanisms provide evidence that CES changes the brain in a way that reduces anxiety, depression, and pain. It also helps people fall asleep by inducing relaxation while decreasing compulsive thoughts.

THE CLINICAL ROLE OF CES

CES may be seen, then, not as a treatment for a specific disorder, but as a bioelectrical intervention that acts through mechanisms known to be consistent with the functions of various physiological functions and the effects of drugs that are frequently prescribed for the same indications.

While the exact mechanism of CES remains unclear, the same is true for pharmacological interventions used to treat mood disorders, and it seems likely that both have similar effects on neurotransmitters or other relevant mechanisms.

Most practitioners in the fast growing fields of complementary, integrative, and alternative medicine assume that the body will heal itself if it has the necessary building blocks (e.g., proper nutrition and sufficient exercise). Reparative processes require energy from ATP, which is produced by oxidative phosphorylation in the electron transport chain. It seems plausible that an electrical boost, whether it be from electroacupuncture, electrical or electromagnetic stimulation from CES, may also fuel or enhance this process. Conscious direction, intentionality, or mindfulness shown to alter EEG patterns could provide similar benefits to restore normal function when homeostasis is threatened.

There are individuals without any obvious significant physical, mental, or emotional problems but many are not functioning or performing optimally. In addition, the numerous psychosocial pressures of modern life place an increasing allostatic load that can contribute to a variety of stress related complaints and disorders. CES may help to prevent, lessen, or alleviate these in an extremely safe and very cost effective fashion.

CLINICAL STUDIES

At present, there is a wealth of data on CES from over 50 years of research. As with the chemical composition of drugs, each CES device has a different waveform so clinicians should not generalize the research to a generic category of CES as results from the various technologies differ widely. In the 1970s when CES was new to the U.S., most of the research was done with the Neurotone device, which used 100 Hz in a 20% duty cycle with a maximum current level of 1.5 milliamperes. The research methodology used

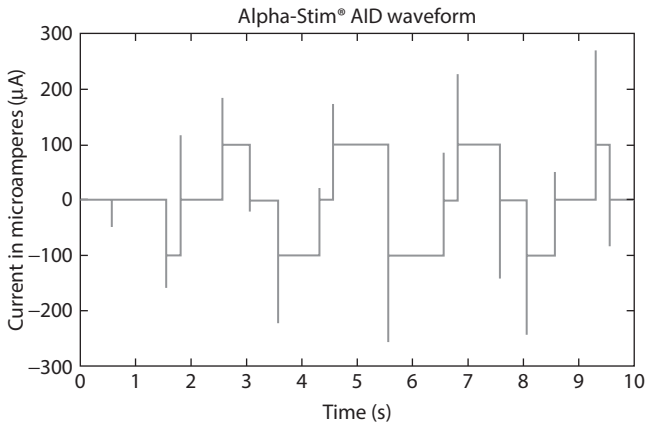

FIGURE 19.2 The Alpha-Stim waveform shown over a 10 s period.

was consistent with the standards of the day, but fall well below modern standards. Depending on the device, the quality of the research protocol, including the blinding method, in those early studies exhibited mixed results.[15] While there are copies of the Neurotone waveform sold under the brand names of CES Ultra and HealthPax, several other private labeled versions of these that are still on the market are produced by small companies with no research studies to support their claims.

Most recent CES studies use reliable and valid outcome measurement scales. The majority of these have been conducted with the Alpha-Stim CES device, which has been progressively refined over the past three decades. It uses a complex and patented bipolar asymmetric waveform consisting of multiple frequencies at a 50% duty cycle having a variable pulse width with a maximum duration of 0.5 Hz (2 s) provided over a 10 s time frame with random factors to avoid habituation by the nervous system. The maximum current level of the device is 600 microamperes. The impedance range within which the waveform parameters remain valid is from 100 Ω to 10 KΩ. The waveform is balanced to achieve 0 net current in either direction as shown in Figure 19.2.

Randomly controlled double-blind trials of CES can be accomplished today in the same manner used to evaluate pharmaceuticals. As dosage can be portrayed as current indirectly proportional to time, double-blinding is achieved by reducing the current to a subsensory 100 microamperes while increasing the usual 20 min treatment time to a full hour. The following is a summary of this modern level of RCT studies, open clinical trials, and scientifically conducted surveys.

SUMMARY OF THREE SURVEYS (N = 5917)

Peer-reviewed outcomes conducted on the Alpha-Stim brand of CES for FDA from 2500 patient surveys published in 2001 correlated well with 47 physicians' reports on 500 patients. This data revealed that a significant effect of at least 25% improvement was reported by nine out of ten in a group of 3000 patients.[15,50] In another survey of 152 Service Members and veterans conducted for FDA in 2011 the outcomes, while still significant, were not quite as robust as prior surveys of civilians.[51] However, a third survey conducted in 2013 of 2861 Service Members, veterans, and civilians was closer to the original survey of civilians. This confirms the observation that Service Members and veterans who use CES most likely suffer from more extreme trauma, and, therefore, experience slightly less efficacy than a civilian-only cohort. Nevertheless, the results remain significant (≥50%) and they should be considered as clinically relevant. Figure 19.3 provides a detailed summary of all three of the post marketing surveys conducted for FDA totaling nearly 6000 Service Members, veteran, and civilian self-reports.

MODERN RESEARCH

As CES has been cleared by the FDA for the treatment of anxiety, insomnia, and depression since 1978, it is used primarily for these indications. As a result, there are numerous supportive studies and publications but only recent ones that comply with the more rigid current standards will be described in this section.

ANXIETY DISORDERS

Anxiety disorders are characterized by anticipation of a future threat, excessive fear, and related behavioral disturbances. Fear is associated with the stress response, or surges of sympathetic arousal seen in fight or flight responses, thoughts of immediate danger, and escape behaviors. Anxiety is also often associated with increased muscle tension and vigilance in preparation for future danger along with cautious or avoidant behaviors. Anxiety patients typically overestimate the danger in situations they fear or avoid. Anxiety is about twice as prevalent in women.[52]

The key features of general anxiety disorder or GAD are persistent and excessive anxiety and worry, which impairs work or school performance that the individual finds difficult to control. In addition, affected patients experience physical symptoms, including restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbances.[52]

Anxiety disorders affect 40 million American adults aged 18 and older, or about 18.1% of the population. Anxiety disorders frequently co-occur with depressive disorders or substance abuse and most people who are diagnosed with one type of anxiety disorder often develop others.[53]

Table 19.1 lists nine randomized controlled trials (RCT), eight of which are double-blind and one that is investigator-blind with summaries of the research outcomes based on the measurement scales used. Table 19.2 shows four open-label studies and four user surveys investigating the efficacy or treating anxiety with CES. Table 19.3 summarizes the findings of two meta-analyses of CES studies of anxiety. The

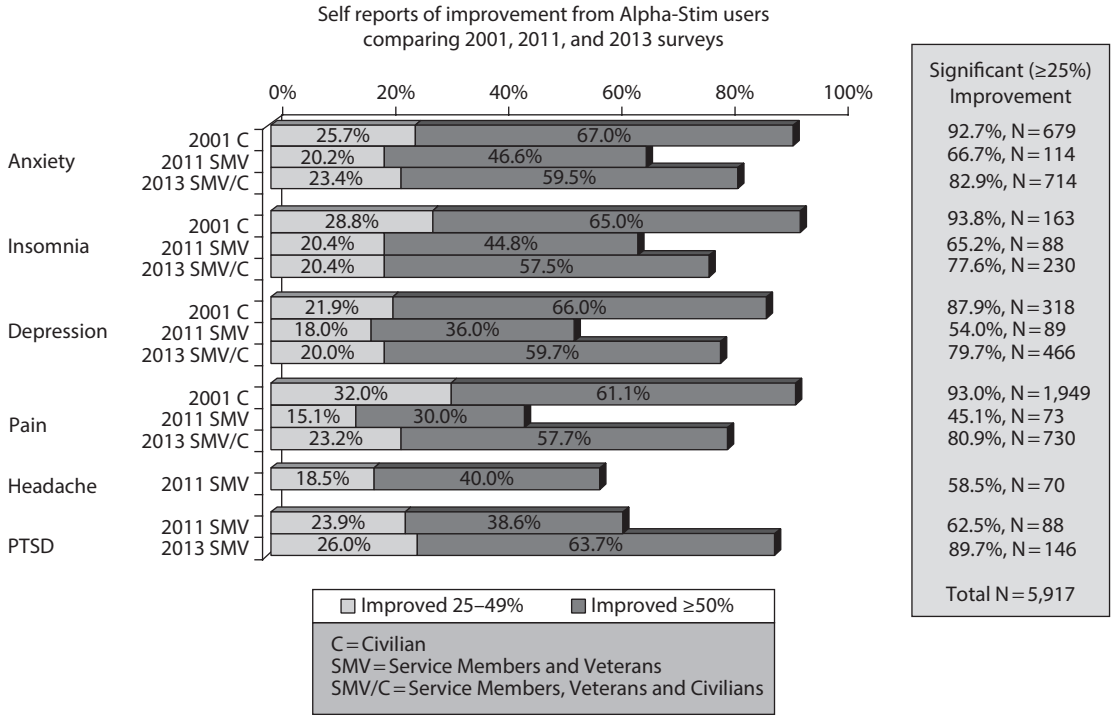

FIGURE 19.3 Summary of three surveys of cranial electrotherapy stimulation users (n = 5917).

TABLE 19.1
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT) Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Barclay et al.[54]	115	Anxiety Patients	RCT, DB	Hamilton Anxiety Rating Scale (HAM-A): In the active treatment group, 83% had a decrease of ≥50% in scores from baseline to endpoint on the HAM-A ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.94$) from baseline to endpoint of study. The mean decrease on the HAM-A in the treatment group of 32.8% (19.89 to 13.37) was more than three (3) times the mean decrease on the HAM-A for the sham group of 9.1% (21.98 to 19.98) from baseline to endpoint of the study.
Lee[55]	50	Preoperative Patients	RCT	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale that the control group, which got the usual care ($p = 0.016$). There was also reduction in withdrawal scores for patients during injections ($p = 0.049$).
Kim et al.[56]	60	Preoperative Patients	RCT, IB	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale than control group at end point of study ($p < 0.05$, $d = -0.88$).
Strentzsch[57]	38	Chronically Mentally Ill Patients	RCT, DB	Spielberger State Trait Anxiety Inventory (STAI): CES group had significantly lower scores from baseline on SAI (indicating less state anxiety) than sham group at endpoint of study ($p = 0.02$, $d = -0.41$).
Chen et al. [58]	60	Children with Mixed Anxiety and Depressive Disorder (MAD)	RCT, IB	Zung Anxiety Scale (SAS); The ANOVA showed that on SAS, the main effect between CES group and sham comparator group was significant ($F = 83.21$ $p < 0.01$). Changes in EEG of Occipital Lobes via brain electrical activity mapping (BEAM): on left and right $\alpha 1$ revealed the main effect of group was significant ($F = 5.98$, $p < 0.05$; $F = 6.39$, $p < 0.05$); on left and right $\alpha 2$, the main effect of group was also significant ($F = 7.54$, $p < 0.01$; $F = 6.72$, $p < 0.05$).
Cork et al. [27]	74	Fibromyalgia Patients	RCT, DB, OL	Profile of Mood States (POMS) for anxiety: CES group had significantly lower scores from baseline on POMS (indicating less anxiety) than sham group at end point of study ($p < 0.01$). Open label CES group had significantly lower scores on POMS at post-test from baseline scores ($p < 0.001$).

TABLE 19.1 (continued)
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT) Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Lichtbroun[26]	60	Fibromyalgia Patients	RCT, DB, OL	Profile of Mood States Anxiety Subscale (POMS-A): CES group had significantly lower scores on POMS-A (indicating less anxiety) from baseline than sham group at end point of study ($p = 0.02$, $d = -0.60$). There was no significant difference in Open Label crossover group from pretest to post-test on POMS-A ($p > 0.05$).
Winick[59]	33	Dental Patients	RCT, DB	Visual Analog Scale (VAS), Inverse Likert Scale: CES group had significantly lower scores from baseline, indicating less anxiety, on the VAS ($p < 0.02$, $d = -0.61$) and higher scores on Likert Scale, indicating less anxiety ($p < 0.01$) than sham group at end point of study.
Voris[59]	105	Psychiatric Patients with Anxiety	RCT, DB	State Anxiety Inventory (SAI): CES group had significantly lower scores (indicating less anxiety) on SAI than the sham and control groups at end point of study ($p = 0.0001$, $d = -1.60$). CES group had significantly higher finger temperature scores ($p = 0.001$, $d = 0.50$) and significantly lower EMG scores ($p = 0.0001$, $d = -1.08$), indicating less anxiety, than sham CES and control groups.

IB: investigator blind; DB: double blind; OL: open label; n = 595 for anxiety RCT Studies.

TABLE 19.2
CES Open Label and Survey Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Price[61]	146	Service Members and Veterans with PTSD	Survey	7-point Likert scale. Of the total group, 63.7% reported fewer PTSD symptoms and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 26.0% reported clinical improvement of PTSD symptoms between 25% and 49% (improvement of moderate clinical importance). In the total group, 89.7% of respondents reported ≥25% fewer PTSD symptoms and clinical improvement with the majority of these respondents reporting ≥50% improvement in PTSD.
Price[61]	714	Civilians, Service Members and Veterans with anxiety	Survey	7-point Likert scale. Of the total group, 59.5% reported less anxiety and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 23.4% reported clinical improvement of anxiety between 25% and 49% (improvement of moderate clinical importance). In the total group, 82.9% of respondents reported ≥25% less anxiety and clinical improvement with the majority of these respondents reporting ≥50% improvement.
Bracciano[62]	2	Veterans with PTSD	OL	Daily Symptom Severity Ratings—Treatment Log (0–10) decreased from a baseline mean of 6 to a post-test mean of 2 ($p < 0.05$, $d = 1.61$). PTSD Symptom Scale Interview (PSS-I) was reduced from 34 to 13 and 29 to 10 in the respective patients and re-experiencing decreased from 7 to 2 and 9 to 2. Avoidance decreased from 15 to 7 and 9 to 5, and Increased arousal decreased from 12 to 4 and 11 to 3.
Bystritsky[63]	12	General Anxiety Disorder Patients	OL	Hamilton Rating Scale for Anxiety (HAM-A), Four Dimensional Anxiety and Depression Scale (FDADS): Anxiety scores decreased significantly on HAM-A from baseline to endpoint of study ($p = 0.01$, $d = -1.52$). Anxiety scores were significantly lower on FDADS at end point of study from baseline ($p < 0.039$, $d = -0.75$).
Lu et al.[64]	32	Children with Emotional Disorders (Anxiety)	OL	Zung Anxiety Scale (SAS); From baseline of 58.30 ± 11.50 to post-test 45.91 ± 10.36 ($p > 0.01$); 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in two cases (6%); the total effective rate was 94%. Skin temperature rose ($p < 0.01$); systolic blood pressure dropped and the pulse slowed down after the treatment, and the differences were significant ($p < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and 2 cases had relapse of symptom where drugs were needed to control their symptoms.
Overcash[65]	197	Anxiety Disorder Patients	OL	0–100 Numerical Rating Scale (NRS): Subjects rating of anxiety was significantly less from baseline to post-test ($p < 0.05$). Subjects' physiological measures of anxiety—EMG, EDR and Temp—changed significantly from baseline to post-test indicating less anxiety ($p < 0.05$).

(*continued*)

TABLE 19.2 (continued)
CES Open Label and Survey Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Kirsch et al.[51]	202	Service Members and Veterans with anxiety (includes PTSD)	Survey	7-point Likert scale: Anxiety (n=114). Of the total group, 46.5% reported less anxiety and clinical improvement of ≥50% while 20.2% reported clinical improvement of anxiety between 25% and 49%. In the total group, 66.7% respondents reported ≥25% improvement in anxiety. In the CES only group (no medications), 57.7% reported decreased anxiety and clinical improvement of ≥50% while 15.4% reported clinical improvement of anxiety between 25% and 49%. In the total group, 66.7% respondents reported ≥25% improvement in anxiety. In the CES only group (no medications), 57.7% reported decreased anxiety and clinical improvement of ≥50% while 15.4% reported clinical improvement of anxiety between 25% and 49% for a total of 73.1% of respondents who reported less anxiety and clinical improvement ≥25%. In the CES and medications group, 43.2% of respondents reported decreased anxiety and clinical improvement ≥50% while 21.6% reported decreased anxiety 25%–49% improvement for a total of 64.8% of respondents who reported decreased anxiety and clinical improvement ≥25%. PTSD (n = 88). Of the total group, 38.6% reported less anxiety and clinical improvement of ≥50% while 23.9% reported clinical improvement of anxiety between 25% and 49%. In the total group, 62.5% respondents reported ≥25% improvement in anxiety. In the CES only group (no medications), 50.0% reported decreased anxiety and clinical improvement of ≥50% while 22.2% reported clinical improvement of anxiety between 25% and 49% for a total of 72.2% of respondents who reported less anxiety and clinical improvement ≥25%. In the CES and medications group, 35.7% of respondents reported decreased anxiety and clinical improvement ≥50% while 24.3% reported decreased anxiety 25%–49% improvement for a total of 60.0% of respondents who reported decreased anxiety and clinical improvement ≥25%.
Alpha-Stim User Survey, 1995–1998[15]	679	Patients with anxiety	Survey	4-point Likert Scale: Anxiety (alone), n = 128. Of this group, 67.19% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 22.66% reported less anxiety and improvement between 25% and 49%. A total of 89.84% of these respondents reported ≥25% improvement in anxiety. Anxiety (with other condition), n = 370. Of this group, 68.11% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 22.97% reported less anxiety and improvement between 25% and– 49%. A total of 91.08% of these respondents reported ≥25% improvement in anxiety. Anxiety (with depression), n = 58. Of this group, 62.07% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 32.76% reported less anxiety and improvement between 25% and –49%. A total of 94.83% of these respondents reported ≥25% improvement in anxiety. Stress, N = 123. Of this group, 70.73% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 24.39% reported less anxiety and improvement between 25% and –49%. A total of 95.12% of these respondents reported ≥25% improvement in anxiety.

OL: open label; PTSD: posttraumatic stress disorder; PSS-I: PTSD symptom scale interview; n = 1984 for anxiety open label and survey studies. Total n = 2579 for all CES anxiety studies.

total number of subjects (n) for all anxiety studies was 4819 with 595 from RCTs.

There are nine RCTs showing that CES has proven to be a safe and effective treatment for anxiety with effect sizes ranging from medium ($d = -0.41$) to very large ($d = -1.60$).[57,60] Three of the studies looked at acute anxiety, such as preoperative anxiety ($p < 0.05$, $d = -0.88$), including anxiety prior to dental procedures ($p = 0.02$, $p = -0.61$). Another that monitored changes in EEG mapping revealed significant changes due to CES on the left and right side of the brain in the $\alpha 1$ and $\alpha 2$ regions.[56,58,59]

There have been two surveys and one open label case series to evaluate the effects of treating posttraumatic stress disorder (PTSD) with CES. The case series lasted for 4 weeks and provided a very large effect size ($d = 1.61$) with statistical significance ($p < 0.05$).[62] Two patients reported a 38% and 34% reduction, respectively, in the PTSD Symptom Scale Interview. The case series results were further supported by the survey data that showed 64% and 39% of respondents reporting clinical improvement of ≥50%.[61] When looking at clinical improvement, the highest category is "substantial clinical importance" which is defined as ≥50%.[68]

TABLE 19.3
Meta-Analyses of CES Studies of Anxiety

Principal Investigator	Total n	Subjects	Study Type	Findings
Kirsch and Gilula[66]	2049	41 studies examined the effect of CES on anxiety	Meta-analysis	The analysis of reordered data on the effect of CES on anxiety yielded an effect size of r = 0.57; a large effect size is ≥0.50.[99] Analysis of the studies that used only a double-bind method produced an effect size for CES on anxiety of r = 0.53. Studies that used extraneous measures of anxiety were removed and only studies for state or trait anxiety that used the Spielberger State/Trait Inventory were analyzed. The effect of CES on state anxiety was r = 0.60 and trait anxiety was r = 0.68. When the results of analysis was corrected for the number of subjects in each study, state anxiety was r = 0.59 and trait anxiety was r = 0.60. The effect sizes for the 41 studies in this meta-analysis ranged from high 50s to low 60s.
Klawansky et al.[67]	241	8 RCT, DB, CES studies that examined the effect of CES on anxiety	Meta-analysis	The pooled result for the eight studies, including 241 subjects, analyzing the effect of CES treatment on anxiety was in favor of CES over sham at a statistically significant level (effect size estimate r = –0.5883, $p < 0.05$). When three studies were dropped because they provided no convincing sensation to their sham protocol, the result in favor of CES remained significant.

The three anxiety specific surveys reported substantial clinical importance in 47%, 60%, and 67% of respondents, as shown in Figure 19.3. In the two anxiety meta-analyses, one combining the results of 41 anxiety studies and the other using eight selected RCTs, both confirmed the effectiveness of CES in treating anxiety with consistently large effect sizes ($d = 0.57$, $d = 0.59$).[66,67]

DEPRESSIVE DISORDERS

The common feature of all depressive disorders is the presence of sad, empty, or irritable mood accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. Major depressive disorder represents the classic condition in this group of disorders since it requires clear-cut changes in affect, cognition, and neurovegetative functions. Diagnostic criteria include five or more of the following symptoms present in a 2-week period with at least one being either depressed mood or loss of interest or pleasure.[52]

- Depressed mood
- Diminished interest
- Significant weight loss
- Insomnia or hypersomnia
- Psychomotor agitation
- Fatigue
- Feelings of worthlessness
- Diminished ability to think or concentrate
- Recurrent thoughts of death

The above symptoms must cause distress in normal social, occupational, or other important areas of functioning.

Major depressive disorder is the leading cause of disability in the U.S. for ages 15–44, affecting approximately 14.8 million American adults or about 6.7% of the population in a given year. The mean age at onset for depressive disorders is 32 and these are seen more frequently in women than men.[53]

Table 19.4 includes eight human studies investigating the effects of CES for the treatment of depression. The table includes three RCTs (two double-blind), two open label trials, and three user surveys. In addition, there is a meta-analysis of 20 CES studies of depression summarized in Table 19.5. The total n for the eight studies was 1113 with 196 from RCTs.

The three RCTs showed significantly decreased depression scores ($p < 0.001$, $p < 0.01$, and $p < 0.01$) using three different scales to measure depression (HAM-D17, Beck Depression Inventory and Zung Depression Scale).[54,58,69]

The two open label trials showed significant improvements as well, with one study reporting a medium effect size ($d = -0.41$) and the other a total effective rate of 94%.[63,64] Upon follow-up of 26 cases, 24 had long lasting efficacy of relieved or eliminated symptoms. Lu also measured physiological changes during and after treatment with significant changes seen in skin temperature, systolic blood pressure and pulse ($p < 0.05$).[64]

The three separate user surveys reached substantial clinical importance in 66%, 58%, and 36% of depression patients, with the lowest score reported by Service Members and veterans. The meta-analysis for depression included 937 patients across 20 separate studies and reported a large effect size of 0.050 (Table 19.5).[70]

In a double-blind RCT, 82% of the active treatment group reported ≥50% reduction in depression scores. These active treatment group results were 12 times higher than the sham treatment group. There was some initial transient improvement in the anxiety scores among the sham group but no change in their depression scores.[54]

INSOMNIA

Insomnia is considered a sleep-wake disorder. Its diagnostic criteria is a predominant complaint of dissatisfaction with

TABLE 19.4
Cranial Electrotherapy Stimulation (CES) Depression Studies

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Outcomes
Barclay et al.[64]	115	Anxiety Patients	RCT, DB	Hamilton Depression Rating Scale17 (HAM-D17): In the active treatment group, 82% had a decrease of ≥50% in scores from baseline to endpoint on the HAM-D ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.78$) on the HAM-D17 from baseline to endpoint of study. The mean decrease on the HAM-D17 in the treatment group of 32.9% (9.64 to 6.47) was more than twelve (12) times the mean decrease on the HAM-D17 for the sham group of 2.6% (10.22–9.96) from baseline to endpoint of study.
Price[61]	466	Civilians, Service Members and Veterans with depression	Survey	7-point Likert scale. Of the total group, 59.7% reported less depression and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 20.0% reported clinical improvement of depression between 25% and 49% (improvement of moderate clinical importance). In the total group, 79.7% of respondents reported ≥25% less depression and clinical improvement with the majority of these respondents reporting ≥50% improvement in depression.
Kirsch et al.[51]	89	Service Members and Veterans with Depression	Survey	7-point Likert scale: 36% of the total group reported decreased depression and clinical improvement of ≥50% while 18% reported clinical improvement of depression between 25% and 49%. 54.0% of the total group reported ≥25% improvement in depression. In the CES only group (no medications), 38.5% reported decreased depression and clinical improvement of ≥50% while 23.1% reported clinical improvement of depression between 25% and 49% for a total of 61.6% of respondents who reported decreased depression and clinical improvement ≥25%. In the CES and medications group, 35.5% of respondents reported decreased depression and clinical improvement ≥50% while 17.1% reported decreased depression between 25% and 49% improvement for a total of 52.6% of respondents who reported decreased depression and clinical improvement ≥25%.
Mellon[69]	21	Depressed Jail Security and Patrol Officers	RCT, DB	Beck Depression Inventory (BDI), Brief Symptom Inventory Depression Subscale (BSI-D): The CES group had significantly less depression from baseline than sham group at end point of study on BDI ($p < 0.01$) and on BSI-D ($p < 0.05$).
Bystritsky et al.[63]	12	Generalized Anxiety Disorder Patients with Depression	OL	Hamilton Depression Scale 17. Depression scores were significantly less on HAM-D_{17} at end point of study from baseline ($p = 0.01$, $d = -0.41$).
Chen et al.[58]	60	Children with Mixed Anxiety Depressive Disorder (MAD)	RCT, IB	Zung Depression Scale (SDS); The ANOVA showed that on SDS, the main effect between CES group and sham comparator group was significant ($F = 36.56$, $p < 0.01$).
Lu et al.[64]	32	Children with Emotional Disorders (Depression)	OL	Zung Depression Scale (SDS); From baseline of 0.64 ± 0.08 to post-test 0.52 ± 0.10 ($p > 0.01$); 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in two cases (6%); the total effective rate was 94%. Skin temperature rose ($p < 0.01$); systolic blood pressure dropped and the pulse slowed down after the treatment, and the differences were significant ($p < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and two cases had relapse of symptom where drugs were needed to control their symptoms.
Alpha-Stim User Survey, 1995–1998	318	Depressed Patients	Survey	Four point Likert Scale: Depression (alone), n = 53. Of this group, 66.04% reported less depression and clinical improvement of ≥50%, while 20.75% reported less depression and improvement between 25% and 49%. A total of 86.79% of these respondents reported ≥25% improvement in depression. Depression (with other condition), n = 265. Of this group, 66.03% reported less depression and clinical improvement of ≥50%, while 23.02% reported less depression and improvement between 25%and 49%. A total of 89.06% of these respondents reported ≥25% improvement in depression.

RCT: randomized controlled trial; DB: double blind; IB: investigator blind; OL: open label. Total n = 1113 for all CES depression studies.

TABLE 19.5
Meta-Analysis of CES Studies of Depression

Principal Investigator	Total n	Subjects	Study Type	Findings
Kirsch and Gilula[70]	937	20 Studies that included depressed patients and investigated the effectiveness of CES on depression	Meta-analysis	20 studies which included 937 patients with depression were analyzed to determine the effect of CES on depression and produced an effect size of r = 0.50 defined as a large effect size (p.115).[99] Note: A Cochrane Systematic Review by Moncrieff and colleagues (2004)[100] on the effect of antidepressants on depression that included nine studies involving 751 participants produced a pooled estimate of effect of r = 0.39 standard deviations (0.24 to 0.54) in favor of the antidepressant measured by improvement in mood. One study was then removed as it was a strongly positive trial. Sensitivity analysis after omitting this trial reduced the pooled effect to r = 0.17 (0.00 to 0.34).

sleep quantity, associated with one (or more) of the following symptoms:

- Difficulty initiating sleep
- Difficulty maintaining sleep
- Early-morning awakening with inability to return to sleep

Sleep disturbances cause clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. The sleep difficulty must occur at least three nights a week for at least 3 months despite adequate opportunity for sleep.[52]

A study done by the National Institutes of Health in 2005 estimated that approximately 10% of Americans suffer from insomnia.[53]

Tables 19.6–19.8 include six human studies and one equine study investigating the effects of CES for the treatment of insomnia. The tables include three RCTs (all double-blind), three user surveys, and a meta-analysis. The n for the six human studies totaled 654, with 163 from RCTs.

When comparing data from the three RCT studies, we have one small effect size ($d = -0.03$, $p = 0.001$) and one medium effect size ($d = 0.54$, $p = 0.02$).[72,26] The third RCT did not report effect sizes but did see significant improvement at day 1 ($p = 0.04$) and day 4 ($p = 0.03$) during the study. The study design called for 5 consecutive days of CES treatment in an attempt to improve sleep among active duty Service Members. After 5 days of treatment, the subjects in the active group saw an average of 43 more minutes of sleep per night compared to 19 min less sleep over those 5 days in the sham treated group.[71]

The three separate user surveys reached substantial clinical importance in 65%, 58%, and 45% of insomnia patients. The lower score of 45% is from a survey given to Service Members and veterans, which are typically a more difficult population to treat. The meta-analysis grouped the results from 20 insomnia studies, encompassing 1087 patients and reported a large effect size of 0.64.[66]

A RCT focusing on the sleeping habits of fibromyalgia patients showed significant clinical improvement during the rigid double-blind portion of the study, then even better results coming in the open label phase when patients were allowed to control the current, duration, and time of day the treatment took place.[26]

The Service Member and veteran survey divided the patients up into sub groups depending on medication use; 40.3% of patients using CES in combination with sleeping medications reported ≥50% improvement, while 65.2% of patients using CES *without* medications reported ≥50% improvement. This trend was consistent among each category that was studied (anxiety, PTSD, insomnia, depression, pain, and headache) as seen in Figure 19.9.[51]

PAIN

Chronic pain affects almost 100 million Americans with a total annual cost to health care ranging from $560 billion to $635 billion in 2010. Chronic pain also has the greatest economic impact due to disability days and lost wages and productivity.

An estimated 20% of American adults (42 million people) report that pain disrupts their sleep at least a few nights a week. Even with the options we have available for pain management now, more than half of all hospitalized patients experienced pain in the last days of their lives with 50%–75% of patients dying of cancer reporting moderate to severe pain.[74]

Table 19.9 includes seven double-blind RCTs, one open-label, and two user surveys investigating the efficacy of treating chronic pain with CES. The total n from this pain research is 1712 with 366 from double-blind RCTs.

The RCTs included patients suffering with fibromyalgia, Parkinson's, and spinal cord injuries. All reported effect sizes were measured as large with p-values ranging from $p = 0.03$ to $p < 0.001$. Most of the double-blind studies added an open-label arm at the end of the double-blind portion in sham treated subjects so that all participants had an opportunity to receive treatment. In each case, subjects in the open-label phase also achieved significant pain relief (see Table 19.9).

The results from two different surveys included substantial clinical importance (≥50% improvement) in patients with pain (30%), headaches (40%), reflex sympathetic dystrophy (53%), fibromyalgia (54%), and migraine headaches (57%).[15] As with

TABLE 19.6
Cranial Electrotherapy Stimulation (CES) Insomnia Studies

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Outcomes
Price[61]	230	Civilians, Service Members and Veterans with insomnia	Survey	7-point Likert scale. Of the total group, 57.5% reported less insomnia and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 20.4% reported clinical improvement of insomnia between 25% and 49% (improvement of moderate clinical importance). In the total group, 77.6% of respondents reported ≥25% less insomnia and clinical improvement with the majority of these respondents reporting ≥50% improvement in insomnia.
Lande and Gragnani[71]	57	Active Duty Service Members with Insomnia	RCT, DB	Pittsburg Insomnia Rating Scale: The active CES group had a longer total time slept (43 min) from baseline than the sham CES group who average 19 min less total time slept. The difference between the active CES and Sham CES groups approached significance ($p = 0.079$). A gender difference was noted. Men who completed five sessions of CES had significant improvement in total time slept after the first CES treatment ($p = 0.04$) and on day 4 ($p = 0.03$). Men in the active CES group slept an average of 53 min more total time slept after the first CES treatment and an average 61 min more total time slept on day 4 compared to the sham CES group. There were no significant changes in total time slept among the females in the study.
Taylor et al.[72]	46	Fibromyalgia Patients	RCT, DB	General Sleep Disturbance Scale (GSDS): CES group had significantly lower scores on GSDS (indicating less sleep disturbance) than sham from baseline at end point of study ($p = 0.001$, $d = –0.30$) and completed the study with scores below the range of insomnia.
Lichtbroun et al.[26]	60	Fibromyalgia Patients	RCT, DB, OL	0–10 Numerical Rating Scale (NRS): CES group had significantly higher scores on the quality of sleep outcome measure than the sham and control groups at end point of study ($p = 0.02$, $d = 0.54$).
Kirsch et al. [51]	98	Service Members and Veterans with Insomnia	Survey	7-point Likert scale: of the total group, 44.8% reported less insomnia and clinical improvement of ≥50% while 20.4% reported clinical improvement of insomnia between 25% and 49%. In the total group, 65.2% of respondents reported ≥25% improvement in insomnia. In the CES only group (no medications), 62% reported decreased insomnia and clinical improvement of ≥50% while 23.8% reported clinical improvement of insomnia between 25% and 49% for a total of 85.8% of respondents who reported less insomnia and clinical improvement ≥25%. In the CES and medications group, 40.3% of respondents reported decreased insomnia and clinical improvement ≥50% while 19.5% reported decreased insomnia 25%–49% improvement for a total of 59.8% of respondents who reported decreased insomnia and clinical improvement ≥25%.
Alpha-Stim User Survey, 1995–1998	163	Insomnia Patients	Survey	4-point Likert Scale: of this group, 65.03% reported less insomnia and clinical improvement of ≥50%, while 28.83% reported less insomnia and improvement between 25% and 49%. A total of 93.87% of these respondents reported ≥25% improvement in insomnia.

RCT: randomized controlled study; DB: double blind; OL: open label; n = 654 for all insomnia studies.

TABLE 19.7
Meta-Analysis of CES Studies of Insomnia

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Findings
Kirsch and Gilula[66]	1087	20 Studies that examined the effect of CES on insomnia	Meta-analysis	Twenty (20) studies, which included 1087 patients, were analyzed to determine the effect of CES on insomnia produced an effect size of r = 0.64 defined as a large effect size (p.115).[99] Note: A meta-analysis by Huedo-Medina and colleagues (2012) on the effect of non-benzodiazepine hypnotics that included 13 studies involving 4378 subjects produced a "significant, but small to medium difference" on subjective sleep latency (–0.33) and polysomnographic sleep latency effect (–0.36) in favor of the treatment versus the control group.

TABLE 19.8
CES Study of Insomnia in Horses

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Outcomes
Clarke et al.[73]	8	6 Horses, 1 Mare, and 5 Geldings	OL	The proportion of time spent standing dozing throughout the four trial phases was analyzed. In phase three, values are higher or equal to the values in phase one. A paired t-test comparing the mean values during these phases one and three suggests the difference is significant ($t = -2.44$, $p < 0.05$). In phase four, the same trend is seen with each horse's value higher ($n = 6$) or equal ($n = 2$) to that in phase one. A paired t-test confirms the significance of this difference ($t = -3.29$, $p < 0.05$). The proportion of time spent standing dozing across the phases was also found to have positive correlation with trial phase ($r = 0.220$, $p = 0.013$), time spent with lower lip relaxed ($r = 0.620$, $p < 0.001$), time spent with lower lip quivering ($r = 0.484$, $p < 0.001$), the time spent with the left ear back ($r = 0.265$, $p = 0.002$) time spent with the right ear back ($r = 0.268$, $p = 0.002$), and head wobbling ($r = 0.353$, $p < 0.001$). Time spent standing dozing across the trial phases was also found to have a negative correlation with time spent standing alert ($r = -0.945$, $p < 0.001$), time spent eating bedding ($r = -0.205$, $p = 0.05$), and time spent eating forage ($r = -0.331$, $p < 0.001$).

the anxiety, insomnia and depression surveys conducted with Service Members and Veterans achieved less pain relief.[51] This is believed to be the result of the type of injury and associated pain incurred by Service Members in theaters of war.

The most recent fibromyalgia RCT used functional MRI studies to determine the areas of the brain that are responsible for processing pain during a fibromyalgia flare-up. Once these key areas had been identified, patients using active CES and sham CES were examined, revealing that consistent with all other factors measured, only the active CES treatment group was experiencing less pain.[49] Heffernan was able to measure and identify EEG patterns of patients with pain and was then able to normalize the pattern exclusively with the use of the Alpha-Stim CES device, but not the other devices he tested.[78]

Unfortunately, the FDA is arbitrary and capricious in performing its duties in regulating medical devices. In fact, they have authorized the marketing of CES devices with no research at all by allowing them to use studies conducted on other devices with widely differing waveform characteristics

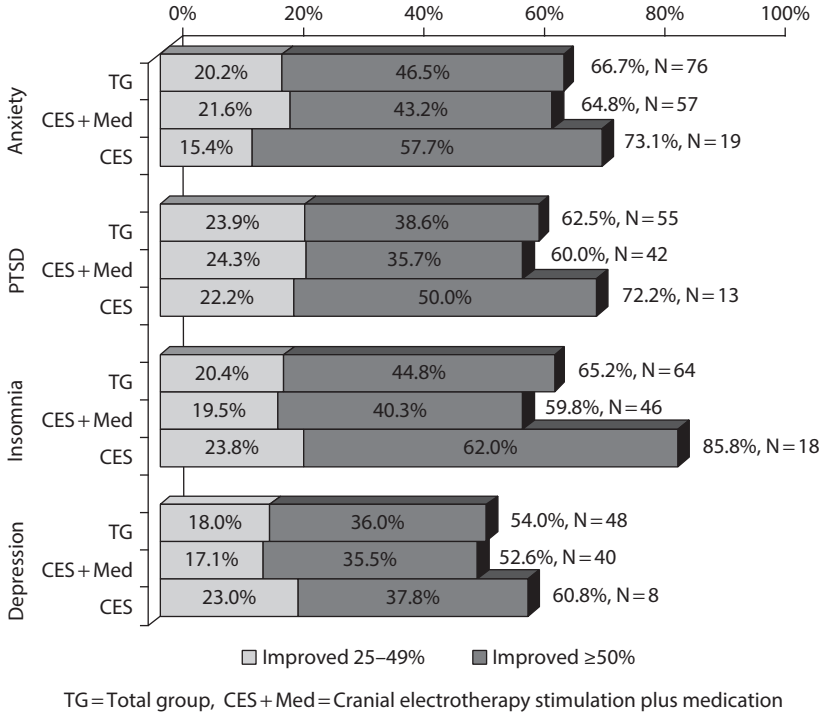

FIGURE 19.4 Service Member and Veteran survey comparing the use of cranial electrotherapy stimulation (CES) as a stand-alone treatment to CES with medications.

TABLE 19.9
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT), Surveys and Open-Label Studies of Pain

Principal Investigator	n	Subjects	Design	Measurement Scales/Outcomes
Taylor et al.[49]	46	Fibromyalgia Patients	RCT, DB	0–10 NRS: Those individuals using the active CES device had a significant decrease in average pain ($p = 0.023$) when compared to those individuals using the sham device or those receiving usual care alone over time.
Tan et al.[28]	105	Military, Spinal Cord Injury	RCT, DB, OL	0–10 NRS: Pain Intensity and Pain Interference Subscales of the BPI: The active CES group reported a significantly greater average decrease in pain pre to post daily treatments than the sham group ($p < 0.05$). The active CES group showed larger pre- to post-treatment decreases in pain interference than the sham group did ($p < 0.01$, $d = 0.59$). The active CES group had a significant mean pain intensity decrease of 0.60 points on the 0–10 scale ($p < 0.001$, $d = 0.73$).
Rintala et al.[75]	13	Veterans, Parkinson's Disease	RCT, DB	0–10 NRS: Subjects receiving active CES had, on average, a 1.14-point decrease in pain compared with a 0.23-point decrease for those receiving sham CES ($p = 0.028$).
Tan et al.[76]	38	Military, Spinal Cord Injury	RCT, DB, OL	0–10 NRS: Active CES group had significantly less pain intensity, pre to post CES session, compared to sham group ($p = 0.03$, $d = 0.76$). Active CES group reported significantly decreased pain interference ($p = 0.004$, $d = 0.50$), pre versus post intervention, while there was a nonsignificant decrease in pain interference in the sham CES group, (pre versus post-intervention. Open Label group had significantly less pain intensity from baseline to endpoint of study ($p = 0.03$).
Cork[27]	74	Fibromyalgia Patients	RCT, DB, OL	0–5 NRS: Active CES group had significantly less pain intensity compared to sham group at endpoint of study ($p < 0.01$). NRS, 0–10: Active CES group has lower tender point scores compared to sham group ($p = 0.01$). McGill: No significant difference in pain scores between Active CES and Sham groups. 0–5 NRS: Open Label group had significantly decrease pain from baseline to end point of study ($p < 0.001$). McGill: Open Label group had significantly decreased pain from baseline to end point of study ($p < 0.001$).
Lichtbroun[26]	60	Fibromyalgia Patients	RCT, DB, OL	0–10 NRS: The active CES group had significantly lower pain scores ($p = 0.002$, $d = -0.65$), lower tender point scores ($p = 0.01$, $d = 0.36$), higher quality of sleep scores ($p = 0.02$, $d = 0.45$), higher feelings of well-being scores ($p = 0.005$, $d = 0.73$), higher quality of life scores ($p = 0.03$, $d = 0.97$), lower fatigue scores ($p = 0.03$, $d = -0.72$) and lower anger scores ($p = 0.04$, $d = -0.60$) than the sham and control groups. The open label group had significant gains on tender point scores ($p < 0.001$) and decreased pain ($p < 0.005$) from baseline to endpoint of study. The active CES group and open clinical CES group had a 27% reduction in self-rated pain scores and a 28% decrease in tender point scores.
Alpha-Stim User Survey, 1995–1998[15]	678	RSD, Fibromyalgia and Migraine patients	Survey	5-point Likert Scale: Reflex Sympathetic Dystrophy (RSD), n = 55. Respondents reported improvement of pain as follows: 52.73% reported pain relief of ≥50%, 29.09% reported pain relief between 25%and 49%. A total of 81.82% of respondents reported pain relief as ≥25%. Fibromyalgia (alone), n = 142. Respondents reported improvement of pain as follows: 53.52% reported pain relief of ≥50%, 37.32% reported pain relief between 25% and 49%. A total of 90.85% of respondents reported pain relief as ≥25%. Fibromyalgia (with other condition), n = 363. Respondents reported improvement of pain as follows: 54.82% reported pain relief of ≥50%, 36.09% reported pain relief between 25% and 49%. A total of 90.91% of respondents reported pain relief as ≥25%. Migraine (n = 118), respondents reported improvement of pain as follows: 56.78% reported pain relief of ≥50%, 41.53% reported pain relief between 25% and 49%. A total of 98.31% of respondents reported pain relief as ≥25%.

TABLE 19.9 (continued)
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT), Surveys and Open-Label Studies of Pain

Principal Investigator	n	Subjects	Design	Measurement Scales/Outcomes
Kirsch et al.[51]	143	Pain Patients, Service Members and Veterans	Survey	7-point Likert scale: Pain (n = 73); 30% of the total group reported decreased pain and clinical improvement of ≥50% while 15.1% reported clinical improvement between 25% and 49%. A total of 45.1% of total group participants using CES reported ≥25% clinical improvement. In the CES only group (no medications), 61.6% of respondents reported decreased pain and clinical improvement ≥25% (46.2% ≥50%, 15.4% between 25% and 49% improvement) while 41.7% of the CES and medications group reported decrease pain and clinical improvement ≥25% (26.74% ≥50%, 15% between 25% and 49% improvement. Headache (n = 70); 40% of the total group reported decreased pain and clinical improvement of ≥50% while 18.6% reported clinical improvement between 25% and 49%. Of the total group, 58.6% of participants reported ≥25% clinical improvement. In the CES only group (no medications), 100% of respondents reported decreased pain and clinical improvement ≥25% (64.7% ≥ 50%, 35.3% between 25% and 49% improvement) while 45.3% of the CES and medications group reported decrease pain and clinical improvement ≥25% (32.1% ≥50% pain relief and 13.2% reported between 25% and 49% improvement.
Holubec[77]	525	Pain Patients	OL	1–10 NRS: 525 consecutive pain patients in a pain management clinic were administered 20 min of CES treatment. Of those, 261 were given a second treatment at their next visit, 160 were given three treatments, 57 were given four treatments, and 26 were given five treatments. The 79.81% who responded to the first treatment experienced a 42.40% reduction in self-rated pain, with 5.14% of the patients declaring they were pain free. Cumulative results were seen among those subsequently treated. There was a 70.64% reduction in pain after five treatments, including 15.38% of the remaining patients reporting no pain.
Heffernan[78]	30	Chronic Pain Patients	RCT, DB	5-point Likert Pain Scale: The active Alpha-Stim CES group's brain wave pattern changed from an uneven, jaw-tooth pattern consistent with pain to a smooth spectral pattern consistent with a pain-free pattern. The active CES group had significantly less pain as measured by the five point Likert pain scale than the Liss CES and control device groups ($p < 0.01$).

RCT: randomized control trial; DB: double blind; OL: open label; NRS: numerical rating scale; n = 366 for RCTs; n = 1346 OL and survey studies; total n = 1712 for all CES pain studies.

while also allowing spurious "CES devices" that never registered with FDA to be sold openly through magazine ads and websites. Conversely, FDA applies adverse events, however minor, equally to all CES devices that comply with the FDA definition, and limits what device manufacturers and distributors may say about effects from their legally marketed devices, even when such statements are accurate and truthful rather than misleading. These and other problems with the Center for Devices and Radiological Health (CDRH) approval process is discussed in Chapter 49.

OTHER POTENTIAL APPLICATIONS

Tinnitus

As indicated in the first edition of *Bioelectromagnetic Medicine*, various forms of cranial electrical stimulation have been used to treat tinnitus for over 200 years.[79]

Over the past decade, there has been increased interest and numerous advances in the use of this approach, not only with respect to rTMS but also vagal nerve stimulation.[80–83] Pulsed signal therapy (PST), widely used for the treatment of osteoarthritis in Europe, has also been found to be effective, and, although available in 20 other countries, it is only approved in the USA for veterinary use.[84]

At the Veterans Administration Medical Center in Cleveland, OH, USA, the use of Alpha-Stim technology to treat tinnitus was evaluated in a two arm experimental study.[85] The first arm consisted of seven males and three females from 23 to 69 years old (mean of 43 years) having tinnitus in a total of 18 ears. Otological and audiological evaluations revealed all subjects except one had varying degrees of sensory hearing loss. Between one and 17 treatments of 50 μA Alpha-Stim stimulation was given at 13 sites around the ear for 24 s to 2 min. The tinnitus was matched after each treatment with simulated sounds from a Norwest

SG-1 Tinnitus Synthesizer using an ascending procedure. Six of the ten subjects reported at least a 60% improvement in eight of the 18 ears, confirmed by tinnitus matching. Three additional subjects were undecided whether improvement had occurred. The permanence of improvement lasted from 8 h to 2 months (last contact with the experimenter).

In the second arm, 20 subjects were divided into two groups, an active and a control group, in a single blind protocol. All subjects were male, with either normal hearing or sensory hearing loss, most having idiopathic or noise exposure tinnitus. Each subject received a baseline audiological evaluation utilizing standard equipment referenced to ANSI standards of air conduction, speech reception threshold, most comfortable loudness level, speech discrimination (W-22 word lists), and when indicated, bone conduction, impedance battery, and tone decay. The treatment was identical to the first arm except the current was at 50 or 100 μA, and the stimulus duration was either 12 or 24 s at the 13 sites. After each treatment, the tinnitus was again analyzed using the same protocol. The control group had the identical procedure repeated twice, the first time without stimulation, followed by actual stimulation. Of 17 ears treated in the experimental group, only one subject (both ears) were perceived as not having improved by stimulation. Thus, nine of ten subjects (90%) corresponding to 15 of 17 ears (88%) reported improvement in their tinnitus. The decrease in tinnitus frequency for the subjective improvement ranged from 48% in one subject to complete remission (none) in the six ears combined for four subjects. One subject did not perceive a 19% decrease as being significant. In the control group of 15 ears, in only one ear did a subject believe there had been any change, and measurements indicated a 13% decrease in frequency. The range of change for the 15 ears was from +16 (after sham stimulation, frequency was measured as higher) to –22%. Once the control group had actual stimulation, 80% reported improvement in at least one ear. The measured decrease in tinnitus frequency ranged from 28% to complete remission (none) in four subjects.

Because both groups in the second arm had actual stimulation, the data was pooled. Overall improvement was 82% as reported by 20 subjects (27 of 33 ears). In ten cases, there was complete remission. In the remaining 17 ears, the range of frequency decrease was from 28% to 92%. The permanence of the improvement ranged from 20 min to at least 6 months (last contact with investigators). Most of the subjects had either one or two treatment sessions; however, one subject who had seven sessions found that each session tended to increase the duration of improvement and he concluded that he could live with his tinnitus after the seventh session and requested to be discharged from the program. Age, duration of tinnitus prior to stimulation, and frequency of the tinnitus did not appear to be a determinant to the success of treatment. Some subjects reported the current of 100 μA felt like "pin pricking" but were able to tolerate that level of current. Others could not tolerate greater than 50 μA because of marked sensitivity. There were no other adverse effects reported either during or immediately following CES stimulation.

A significant number of subjects reported improvement in hearing activity but this could not be verified by objective evaluation. The authors concluded that the 82% success rate in improvement in tinnitus implies a feasible treatment procedure in this often devastating disorder that can predispose to suicidality.

In another small pilot study of five patients treated with Alpha-Stim in a university-based neurotherapy clinic, tinnitus handicap and tinnitus severity, as well as EEG pre and post measures, were used for baseline and treatment outcomes. The researchers reported that 40% of the participants (those with unilateral tinnitus fluctuating in intensity) evidenced appreciable improvements in their tinnitus symptoms and that responsiveness to treatment in this subgroup may occur as early as the first treatment session.[86]

A cochlear implant that can be activated with "low rate electric stimulation" was attempted and appeared to be very effective for deaf patients with tinnitus but is presently contraindicated in others because of associated nerve damage.[87]

Cancer

Therabionic noninvasive low energy emission therapy (LEET), another form of cranial electrotherapy stimulation, has been found to be the most effective treatment for hepatocellular carcinoma and has shown promising results in certain metastatic malignancies. There are no adverse side effects, and the daily three 1 h sessions can be self-administered at home while the patient is reading or watching television.[88–91]

Novocure tumor treating fields (TTF) has been approved by the FDA for treating glioblastoma multiforme and clinical trials are in progress to extend this to lung cancer and metastatic brain lesions.[92] TTF therapy is delivered using noninvasive, insulated transducer arrays placed directly on the skin area surrounding the tumor in a manner that allows patients to maintain their normal daily activities while treating their disease. While it has been referred to as "24/7 CES," TTF therapy does not deliver any electric current to the tissue, stimulate nerves, or heat tissue. Rather, it creates an alternating electric field that interferes with mitosis and cell division within the tumor. The only side effects are occasional skin irritation at the transducer array sites.

Whether FDA cleared CES devices may have antitumor effects is not yet known, although anecdotal reports, such as one published in the form of a book by Margaret Waddington, MD, a retired neurologist with lymphatic leukemia, suggest this possibility. Her oncologist gave her a maximum 2-year prognosis if she refused chemotherapy. As this book goes to print it has been over 20 years since Dr. Waddington refused chemotherapy and relied on electrical therapy for her apoptosis treatment. Yet she is still able to live alone and continue having a productive life while running a 105-acre maple tree farm in Vermont.[93]

Preliminary studies also support the use of CES in cancer patients to reduce the sequelae of radiation therapy for

cancer. In one study, the authors concluded that the clinical impression at M.D. Anderson Cancer Center is that Alpha-Stim therapy is similar to hyperbaric oxygen and both of these modalities are achieving a degree of tissue repair and revascularization of the irradiated field. Although it is still unclear what is specifically occurring physiologically and histologically, the irradiated soft tissues appear to become revascularized. It is apparent that these modalities have relieved discomfort, enhanced healing of irradiated hard and soft tissues, and improved the quality of the irradiated soft tissues.[94]

A 61-year-old male veteran receiving 6000 rads of radiation therapy by a megavolt cobalt linear accelerator for T2N1M0 squamous cell carcinoma of the right tonsilar area at the Cleveland VA Medical Center was given a maximum of 30 min of Alpha-Stim therapy of 50–500 μA at 0.5 Hz, immediately following each radiation treatment. The following adverse reactions to radiation were expected: irreversible xerostomia because all the salivary glands were included in the radiation field, temporary dysgeusia, throat pain, possible mucositis, and radiation dermatitis. Following the CES treatments, all adverse reactions were reduced drastically and xerostomia and dysgeusia were eliminated. The patient required no regimen of pain medication because CES reduced the level of pain each day following radiation; he showed no signs of mucositis or radiation dermatitis at any time which is highly unusual as some degree of xerostomia and mucositis is anticipated in all such irradiated patients. The author added that several patients have been seen at the Cleveland VA Medical Center for Alpha-Stim treatment for postradiation dryness, with equally good results.[95]

ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AUTISM, PTSD

Transcranial magnetic stimulation uses a magnetic field to create electrical changes in the brain. As such, it can be considered an indirect form of CES. Brainsway's patented DEEP TMS technology differs from other transcranial magnetic stimulation approaches by using several Deep TMS coils (termed H coils) rather than a single focal stimulation. This is designed to stimulate deeper brain lesions without increasing the electrical field intensity of superficial cortical regions or excessively stimulating facial nerves. Typical treatment protocol consists of 15–20 sessions, each lasting 15–20 min, over a course of 3–4 weeks. DEEP TMS was approved by the FDA in 2013 for the treatment of major depressive disorder or in patients who did not respond to antidepressant drugs. In the European Economic Area, it also has CE marking for Alzheimer's disease, autism, bipolar disorder, chronic pain, Parkinson's disease, and PTSD; approval for some of these in the USA are planned.

CLINICAL CONSIDERATIONS AND GUIDELINES

To integrate CES into clinical practice we recommend a trial series of treatments in a clinic or office to evaluate responses in each individual. After the initial trial, patients can be prescribed a CES device to use at home giving them increased control over the management of their symptoms. In addition to a regular 20–60 min treatment daily or every other day, patients can add treatments as needed. Some clinicians find it useful to set up a CES lounge where patients can come in for unattended low cost treatments whenever they feel stressed. This concept was studied at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, TX, USA. After being trained to use five different types of stress relieving devices at a walk-in pain clinic, veterans preferred Alpha-Stim CES 73% of the time. The benefits observed included improved attendance and veterans' involvement in group-based therapies, reductions in reported pain and anxiety, improved sleep, and an increased sense of emotional well-being in the participants. Decreases on the 0–10 Numerical Rating Scale of pain intensity during the study period were statistically significant at $p < 0.001$, and represented a large effect size of 0.93.[96]

DURING PSYCHOTHERAPY SESSIONS

CES may also be used during psychotherapy sessions. Using CES during a talk therapy session decreases anxiety and usually improves the patient's desire and ability to share problems, concerns and worries with the therapist, as well as to respond to the therapist's questions more effectively. Anecdotal reports from psychiatrists, psychologists and other mental health professionals on the use of CES during therapy are consistently enthusiastic. CES induces a prehypnotic relaxed state of mind and body that is complementary with talk, biofeedback, eye movement desensitization and reprocessing (EMDR), hypnotherapy, and many other interventions.

CONCURRENT PHARMACOTHERAPY

CES can be used with pharmacologic therapy without concern about potential polypharmacy interactions. However, it is important to inform the patient that CES may decrease the need for medication. As the patient improves, both the clinician and patient should be alert for symptoms that may indicate a need for a dosage adjustment.

SELF-DIRECTED HOME TREATMENT

Most individuals are capable of doing self-directed CES therapy at home. The USA is the only country in the world that requires CES devices to be sold only by, or on the order of, a licensed healthcare practitioner. Treatments may need to be done daily during the first 1 to 3 or 4 weeks, then two to three times per week during a maintenance phase. The individual can also use CES as often as needed, as there are no side effects from extended use. This is especially beneficial for those individuals diagnosed with PTSD and others who experience panic attacks.[97]

EVALUATING IMMEDIATE AND LONG-TERM EFFECTS

Feelings experienced during a CES treatment are shown in Figure 19.5. If the patient feels heavy, groggy, or euphoric at the end of the allotted time, it is important to continue the treatment session until the patient feels "light." At the end of a CES session, the majority of patients will feel more relaxed while remaining alert, and have an increased sense of well-being. CES is demonstrably effective by both the patient receiving treatment and those observing its relaxation and other benefits, which are sometimes evident after the first treatment.

Accordingly, evaluating a single 20–40 min trial of CES in a clinic or office will help identify those individuals who are likely to respond rapidly to treatment. However, CES effects are cumulative so those who do not respond initially may benefit when given daily treatments (20–60 min) for 1 month or longer.[28,77] This is particularly true in depression and fibromyalgia which may take several treatments to induce a preliminary effect.

A clinician who would like to document treatment progress in CES patients may choose to use the Hamilton Anxiety Rating Scale (HARS), State-Trait Anxiety Index (STAI), Hamilton Depression Rating Scale (HAM-D17) and/or Beck Depression Inventory, the Pittsburg Sleep Quality Index (PSQI), Numerical Rating (NRS), Visual Analog Scale (VAS), or Likert Scale, all of which have proven useful in evaluating CES outcomes. The anxiety testing should be administered before and immediately after the first treatment, and after 3 weeks and 6 weeks of daily use. For depression and insomnia, which typically respond more slowly, patients should be tested before, but not immediately after the first treatment. Measurements at 3–4 weeks and then again at 6–8 weeks provide useful assessments of patient progress.

CONTRAINDICATIONS, PRECAUTIONS AND ADVERSE EFFECTS

There are no known contraindications to the use of CES. The only precaution is regarding use during pregnancy. A study of potential teratogenic effects from CES was conducted on 844 Spraque-Dawley fetal rats.[98] The treated rats were divided into three groups and given CES 1 h daily throughout their pregnancy at either 10, 100, or 1000 Hz, while the parameters of 1 volt, 0.125 milliampere, at a 0.22 microseconds pulse width remained constant. On day 18 of pregnancy, the dams were killed and cesarean section was performed immediately. After thorough external examination, autopsies evaluated the palate, heart, major vessels, lungs, liver, kidneys, ureters, and bladder. Examinations under light microscopy revealed no neural tube defects, limb reduction deformities, or anterior abdominal wall abnormalities in the controls, or in any of the treatment groups. Skeletal surveys of the fetal rats found no vertebral column, rib, or long bone deformities. Comparison between groups revealed more pregnancy resorptions and fewer offspring in all treatment groups compared to the control group, with the difference only reaching significance in the 1000 Hz treatment group. Average fetal weights were inversely proportional to frequency and were significantly different among groups. Fetal brain weight followed a similar pattern of reduction, except that weights were not significantly different between the medium and highest frequency treatment groups.

In their discussion, the researchers stated that while the incidence of congenital anomalies was zero, the reason pregnancy resorptions were increased may be due to the CES treated rats being more complacent. Their behavior resembled the calming effects of CES in humans. The treated rats were not as active as the controls. Accordingly, it is possible that

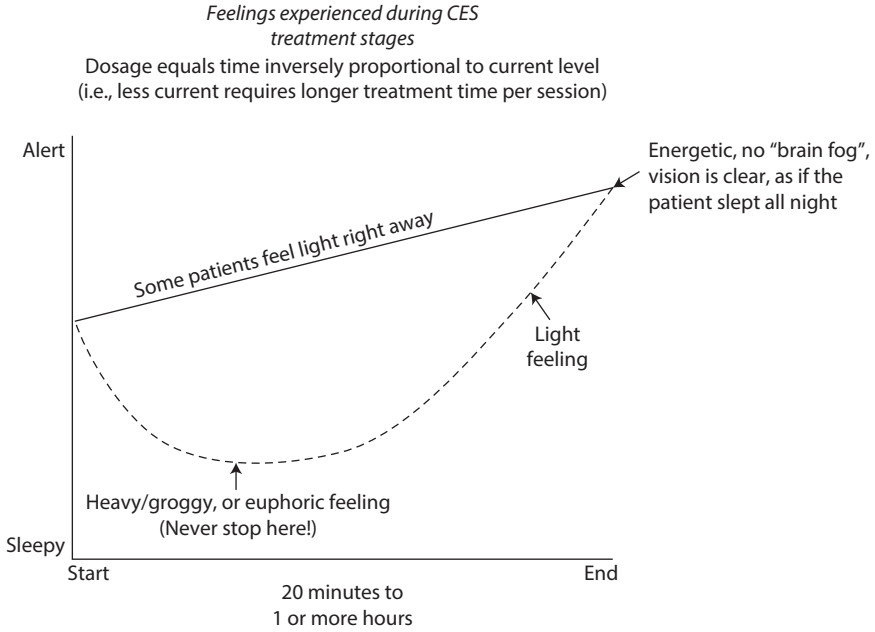

FIGURE 19.5 Cranial electrotherapy stimulation dose response curve.

food intake was lowered in the treatment group, a reasonable implication given the reduction in fetal weights. They concluded that CES may be embryolethal in the very early stages of pregnancy in the rat and might cause some miscarriages, especially at 1000 Hz, but there is no evidence of fetotoxic effects. The relevance of these findings to humans is unknown.

Adverse effects of CES in humans occur in less than 1% of cases and they are mild and self-limiting. These include vertigo, skin irritation at electrode sites, and headaches. Headaches and vertigo are usually experienced when the current is set too high for a particular individual. These effects resolve when the current is reduced or within minutes to hours following treatment. Irritation at the electrode site can be avoided by moving electrodes around slightly during treatments. No serious adverse effects have ever been reported from using CES.[15]

CONCLUSION

CES can improve the safety and effectiveness of treatment for anxiety, insomnia, and depression as well as contribute to the management of pain and other disorders. When prescribed for home use, patients are empowered to regulate their own moods, to overcome their sleep problems, and manage their own pain, thus enhancing outcomes. Compared to other neuerostimulation techniques for brain repair, CES is noninvasive, less expensive, and can be used safely and conveniently by patients at home. It is useful both as an adjunct to medication or psychotherapy or as a stand-alone treatment. While the efficacy of CES in cancer and other serious diseases with poor responses to conventional treatment is currently supported only by anecdotal reports, such patients can certainly benefit from its ability to improve mood and sleep as well as relieving pain.

Historically CES has been used as a last resort when medications and other interventions fail or are not well tolerated because of adverse side effects. CES often provides benefits in such "treatment-resistant" patients, and, because it is so safe and cost effective, should be considered a first line treatment for anxiety, insomnia, depression, pain, and possibly some of the other disorders noted above.

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20 Chronic Therapeutic Brain Stimulation
History, Current Clinical Indications, and Future Prospects

*Nrupen Baxi, Ali Rezai, and Alon Y. Mogilner**

CONTENTS

First performed over 50 years ago, chronic electrical stimulation of the human brain has only recently begun to achieve its clinical potential. The dramatic benefit of the technique in the treatment of severe movement disorders, including Parkinson's disease (PD), essential tremor, and dystonia, has spurred its use in a number of other disease conditions. These include epilepsy, chronic pain, and neuropsychiatric disorders, such as obsessive–compulsive disorder (OCD), treatment-resistant depression, and Tourette's syndrome, while other emerging indications await.

HISTORICAL OVERVIEW

The relationship between electricity and biology was known to the Romans in the first century AD, who used the electrical discharges of the torpedo fish to treat headaches and gout. Following the observation made by Luigi Galvani (1737–1798) that twitches could be elicited by touching the leg of a frog with two metallic wires, Jean Aldini, professor of anatomy in Bologna in 1804, performed what could be considered as the first human electrical brain stimulation, by applying a conductor from a Volta battery to the scalp of a subject who experienced a strong discharge. Aldini then wrote that "it seems highly probable that electrical stimulations might have in the future important therapeutic applications," and half a century later, in 1855, Duchenne de Boulogne published a monograph reporting his experience in physiology and therapeutics.[1]

In 1870, Gustav Fritsch and Eduard Hitzig of Germany reported that electrical stimulation of the canine frontal lobes could elicit contralateral body movements.[2] While these authors refer to stimulation of the human brain in a footnote, it is unclear whether they stimulated the brain surface directly or transcutaneously via an electrode placed on the mastoid process.[3] Similar findings in dogs were reported 3 years later by David Ferrier of London.[4] The first unequivocal report

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of direct stimulation of the human brain was by Roberts Bartholow of Cincinnati, OH, USA, in 1874.[3–6] Having read the work of these pioneers, Bartholow proceeded to perform the same on humans, writing:

> Having had a case recently in which a considerable portion of the posterior lobes of the brain was exposed by disease without any interruption of its functions, I ventured to make some experiments on the plan pursued by Fritsch and Hitzig and Ferrier.[7]

Bartholow inserted insulated needle electrodes through the exposed dura and brain of a 30-year-old woman with a scalp defect secondary to an erosive basal cell carcinoma. Electrical stimulation produced a variety of effects, including contractions of the contralateral extremities, unpleasant sensory experiences, and, with increasing amounts of current, focal and then generalized seizures. Ultimately, the patient exhibited recurrent seizure activity over the next few days and expired soon thereafter. Postmortem examination performed by Bartholow revealed multiple electrode tracts, as well as extensive sagittal sinus thrombosis and a subdural empyema.

After finding considerable disapproval with his actions in the scientific community, Bartholow later wrote in a letter to the *British Medical Journal*:

> To repeat such experiments with the knowledge we now have that injury will be done by them … would be in the highest degree criminal. I can only now express my regret that the facts which I hoped would further, in some slight degree, the progress of knowledge, were obtained at the expense of some injury to the patient.[8]

It was not until 74 years later that this technique was used for therapeutic purposes. The first neurosurgeon to do so was J.L. Pool of Columbia University's Neurological Institute,[9] who considered brain stimulation as an alternative to the ablative psychosurgical procedures of his era. In 1948, via open craniotomy, Pool implanted a silver electrode in the caudate nucleus of a woman suffering from depression and anorexia, who, incidentally, suffered from advanced Parkinson's disease. Electrical stimulation via an implanted induction coil was carried out over a period of 8 weeks, and it improved her mood as well as her appetite. Stimulation was discontinued only after one of the wires broke. (No mention was made of the effects of stimulation on her Parkinson's disease.) That same year, Pool placed a stimulating electrode in the cingulate gyrus of a psychotic patient—the results of which were not reported. No specific rationale was provided by Pool for the target selection in these two patients. By the time Pool published these results in 1954 in the *Journal of the American Geriatric Society*, similar psychiatric neurosurgical procedures had been performed by others, most notably R.G. Heath[10] at Tulane University, starting in 1950.

Heath and coworkers implanted electrodes in the septal region of patients, the majority of whom were schizophrenics, but also in four patients suffering from diffuse metastatic carcinoma with intractable pain, as well as one patient with advanced rheumatoid arthritis. The electrodes were placed in a region anterior and inferior to the foramen of Monro at the base of the anterior portion of the septum pellucidum. Anatomic and physiologic studies in animals by Heath and colleagues had demonstrated that electrical activation of the septal region resulted in an electroencephalograpic activation of motor cortex. The initial patients were schizophrenics, and a deactivation of motor cortex was thought by Heath and colleagues to be a key etiologic component of the disease. Thus, a target that would activate frontal cortex was chosen.[10] Stimulation was applied at a frequency of 100 Hz with a 1 ms square wave pulse, at voltages up to 20 volts. All patients reported pain relief from electrical stimulation. Pool, using Heath's stereotactic technique, reported pain relief in one patient with septal stimulation. Nevertheless, Pool stated that brain stimulation should "probably be used only in desperate cases in which there is virtually nothing else to offer."[9] In 1960, Heath and Mickle reported their long-term follow-up data on patients undergoing septal stimulation for the treatment of both schizophrenia and chronic pain. Chronic stimulation of the septal region successfully relieved pain in all patients.[11]

During the same time period, another technical development in neurosurgery significantly influenced the evolution of brain stimulation. Stereotactic neurosurgery, introduced by Spiegel and Wycis in 1947,[12] offered a less invasive alternative to open neurosurgical ablative procedures pioneered by Egaz Moniz in Portugal for the treatment of psychiatric disorders and movement disorders. At that time, these conditions were treated surgically with procedures including prefrontal lobotomy and pedunculotomy, performed via craniotomy with its associated morbidity. It soon became evident that this technology was well suited for the placement of stimulating electrodes into the brain[13] with decreased risk to the patient as compared with open procedures. Consequently, the histories of brain stimulation and stereotactic neurosurgery became inextricably linked.

While Heath and colleagues began using the stereotactic method to place their stimulating electrodes for the treatment of psychiatric disorders and chronic pain, intraoperative electrical stimulation became part and parcel of functional stereotactic neurosurgery for the treatment of movement disorders. Intraoperative stimulation was routinely used prior to placement of a lesion, both to verify the efficacy of the planned lesion as well to detect any adverse side effects.[13] By 1960, Hassler had reported his observations that electrical stimulation of the globus pallidus had opposite effects on tremor, depending on the frequency of stimulation.[14,15] Stimulation at 4–8 Hz was noted to evoke tremor, while higher frequency stimulation at 25–100 Hz could reduce or even arrest it. Indeed, Spiegel and Wycis reported that low frequency stimulation of the globus pallidus could elicit or augment tremor—no note was made of tremor arrest via stimulation.[16] Throughout the literature, the effects of intraoperative electrical stimulation were reported, mentioning either a worsening or an alleviation of symptoms, including tremor, incidentally providing information about the parameters that were employed, in particular low or high frequency,

without a specific rationale. This did not lead to the recognition of a clear relationship between the excitatory or inhibitory observed effects and the frequency of the stimulus.

Postmortem studies of initial patient undergoing pallidal lesioning by Smith identified the field of Forel as the ideal target in Parkinson's disease as the degenerated pallidofugal and dentatorubrothalamic fibers pass through this area. She also noted that degenerated fibers in the dorsal subthalamic nucleus, an observation that would be exploited by neurosurgeons in years to follow.[17,18] Work by Velasco promoted the subthalamic nucleus (STN) as a target for Parkinson's disease with recording of rhythmic activity and arrest of tremor on placement of the electrode.[18,19]

As neurosurgery for psychiatric disorders fell out of favor by the 1960s, chronic pain became the sole indication for brain stimulation, in parallel to attempts to control spasticity and epilepsy by stimulation of the cerebellum.[20] Furthermore, the advent of levodopa for the treatment of Parkinson's disease in the late 1960s resulted in a significant reduction in the number of functional neurosurgical procedures performed during that era. Brain stimulation for the treatment of movement disorders, as we shall see later in this chapter, continued to be performed by a small number of neurosurgeons during the 1970s and 1980s for a variety of clinical indications, with a variety of different targets and stimulation parameters. The modern era of stimulation for movement disorders can be considered to start in 1987, when A.L. Benabid (Grenoble, France) first reported the use of high frequency (130 Hz or greater) Ventralis Intermedius (Vim) thalamic stimulation for the treatment of tremor.[21] The introduction of bilateral subthalamic nucleus stimulation by Benabid in 1993 further demonstrated the remarkable efficacy of this technique in treating the cardinal symptoms of Parkinson's disease, including not only tremor but rigidity, bradykinesia, and gait and postural instability.

MECHANISM OF ACTION

The exact mechanism of action of brain stimulation remains unknown. There is now sufficient evidence to suggest that brain stimulation exerts its effects via a number of differing but interrelated mechanisms that come in to play depending on the site being stimulated, the disease entity being treated, and the stimulation parameters used. Undoubtedly, the clinical effects seen with brain stimulation reflect the complex combination of inhibition and activation of cell bodies and axons, and depend on the orientation of the electrode, the cytoarchitecture of the structure being stimulated as well as the frequency, pulse width, and duration of stimulation.

The mechanisms of action can be classified into four categories: inhibition of the target, activation of the target, combined inhibition and activation, and disruption of pathological oscillations using white noise.[22]

The similarity between the clinical effects of high frequency stimulation and ablative procedures provides evidence for the first mechanism where high frequency deep brain stimulating (DBS) effects a functional inhibition of the target structure.[23] An *in vitro* study in the rat demonstrated that high frequency (100–250 Hz) stimulation of subthalamic nucleus resulted in a transient blockade of the persistent sodium current as well as L- and T-type calcium currents, results also consistent with an inhibitory effect of stimulation,[24] while others report inhibition of the STN following high-frequency stimulation.[25]

Other studies have shown the opposite result providing evidence for the second mechanism, namely that high frequency stimulation acts via an excitatory mechanism, by increasing neuronal output of the target structure.[26] More recently, the last mechanism has been suggested that HFS, rather than simply inhibiting a hyperactive structure, acts via a resynchronization of abnormal output patterns present in disease[27,28] or via a "jamming" of these abnormal patterns by HFS providing physiologic white noise.[25] The suppression of β band signals (13–30 Hz) in the basal ganglia-cortical loop has been shown to improve motor symptoms in patients with DBS.[22] Clearly, further studies are needed to improve our understanding of these complex mechanisms.

EQUIPMENT

The standard equipment used for intracranial stimulation includes the stimulating electrodes, extension leads, and implantable pulse generators (IPGs). Whereas only one system (Medtronic) is approved for use by the U.S. Food and Drug Administration (FDA), other device manufacturers (St. Jude and Boston Scientific) have systems approved for use in the European Union, Asia, and Australia.

Subcortical Targets

The most widely available devices used for chronic stimulation of subcortical structures, known as "deep brain stimulating" (Medtronic Inc., Minneapolis, MN, USA.), is a 1.27 mm diameter quadripolar platinum/iridium lead (Figure 20.1). Each of the four contacts is 1.5 mm long, and, depending on the model of the electrode, is separated by either 0.5 or 1.5 mm of insulation. The electrode is connected via an extension lead tunneled subcutaneously to an implanted pulse generator (Figure 20.2a and b). Stimulation can be unipolar, bipolar, or multipolar, as each of the electrode contacts can be used as an anode or cathode providing a variety of different electrical field patterns. Stimulation parameters include frequency ranges of 2–185 Hz, voltage range of 0–10.5 V, and square wave pulse widths ranging from 60 to 450 μs. The stimulators are programmed via portable device that communicates with the implanted generator via telemetry. Stimulation can be performed continuously or intermittently, and can be programmed to cycle "on" and "off" during fixed time intervals. Patients are able to activate and deactivate the stimulator via handheld controllers and can modify a subset of the stimulation parameters within given limits set by the medical team. Both rechargeable and primary cell devices are available for implantation. Both St. Jude and Boston Scientific offer alternate systems that primarily operate in constant

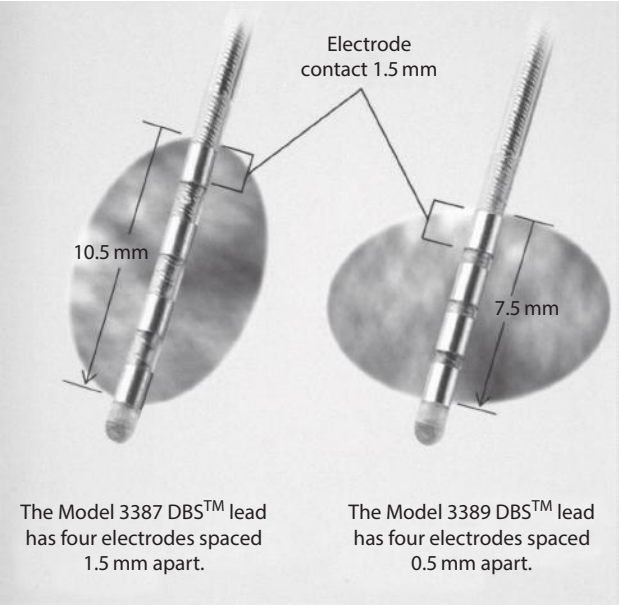

FIGURE 20.1 Quadripolar deep brain stimulating (DBS) electrode. Photograph of the four pole/contact electrode. Each contact is made of platinum/iridium alloy and is 1.27 mm in diameter. The insulated inter-pole distance is 1.5 mm or 0.5 mm depending on the model. (Courtesy of Medtronic.)

current modes. St. Jude's Libra and Brio systems claim to be rechargeable for up to 10 years.[29] Boston Scientific's Vercise system is rechargeable up to 25 years, and has eight contacts on the implanted electrode with current steering capabilities toward particular electrodes.[30] Both devices are not yet approved for use in the United States.

SURGICAL PROCEDURE

Stereotactic neurosurgical techniques allow the localization of any brain structure with millimeter precision. Anatomic localization is achieved with stereotactic imaging via imaging modalities such as magnetic resonance imaging (MRI), and computed tomography (CT). Ventriculography, a technique in which contrast is injected into the cerebral ventricles and an X-ray is obtained, is rarely used nowadays given the accuracy and noninvasive nature of MRI and CT. Dramatic advances in image processing technology allow for rapid, automated fusion of different imaging modalities (Figure 20.3). For example, a high-resolution MRI scan obtained prior to stereotactic frame placement can be fused with a CT scan obtained with the frame in place, allowing for both increased patient comfort as well as removing any potential MRI image distortion induced by the frame. Stereotactic atlases, in which cadaver brains were sliced and oriented with respect to landmarks such as the anterior and posterior commissures[31–34] can be "morphed" to a particular patient's anatomic imaging data, allowing for further increased ease of target selection.

Similarly, a number of methods of physiologic verification of the anatomical target exist: microelectrode recording (MER), semimicroelectrode recording, and macrostimulation. Both microelectrode and semimicroelectrode recording attempt to define the boundaries of a given structure based on the known spontaneous and/or evoked electrical activity of that structure and surrounding structures. Macrostimulation, stimulation through a relatively large diameter electrode (on the order of 1 mm diameter), is used in all DBS cases prior to final implantation of the electrode. Macrostimulation allows the physician to assess for both the therapeutic effects of stimulation (reduction of tremor, rigidity, or pain), as well as for possible untoward effects (i.e., paresthesias, motor contractions, ocular deviation). As the stimulation parameters used during this testing phase are usually similar to those which will be used for chronic stimulation, macrostimulation should approximate the effects of chronic therapy.

As experience with DBS surgery has increased, the optimal stereotactic coordinates for common targets have been refined. Improvements in MR imaging techniques have also enabled direct anatomic targeting of deep nuclei. Large centers have taken these targets and advanced MR imaging techniques to place DBS electrodes without the use of physiologic confirmation techniques such as microelectrode

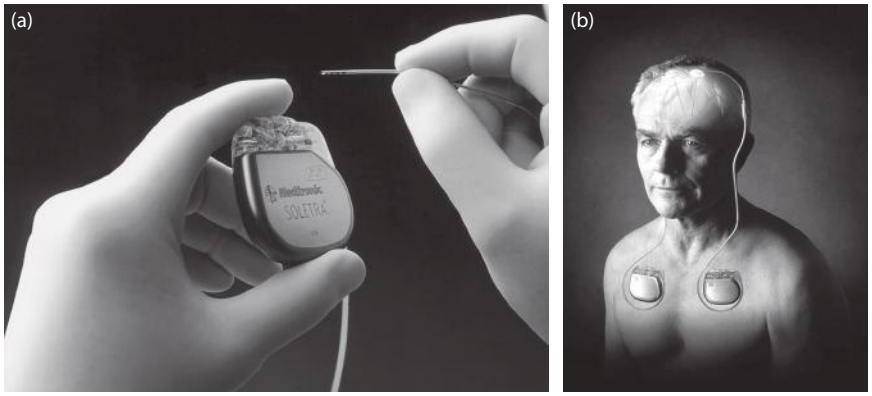

FIGURE 20.2 Pulse generator and deep brain stimulating (DBS) electrode. (a) Photograph of the pulse generator device that is implanted in the infraclavicular region. (b) Photograph showing the overall configuration/positioning of the implanted bilateral electrodes and pulse generators. (Courtesy of Medtronic.)

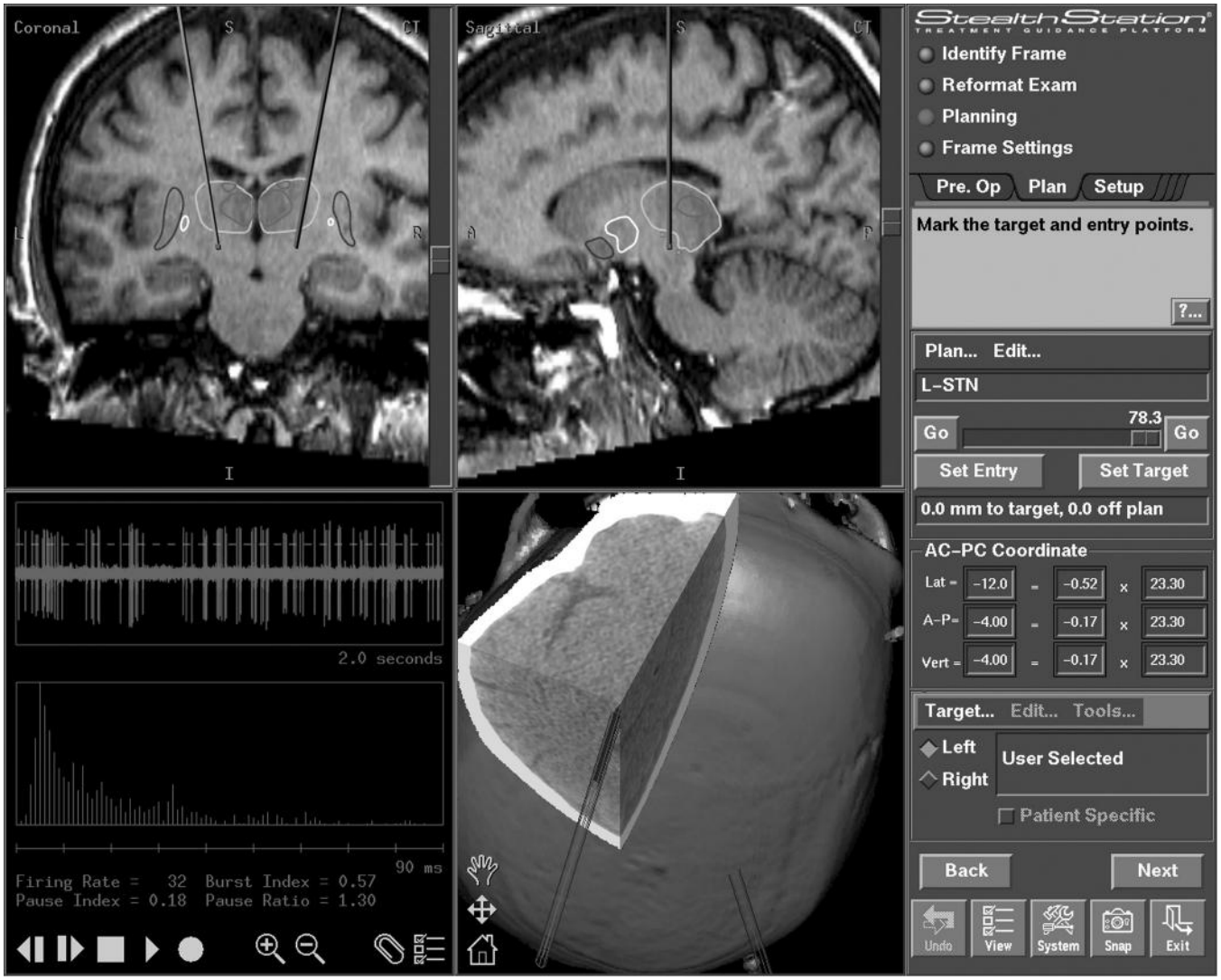

FIGURE 20.3 **(See color insert.)** Computer-guided brain targeting and navigation. Operative computers combine different imaging modalities such as computed tomography and various magnetic resonance imaging (MRI) sequences, along with brain and patient-specific atlases, to provide the target and best trajectory of approach to that target. In this case, an actual path in the brain is shown in the axial, sagittal, coronal, and three-dimensional planes, toward the target—the subthalamic nucleus.

recording.[35–40] These methods often utilize intraoperative CT or MRI to guide electrode placement using frameless methods and confirm electrode placement with intraoperative imaging.[41–45] This allows the surgeries to be performed under general anesthesia, in contrast to the traditional method of performing the surgeries under local anesthesia with sedation in order to provide physiologic confirmation of the target.

A "trial period," where the stimulating wires are externalized for durations on the order of days to weeks, and various stimulation combinations are evaluated for clinical efficacy, is used for pain therapy. Such trial periods were used more frequently in the past for movement disorder therapy. Given the demonstrated efficacy of DBS for movement disorders, DBS electrodes are routinely permanently implanted without a prolonged trial period in movement disorder surgery. The pulse generators may be implanted at the same sitting or at a later date.

CLINICAL INDICATIONS

While the earliest uses of brain stimulation were for the treatment of chronic pain, the most common indication over the past 25 years remains movement disorders, specifically Parkinson's disease and essential tremor. The dramatic success of DBS therapy in movement disorders has spurred renewed interest in other applications including pain, epilepsy, and psychiatric disorders. A summary of common clinical indications and target sites is shown in Figure 20.1.

Movement Disorders

Thalamic Stimulation

Benabid's initial reports[21,46] suggested that chronic Vim stimulation may be useful in those patients who have already undergone unilateral thalamotomy with persistent

symptoms on the nonoperated side. He noted that the thalamotomy provided better tremor relief but that this was most likely due to the frequency limit of 130 Hz on the stimulator. He stated that the optimal frequency appeared to be about 200 Hz, close to the current standard frequency of 185 Hz. His 1991 report in the *Lancet* reported up to 29-month (mean 13 months) follow-up on 26 patients with Parkinson's disease.[47] Complete relief or major improvement in the tremor was noted in 88% of cases. His report of an 8-year follow-up of 80 patients demonstrated the effect to be robust, with half the patients able to decrease dopaminergic medication by at least 30%. However, Vim stimulation was only effective for tremor, and not other Parkinsonian symptoms.[48] Conversely, Vim stimulation was clearly seen to be the surgical treatment of choice for essential tremor, a benign condition in which tremor is the only symptom. Since that time, thalamic stimulation has been well established as a safe and effective treatment of refractory Parkinsonian and essential tremor, with results as good as traditional thalamotomy and with fewer associated significant adverse events.[49–51]

Other Tremor Types: Multiple Sclerosis, Head and Voice tremors

In 1980, Brice and McLellan[52] reported their successful suppression of upper extremity tremor in three patients with multiple sclerosis (MS). Their targets included both the midbrain and the basal ganglia. The effect was durable during the reported 6-month follow-up period. There have been few reports dedicated to DBS for multiple sclerosis-related tremor, but these patients are frequently included in other series of DBS patients. The largest dedicated series is that of Montgomery et al.,[53] involving 15 patients treated with chronic Vim stimulation. While tremor was generally improved, tachyphylaxis was common and frequent programming changes were required. Other small series with similar results have been reported.[54,55]

Multiple small series have demonstrated the potential of thalamic DBS for treating intractable head and voice tremor. The largest series of patients with head tremor is that of Koller et al. in which 38 patients were followed for 12 months.[56] Twenty-four of these patients underwent blinded clinical evaluations. Stimulation significantly reduced head tremor in both the blinded and nonblinded groups. Other small series and the European Multicenter Trial also seem to indicate that bilateral thalamic stimulation is a valid treatment for head tremor.[50,57] The European trial and Carpenter[58] found minimal improvement in voice tremor with thalamic DBS. In both cases, however, larger well-designed trials are needed before making firm conclusions about the utility of DBS for these conditions.

Subthalamic Nucleus Stimulation

Unlike the Vim thalamus and globus pallidus, the STN was previously not considered for lesioning procedures in Parkinson's disease until much later. This was due to fear of causing hemiballism, a well-documented effect of STN lesions in previously normal individuals experiencing intracerebral hemorrhage in this area.[59] Velasco was the first to show a series of patient with tremor arrest upon insertion of an electrode into the STN.[19] The impetus for targeting the subthalamic nucleus resulted from a number of studies in the MPTP-lesioned primate model of PD, beginning in the mid-late 1980s. After animal studies confirmed an increased glutaminergic (excitatory) STN output in Parkinson's,[60] STN lesions in MPTP-treated monkeys were clearly demonstrated to alleviate the symptoms of PD,[61–63] and high frequency STN was shown to be effective as well in these animals.[60] Armed with these experimental findings, Benabid, in 1993, implanted a stimulating electrode in the STN of a 51-year-old patient with severely disabling akinetic-rigid PD with severe on-off fluctuations.[64] The first patient was reported in 1994 and a lengthier paper followed in 1995 describing the first three patients to have electrodes implanted chronically in the STN. The activities of daily living (ADL) score portion of the Unified Parkinson's Disease Rating Scale (UPDRS) improved over 50%, as did motor scores. Some stimulation-induced hemiballismus was noted, but was controlled by adjusting the stimulation. One-year follow-up of 24 patients with bilateral STN stimulators demonstrated that UPDRS ADL and motor scores improved by 60% in the off-medication state. The UPDRS subscores for akinesia, tremor, rigidity, and gait improved, in contrast to the results seen with Vim stimulation.[65] Since that time, the STN is increasingly becoming the preferred target for chronic electrical stimulation in PD at most centers, effective in treating the cardinal manifestations of the disease, with improvements in motor function of approximately 80% using the standardized UPDRS rating scale. Furthermore, levodopa intake is reduced following surgery by approximately 50%, resulting in a significant decrease in drug-induced dyskinesia.[66,67]

Side effects appear to be mild in most cases. In those patients who experience an increase in dyskinesia soon after initiating chronic stimulation, a reduction in the dose of dopaminergic medications or an adjustment in stimulation parameters usually suffices to alleviate the problem. Postoperative confusion is more common in elderly patients. In addition, a small number of patients have experienced mood alterations, apparently associated with a more ventral electrode placement closer to or in the substantia nigra pars reticulata.[68] A recent randomized trial of STN stimulation in younger patients with early motor complications in Parkinson's disease showed a statistically significant increase in depression scores. It is unclear whether is due to reductions in dopaminergic medications or an effect directly related to STN stimulation.[69] While one study reported an overall cognitive decline in 30% of patients after 1 year of bilateral STN stimulation,[70] a number of other studies have shown no significant cognitive deterioration with chronic STN stimulation.[71–73]

Globus Pallidus Internus (GPi) Stimulation

Given the known beneficial effects of lesioning of the posterior ventral globus pallidus in alleviating many of the cardinal symptoms of Parkinson's disease including rigidity,

bradykinesia, gait dysfunction, tremor, as well as reducing the severity of levodopa-induced dyskinesias,[74] the GPi became the next target for chronic stimulation. GPi stimulation is currently used by a number of centers for the treatment of refractory Parkinson's disease, with beneficial effects on these cardinal manifestations of PD and reduction in dyskinesias similar to that obtained by pallidotomy.

A series of 36 patients demonstrated that bilateral pallidal stimulation results in a median motor improvement of 37% and an increase from 28% to 64% of the day without disabling involuntary movements.[65] A number of studies have demonstrated the beneficial effects of GPi stimulation on dyskinesias, on-off fluctuations, and tremor.[65,75–77]

GPi vs. STN Stimulation for Parkinson's Disease

A handful of head-to-head comparisons of GPi and STN stimulation have been published. The largest multicenter study found that STN stimulation was significantly more efficacious.[65] Burchiel conducted a randomized trial of pallidal versus STN stimulation. While the results off medication were similar for the two groups, pallidal, but not subthalamic, stimulation improved Parkinsonian symptoms, while patients were in the medication-on state. Furthermore, while rigidity, bradykinesia, and tremor were equally affected by both targets, axial symptomatology was relieved only by GPi stimulation. However, only STN stimulation provided enough relief to allow patients to reduce their medication dosage.[78] Other reports also favored the STN.[79–81] More recently, larger randomized clinical trials comparing STN to pallidal stimulation have found no significant difference in UPDRS-III scores in patients receiving STN versus pallidal stimulation up to 2–3 years in follow-up They have also confirmed the higher reductions of medications in those receiving STN versus pallidal stimulation. However, again higher rates of depression were found in patients receiving STN stimulation.[82,83] It remains unclear as to whether the increased depression is due to a direct effect of STN lead placement/chronic stimulation, or a secondary effect from reductions in dopaminergic medications after effective STN-DBS which may only address the motor symptoms of Parkinson's disease.

Other Movement Disorders

With the success of DBS for PD and tremor, investigators have attempted to expand the range of indications for the procedure. Dystonia, with a long history of neurosurgical treatment, has always been a target for DBS, and reports continue to emerge describing its use in dystonia with a variety of subcortical targets. However, dystonia is extremely heterogenous, with a widely varying clinical spectrum and multiple etiologies (generalized versus focal, idiopathic, genetic, post-traumatic, post-stroke, etc.), making the assembly of large patient populations problematic.

Recent reports have demonstrated the efficacy of deep brain stimulation of the thalamus and GPi for various forms of dystonia, with more beneficial effects on primary and generalized dystonias, as opposed to secondary and focal dystonias, and with the suggestion that the GPi may be a more suitable target.[84–91] More recently, several randomized clinical trials have confirmed quality of life improvements and reductions in Burke-Fahn-Marsden Dystonia Rating Scale scores of nearly 50%[92–95] Both STN and pallidal targets have been used with success. This has led to a humanitarian device exemption from FDA in the United States to treat dystonia with DBS.

The procedure is complicated in these patients by their very disease in that cervical torsion complicates frame placement, imaging, and image fusion. Moreover, patient tolerance of the procedure is limited as they are restrained in a fixed frame for several hours. In addition, cervical torsion puts these patients at high risk for such complications as lead fracture and other wound-related complications. Future directions point towards expanding the use of DBS and enabling feedback mechanisms for the better treatment of movement disorders. Huntington's chorea may also be amenable to DBS therapy.[96,97]

Brain Stimulation for Chronic Pain

In contrast to the field of movement disorder surgery, there are few systematic, multicenter controlled trials of brain stimulation for pain in the literature. The initial use of brain stimulation for pain control by Pool, Heath and others targeted the so-called "affective" state of the individual, and thus, it was viewed more as a psychosurgical intervention. Targets stimulated included the septal region, cingulate gyrus, and caudate nucleus. Subsequently, other subcortical sites were targeted, and recently the precentral cortex appears to show promise in selected patients. DBS has been used in recent years to treat post-stroke pain, cephalalgias, anesthesia dolorosa, pain related to multiple sclerosis, and genital pain.[98] Targets have included the sensory thalamus in combination with the periaqueductal gray matter for most chronic pain conditions. The posterior hypothalamus has also been used to treat cephalagias with autonomic features.[99]

Subcortical Targets

Sensory thalamic (VC or VP) stimulation, first reported by Mazars and colleagues,[100–102] results in the production of paresthesias in the area of pain, associated with pain relief, similar to that obtained with stimulation of the dorsal columns of the spinal cord. The exact mechanism by which paresthesia-evoking thalamic stimulation results in pain relief is not known. One concept is that deafferentation causes an abnormal firing pattern in thalamic neurons and that thalamic stimulation inhibits this abnormal neural activity.[103–105] Gerhardt et al. showed that stimulation of the VC in monkeys caused inhibition of spinothalamic neurons' evoked responses to noxious cutaneous stimulation.[106] Benabid demonstrated that VC stimulation inhibited the response of parafascicular nucleus (Pf) cells to noxious stimuli.[107]

Stimulation of the periaqueductal gray matter (PAG), first reported in 1969, provided yet another proposed pathway of analgesia, via a presumed opioid-related mechanism.[108–110]

PAG/periventricular gray matter (PVG) stimulation is indicated for pain classified as *nociceptive,* which is defined as pain caused by direct activation of the nociceptors (mechanical, chemical, and thermal) found in various tissues. Examples of nociceptive pain include cancer pain from bone or tissue invasion, or noncancer pain secondary to degenerative bone and joint disease or osteoarthritis. This type of pain stands in contrast to *neuropathic* or deafferentation pain, which results from an injury or dysfunction of the central or peripheral nervous system. Examples include thalamic pain, stroke, traumatic or iatrogenic brain or spinal cord injuries, phantom limb or stump pain, postherpetic neuralgia, and various peripheral neuropathies. The sensory thalamus is usually considered a more appropriate target for neuropathic pain conditions. The overall long-term successful pain control reported in the literature with stimulation is approximately 60% for nociceptive pain and 50% for neuropathic pain.[98,99,111–115] Recent meta-analyses have confirmed these overall rates but shown that with increased follow-up time there is a falloff in patients with continued pain relief. Nociceptive pain treated with PAG/PVG stimulation tends to have more sustained relief (61%) than neuropathic pain treated with sensory thalamus stimulation (42%). PAG/PVG stimulation used alone to treat neuropathic pain has an even lower long-term success rate of 23%.[116] Bittar et al. showed that a combination of PAG/PVG and sensory thalamic stimulation lead to the highest rates of long-term success (87%).[117] Boccard et al. published a series of 59 patients treated for neuropathic pain with a mean follow-up of 27.9 months in which overall long-term success was 66%; however, higher rates were seen in subcategories such as phantom limb (89%) and post-stroke (70%).[98,113,114,118]

Cortical Stimulation for Pain

In contrast to the subcortical targets previously mentioned, a common target for the treatment of chronic neuropathic pain is the motor cortex. Cortical stimulation, performed most frequently epidurally, was first reported by Tsubokawa and colleagues. Tsubokawa and colleagues found that stimulation of the precentral (motor cortex) resulted in effective pain relief,[119,120] relief far better than observed with postcentral somatosensory stimulation. Stimulation was applied for 5–10 min at a time from 5–7 times during the day, with frequencies of 50–120 Hz, pulse width 0.1–0.5 ms, and current <1 mA. Stimulation parameters were adjusted to be below the threshold for a motor response. The analgesic effects had a "halo" effect, lasting at times for hours after stimulation was discontinued.

An increasing number of groups are now reporting promising results with this technique. The largest series with the longest follow-up in the literature comprises 32 patients spanning a 4-year period, reported by Nguyen and colleagues.[121] Ten of the 13 patients with central pain (77%) and ten of the 12 patients with neuropathic facial pain had experienced substantial pain relief (75%). At this time, the questions remaining to be answered include indications for surgery, surgical technique, and optimal stimulation parameters to maximize long-term clinical benefit. Unlike paresthesia producing (i.e., sensory thalamic stimulation), motor cortex stimulation does not usually induce paresthesias, making this technique ideal for double-blinded controlled studies. One such study was performed by Velasco et al in 2008 in which 11 patients with neuropathic pain were treated. Eight patients had a successful trial and were implanted. A statistically significant reduction in their visual analog pain scores was seen in all patients with the median reduction of 63%.[122]

The mechanism of action of MCS is a subject of debate. While some have postulated that direct projections from motor cortex to sensory cortex can provide for a stimulation-induced modulation of abnormal sensory cortical activity present in pain states, others suggest that descending cortico-thalamic projections play an important role in the generation of analgesia.[119,120,123]

Brain Stimulation: Other Emerging Areas

Epilepsy

Initial attempts at seizure control using brain stimulation utilized stimulation of the cerebellar cortex. Irving Cooper[20,124–127] was the first to employ cerebellar stimulation for epilepsy. Cooper hypothesized that the massive inhibitory Purkinje cell outflow of the cerebellum could modulate abnormal cortical epileptogenic activity "as the pedals of a mighty organ modulate the output of its chimes."[128] While Cooper reported significant seizure reduction in 56% of patients, other clinical trials failed to demonstrate any benefit.[129,130]

Stimulation of the anterior nucleus of the thalamus for epilepsy was first reported by Cooper as well.[131,132] The rationale for choosing the anterior nucleus involved its important role in the limbic circuitry, receiving projections from the mammillary bodies and projecting to the hippocampus, amygdala, cingulate, orbitofrontal cortex, and caudate. It was thought that anterior nucleus stimulation would modulate abnormal epileptiform activity within the limbic system. Although exact details of the stimulation were not provided, he reported that in five of six patients with intractable seizures, anterior nucleus stimulation reduced seizures by more than 60% in five of six cases, with 30% average decrease in medication requirements.

Recently, a multicenter randomized clinical trial (The SANTE trial) demonstrated showed a 50% reduction in seizure frequency in nearly half of patients who were refractory to any other treatment modality.[133] Ten percent of patients were seizure free at 6 months.

Velasco et al. (Mexico City) were the first to employ bilateral centromedian (CM) nucleus stimulation for the treatment of epilepsy,[134] and their long-term results in 13 patients were recently reported.[135] Stimulation parameters were 60 Hz, 4–6 V, alternating right and left sides. With a mean follow-up of 41 months, they noted a significant decrease (defined as >80% seizure reduction) in the incidence of generalized tonic-clonic seizures and atypical absence seizures, but no change, in the incidence of complex partial seizures.

Initial reports of seizure control following subthalamic nucleus stimulation,[136–138] combined with confirmatory data in a rat model,[139–141] suggested that the STN may be a future target for seizure control using brain stimulation. The largest open label study to date performed by Chabardes et al. included five patients. Three patients had a greater than 50% reduction (64% average reduction) in seizure frequency with two patients being able to reduce their medications.[142]

Psychiatric Disorders

Since the early reports of Pool over a half a century ago, there have few advances in the use of brain stimulation to treat psychiatric conditions. While lesioning procedures including cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leukotomy have all been employed for the treatment of refractory OCD and, to a lesser degree, major affective disorder, chronic electrical stimulation of these lesioning targets has only recently been reported. Nuttin et al. placed quadripolar electrodes bilaterally in the anterior limbs of the internal capsules of four patients suffering from severe OCD. Beneficial effects were seen in three patients.[143]

Obsessive–Compulsive Disorder

Using prior experience with ablative capsulotomies, Nuttin et al. first targeted the anterior limb of the internal capsule as a DBS target to create functional lesions to treat obsessive–compulsive disorder. Researchers progressively moved posteriorly to target the nucleus accumbens and ventral striatum as part of the reward circuitry.[144] Initial results from these studies were promising with four out of eight patients having at least a 35% reduction in YBOCS scores and two more patients having a 25%–35% reduction in Yale-Brown obsessive–compulsive scores (YBOCS).[145] A humanitarian device exception was granted by the FDA to treat refractory OCD with DBS using the initial anterior limb of the internal capsule target. The subthalamic nucleus has also been targeted with all four patients having a greater than 35% reduction in YBOCS scores.[146]

Depression

Functional neuroimaging studies in patients with treatment resistant depression revealed hyperactivity in the subgenual cingulate gyrus (Brodmann's Area 25). Conversely, functional neuroimaging in patients responsive to selective Serotonin reuptake inhibitors (SSRIs) and electroconvulsive therapy (ECT) has demonstrated decreased activity in this region[147] Capitalizing on these findings the subgenual cingulate was chosen as a stimulation site for treatment-resistant depression. In a multicenter open-label trial performed in Canada, early results from case reports were confirmed. Of patients treated with DBS in the subgenual cingulate gyrus, 57% had at least a 50% reduction in baseline HRSD-17 depression scores at 1 month post-procedure. At 6 and 12 months follow-up, 48% and 29% of patients, respectively, continued to have at least a 50% reduction in depression scores. The response rate after the first year increased to 62% when the depression score reduction threshold was adjusted to a 40% reduction.[148] Of note, seven of the 21 patients developed nausea and vomiting with stimulation in the subgenual cingulate gyrus during this study.

The anterior capsule and ventral striatum, targets traditionally lesioned to treat OCD have also been targeted with DBS.[149] Preliminary data, however, from a randomized clinical trial showed that there was no significant difference between therapeutic and sham stimulation. All patients, however, did have substantial improvements from their baselines.[150]

A report of transient depression induced by high frequency stimulation of the substantia nigra pars reticulata,[68] using the lower poles of an electrode placed for subthalamic nucleus stimulation, raised the intriguing possibility that STN and/or SNr stimulation may be a putative target for intervention, although there have not been any significant follow-up studies based on this observation.[151]

Tourette's Syndrome

Refractory Tourette's syndrome has also been successfully treated with both thalamic and pallidal stimulation. Utilizing Hassler's earlier work with thalamic lesioning the 1970s to treat refractory Tourette's syndrome, Vandewalle described the first patient implanted with bilateral medial thalamic electrodes and treated with high-frequency stimulation resulting in an abolishing of his tics at 1-year post-procedure.[97] He later expanded this work and published a small series of patients with similar results.[152] Servello and Porta published a series of 18 patients treated with thalamic stimulation (Vo–CM–Pfc complex). All 18 patients in follow-up of up to 17 months had dramatic reductions in the Yale Global Tic Severity Rating Scale (YGTSS).[153,154] Ackermans performed a randomized double-blinded clinical trial with six patients with all patients having a statistically significant 49% reduction in YGTSS scores pre-stimulation compared to post-stimulation.

Eating Disorders

A long history of animal studies of hypothalamic function has elucidated two hypothalamic regions related to food intake: the ventromedial nucleus as a satiety center, and lateral nucleus as a hunger center.[155–157] Destruction of the ventromedial nucleus in animals leads to hyperphagia and obesity, while lesions of the lateral nucleus lead to weight loss. Over 25 years ago, Quaade et al. performed low frequency stimulation of the lateral hypothalamic nucleus in morbidly obese patients as a prelude to electrocoagulation, without significant long-term benefit.[158] As Benabid and colleagues have reported preliminary work with both lateral and ventromedial hypothalamic stimulation in an animal model,[136] others have followed his lead in investigating this potential application of brain stimulation. Whiting et al. described a small series of patients assessing the safety of lateral hypothalamic stimulation. No adverse events were seen at the end of 2 years and changes in the resting metabolic rate were measured using a calorimetric respiratory chamber to find the optimal parameters for stimulation.[159] Success

with treating intractable anorexia nervosa patients has also been seen with the targets used to treat treatment resistant depression.[160–161]

Brain Injury States

In 1949, Moruzzi and Magoun[164] described the reticular activating system of the brainstem, an area which, when stimulated, evokes arousal responses and electroencephalography (EEG) desynchronization. Within the thalamus, stimulation of the midline projection nuclei (i.e., intralaminar and centromedian) was noted to be effective in eliciting these responses in animals.[165] Based on these observations, a number of targets have stimulated in comatose patients in an attempt to increase their level of consciousness. The midbrain reticular formation, intralaminar thalamus, other thalamic nuclei, and the globus pallidus all have been stimulated without evidence of dramatic improvement.[166–169] It is quite possible that the severe degree of brain damage in these patients may have precluded any possibility of functional recovery. A recent proposal to revisit intralaminar stimulation in a less severely disabled group of patients, described as *minimally conscious*,[170] appears promising. As these patients may not be able to provide informed consent, ethical issues will most likely limit the number of these surgeries performed until that time where a strong multidisciplinary effort is made to address the use of these techniques in these patients.[171] Bilateral thalamic stimulation was performed in a patient who remained in a minimally conscious state 6 years after a traumatic brain injury. Schiff et al. attempted to mimic the normal thalamic state that would have inputs from the cortex and brainstem nuclei. Statistically significant improvements in arousal, motor function, and oral feeding was seen with DBS when compared to the non-DBS state during the crossover phase.[172]

TABLE 20.1
A List of the Most Common Conditions Treated with Chronic Brain Stimulation and the Associated Stimulation Targets

Condition	Stimulation Targets
Movement disorders	Ventral intermediate nucleus of thalamus
	Subthalamic nucleus
	Globus pallidus internus
Tremor	Ventral intermediate nucleus of thalamus
Parkinson's disease	Ventral intermediate nucleus of thalamus
	Subthalamic nucleus
	Globus pallidus internus
Dystonia	Ventral intermediate nucleus of thalamus
	Globus pallidus internus
	Subthalamic nucleus
Chronic pain	Ventralis caudalis nucleus of thalamus
	Periacqueductal/periventricular gray
	Medial lemniscus
	Internal capsule
	Motor cortex
Epilepsy	Centromedian nucleus of thalamus
	Anterior nucleus of thalamus
	Subthalamic nucleus
Treatment-resistant depression	Anterior limb of internal capsule
	Subgenual cingulate gyrus
	Subthalamic nucleus
Obsessive–compulsive disorder	Anterior limb of internal capsule
	Nucleus accumbens/ventral striatrum
	Subthalamic nucleus
Tourette's syndrome	Thalamus (Vo–CM–Pfc complex)
	Globus pallidus internus
	Globus pallidus externa
	Anterior limb of internal capsule
Brain injury states	Intralaminar nucleus of the thalamus
	Midbrain reticular formation

CONCLUSIONS

Advances in anatomical and functional imaging, improvements in device technology, coupled with an increased understanding of the pathophysiology of various neurologic disorders, have provided us with the ability to reversibly modulate the nervous system. It is important to emphasize, however, that the technique remains in its infancy; even so, the indications for DBS have progressed from movement disorders alone into neuropsychiatric disorders. Randomized clinical trials have been undertaken for various indications providing strong evidence for neuromodulation. Future advances in this technology will undoubtedly arise as a result of safer and less invasive surgical methods, as well as from the development of the next generation deep-brain stimulation devices with combined closed loop electrical and chemical sensing and output functions. Finally, continued advances in the neurosciences will provide for the extension of this technology to treat other disease conditions (Table 20.1).

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21 Noninvasive Deep TMS Therapy for Diverse Neuropsychiatric Disorders

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CONTENTS

BACKGROUND

Transcranial magnetic stimulation involves passing an electrical current through a coil placed against the scalp. The rapidly changing electrical current creates a time-varying magnetic field, which passes unimpeded through the scalp and skull and induces an electrical field in the cortex. This electrical field changes neuronal activity at the site of stimulation and within inter-connected neuronal networks. Transcranial magnetic stimulation (TMS) pulses applied in a repetitive train is referred to as repetitive TMS (rTMS). Repetitive TMS can modulate cortical excitability in neural circuits under the coil.

Until several years ago, the capacity of TMS to elicit neuronal responses was limited to superficial structures. The typical coils used for TMS (such as round or figure-8 coils) induce stimulation in superficial cortical regions under the windings of the coil as the intensity of the electric field drops dramatically as a function of distance from the coil.[1–4] Therefore, to stimulate deep brain regions with such coils, a very high intensity would be required, which is not feasible with standard magnetic stimulators. Moreover, the intensity required to stimulate deeper brain regions using typical coils would stimulate both cortical regions and facial nerves at high level, which may lead to facial pain, facial and cervical muscle contractions, epileptic seizures, and other undesirable side effects.[5]

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The difficulty of efficiently activating deep neuronal structures using TMS emerges from both physical properties of the brain and physical and physiological aspects of the interaction of a TMS system with the human brain. As shown by Heller and Van Hulsteyn,[6] the three-dimensional maximum of the electric field intensity will always be located at the brain surface, regardless of configuration or superposition of TMS coils. However, both the TMS coil and the stimulator may be optimized for effective stimulation of deeper brain regions.

The H-coil is a novel rTMS tool, which enables direct stimulation of deeper and larger brain volumes, potentially affecting extensive neuronal pathways including deeper cortical regions and fibers targeting subcortical regions, without a significant increase of the electric field induced in superficial cortical layers.[7–9]

A family of coil designs for stimulation of deeper brain areas, termed H-coils, has been proposed and evaluated.[7–9] Each of these coils are based on common design principles essential for effective deep brain TMS. Yet each specific H-coil must have a unique design and configuration based on the location and size of the deep brain region(s) intended to be activated and the preferred direction(s) of stimulation.

The construction of deep TMS (dTMS) coils should meet several goals

- High enough electric field intensity in the desired deep brain region that will surpass the threshold for neuronal activation

- High percentage of electric field in the desired deep brain region relative to the maximal intensity in the cortex
- Minimal adverse effects, such as pain, motor activation and activation of facial muscles

H-coils are usually encased in a helmet. The H-coils can be positioned over the motor cortex for determination of the individual motor threshold, which is used to establish the treatment stimulation intensity. Then the coil helmet is navigated to the treatment position where the coil is attached to the head for treatment administration. The coil flexibility enables good attachment to the head and compatibility with various head sizes and shapes.

For double-blind placebo-controlled (DBPC) clinical trials, the H-coils helmet can encase a sham coil that can mimic the acoustic artifact and scalp sensations of the active coil, without inducing any significant field anywhere in the brain.

Several clinical trials have tested the feasibility of dTMS in various psychiatric and neurologic diseases. A review of the clinical experience in psychiatric disorders was published in 2012.[10] In the following we survey the up-to-date clinical results obtained with dTMS in different psychiatric and neurologic disorders. A list of the studies, along with the H-coil version, stimulation parameters, disease, target brain regions, numbers of enrolled subjects and main results, are presented in Table 21.1.

SAFETY AND TOLERABILITY OF DTMS

Overall published studies indicated that deep TMS is generally safe and well tolerated by the majority of subjects. The main reported side effects are application site pain or discomfort during application, usually not requiring any special care. A few patients experienced headaches during application and received analgesics. In most cases, this side effect was manifested only in the initial sessions and later on there was an accommodation to the treatment and analgesics were no longer required. Other rare reported side effects are head muscle twitching and facial pain during application, dizziness self-limiting within a few days, onset of a state of insomnia, and a sensation of a bad smell or taste during and after the session. The most adverse reported side effect, similarly to standard TMS, is brief self-limiting seizure during session. To date, out of a total of over 4000 patients treated with dTMS across studies and clinical practice, there have been six seizures. In all these six cases, additional risk factors were present (such as history of epileptic seizures, high doses of medications that lower the seizure threshold, or alcohol consumption). The overall rate of seizures in deep TMS sessions seems to be similar to the rate in standard TMS sessions. It should be noted that the maximal field induced in the brain by a deep TMS coil is lower than the field induced by a standard TMS coil. The difference lies in the electric field distribution of the deep TMS coils that can activate significantly deeper brain structures.

DTMS AS TREATMENT FOR MAJOR DEPRESSIVE DISORDER (MDD)

MDD is a highly prevalent and disabling condition associated with significant morbidity and mortality.[11,12] With a prevalence in the general population of 10%–15%, MDD is one of the most common diseases.[13,14] It has been estimated that 20%–40% of patients do not benefit adequately from accepted interventions, including pharmacotherapy and psychotherapy.[15] The lack of sufficient treatment response and the enormous impact of the illness make the development of alternative treatment approaches a priority.

Many studies have been performed in order to analyze the effect of standard superficial TMS in MDD. Most studies used figure-8 coils and applied either high frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC) or low frequency stimulation to the right DLPFC. Meta-analyses show overall modest efficacy of standard rTMS compared to sham stimulation.[16]

Several clinical trials have been published where dTMS was used to treat pharmaco-resistant patients with MDD. The first study[17] treated 65 MDD patients who did not respond to at least two antidepressant medications in the current episode. The study included three H-coil versions: H1, H2, and H1L. A sketch of the H1 coil and color maps of the electric field distribution induced by the coil in the brain, superimposed on coronal slices of anatomical magnetic resonance images, are shown in Figure 21.1.

The H1 coil is designed to induce activation of left and right lateral and medial prefrontal cortex (PFC) structures, with a preference to the left hemisphere. The H1 coil can induce direct activation of neuronal structures significantly deeper in the PFC compared to standard superficial figure-8 TMS coil. This difference represents additional hundreds of millions of neurons and many more connections in the prefrontal cortex, which is a key region in the manifestation of depression.[18–23]

A sketch of the H2 coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.2. The H2 coil is designed for effective activation of prefrontal, orbitofrontal and temporal neuronal structures, with bilateral symmetry.

A sketch of the H1L coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.3. The H1L coil is designed for effective activation of neuronal structures in the left prefrontal and orbitofrontal cortex, with no supra-threshold field over the right hemisphere.

The subjects were tapered down from antidepressant medications prior to baseline, and randomized to four groups: (i) treatment with the H1 coil at 120% of the hand motor threshold (MT); (ii) treatment with the H2 coil at 120% MT; (iii) treatment with the H1L coil at 110% MT; and (iv) treatment with the H1L coil at 120% MT.

All groups were treated with 20 Hz frequency, train duration of 2 s, inter-train interval of 20 s and 42 trains. Five sessions were conducted per week for five consecutive weeks.

TABLE 21.1
Summary of Reviewed Studies

Study	H-Coil	Stimulation Parameters	Disease	Target Brain Region	Enrolled Patients	Results
Levkovitz et al.[17]	H1	20 Hz, 120% MT (H1 and H2), 110% or 120% MT (H1L), 5 tx/wk for 4 weeks, monotherapy	Major depression	Bilateral PFC with preference to left PFC	65	*Response rates* on week 5 were 47% (H1), 30% (H2), 60% (H1L-120%) and 0% (H1L-110%) with significant differences ($p = 0.0331$). *Remission rates* on week 5 were 42% (H1), 10% (H2), 50% (H1L-120%) and 0% (H1L-110%) with significant differences ($p = 0.0092$).
	H2			Bilateral PFC		
	H1L			Left PFC		
Isserles et al.[24]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks, followed by 1 tx/wk for 4 weeks, add-on to antidepressants	Major depression	Bilateral PFC with preference to left PFC	57	*Response rates* at the end of 4 weeks were 46%. *Remission rates* at the end of 4 weeks were 28%. Mean improvement of 13.4 points in HDRS24 slope across 4 weeks was found.
Harel et al.[25]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks, followed by 2 tx/wk for 8 weeks and 1 tx/wk for 10 weeks,add-on to antidepressants	Major depression	Bilateral PFC with preference to left PFC	29	*Response rates* were 46% after 4 weeks and 31% after 22 weeks. *Remission rates* were 27% after 4 weeks and 31% after 22 weeks. Mean improvement in HDRS21 was 9.48 points after 4 weeks and 10.12 points after 22 weeks.
Rosenberg et al.[26]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks, add-on to antidepressants	Major depression with previous nonresponse to ECT	Bilateral PFC with preference to left PFC	6	*Response rates* were 33%, and remission rates were 17%.
Rosenberg et al.[27]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks, add-on to antidepressants	Major depression	Bilateral PFC with preference to left PFC	7	*Response rates* were 57%, and *remission rates* were 14%. Mean improvement of 14.8 points in HDRS24 slope across 4 weeks was found.
Rosenberg et al.[28]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks, add-on to antidepressants	Major depression patients who relapsed after previous response to deep TMS	Bilateral PFC with preference to left PFC	8	Mean improvement of 13.2 points in HDRS slope across 4 weeks was found.
Levkovitz et al., submitted	H1	18 Hz, 120% MT, 5 tx/wk for 4 weeks, followed by 2 tx/wk for 12 weeks, monotherapy	Major depression	Bilateral PFC with preference to left PFC	212	In HDRS21 (primary end point) active (sham) TMS yielded adjusted slope of 6.39 (3.28) points across 5 weeks ($p = 0.008$). *Response rates* for active (sham) groups on week 5 were 38.4% (21.3%) ($p = 0.013$) and on week 16 the rates were 44.3% (25.6%) ($p = 0.0086$). *Remission rates* for active (sham) groups on week 5 were 32.6% (14.6%) ($p = 0.005$) and on week 16 the rates were 31.8% (22.2%) ($p = 0.1492$).

(*continued*)

TABLE 21.1 (Continued)
Summary of Reviewed Studies

Study	H-Coil	Stimulation Parameters	Disease	Target Brain Region	Enrolled Patients	Results
Harel et al.[41]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks, add-on to antidepressants	Bipolar disorder	Bilateral PFC with preference to left PFC	19	A significant mean decrease of 12.9 points in the HDRS-24 scale ($p = 0.001$) was found. Response rates were 63.2% and remission rates were 52.6%.
Isserles et al.[49]	H1	20 Hz, 120% MT, 3 tx/wk for 4 weeks	PTSD	Medial PFC	30	CAPS scores after 4 weeks improved by 27 pts in the active (EXP-STIM) compared to 10 pts in the two other groups. *Response rates:* EXP-STIM group- 44%. NOEXP-STIM group—12.5%. EXP-SHAM group—0%. Heart rate responses to the brief script-driven imaginal traumatic exposure demonstrated a significant attenuation throughout the treatment only in the EXP-STIM group. Follow-up assessments 2 weeks and 2 months post-treatment found that the therapeutic effect was still significant and maintained.
Levkovitz et al.[60]	H1	20 Hz, 120% MT, 5 tx/wk for 4 weeks	Negative symptoms of schizophrenia	Bilateral PFC with preference to left PFC	15	A mean decrease of 17% in SANS score (11.8 ± 3.3 points), and significant improvements in PANSS, SOFAS and CDS scores were found at end of study, and maintained for all scales in 2-weeks follow up. *Response rates* were 47%.
Rosenberg et al.[70]	H1	1 Hz, 110% MT, 5 tx/wk for 2 or 4 weeks	Auditory hallucinations of schizophrenia	Left temporoparietal cortex	8	There was a significant reduction in AHRS score (31.7% ± 32.2%) and to a lesser extent reduction in SAPS results (16.5% ± 20.3%).
Rosenberg et al.[71]	H1	1 Hz, 110% MT, 5 tx/wk for 2 weeks	Auditory hallucinations of schizophrenia	Left temporoparietal cortex	18	AHRS scores post treatment improved by 12% in the active group and 13.5% in the sham group, with no statistical difference in any of the scales between the groups.
Krause et al.[83]	HAUT	1 Hz, 100% MT, 1 session	ToM aspects	Medial frontal cortex	16 healthy subjects	deep rTMS but not sham treatment disrupted affective ToM performance for those with high self-reported empathy, but improved affective ToM performance for those with low self-reported empathy. of improvements after deep rTMS. These were primarily in the domain of social relating and interpersonal understanding and were corroborated by family members.
Enticott et al.[84]	HAUT	5 Hz, 100% MT, 10 sessions	Autism	Medial frontal cortex	28	From pre-treatment to one month follow-up, subjects in the active but not sham group showed a significant reduction in self-reported social relating symptoms ($p = 0.019$) and self-oriented anxiety during difficult and emotional social situations ($p = 0.004$).

Onesti et al.[102]	HMMC	20 Hz, 100% leg MT, 5 txs	Chronic pain	Medial leg motor cortex	25	Repeated measures ANOVA showed a significant decrease in VAS of subjective pain sensation in active but not sham group ($p = 0.01$) and in RIII reflex area following active but not sham treatments ($p < 0.01$). Improvements were maintained and were significantly better than sham also 3 weeks after last session.
Dalla Libera et al.[109]	H7	20 Hz, 110% MT, 3 tx/wk for 6 weeks	Migraine	Medial PFC	22	Ten patients presented with a significant reduction (50%) in headache days ($p < 0.0001$) and attacks ($p = 0.02$), and pain intensity ($p = 0.005$); a parallel decrease in the number of acute medications ($p < 0.01$) was evident, together with improvement in quality of life items ($p < 0.01$). A partial response to treatment (20%–40% attacks reduction) occurred in seven other patients. Five patients reported no modification in their headache.
Kranz et al.[115]	HBL	0.2 Hz, 100% MT, 15 min, 1 session	blepharospasm	Medial PFC	12	Stimulation with the HBL and circular coils, but not sham coil, resulted in significant improvements in blink rate as rated by a blinded physician and patient and in blink reflex recovery. For the blink rate assessments the improvements were still detectable 1 h after stimulation.
Chieffo et al.[124]	HMMC	10 Hz, 100% MT, 1 session; 1 Hz, 100% MT, 15 min, 1 session	Stroke rehabilitation	Right inferior frontal gyrus	5	Only the 10 Hz stimulation was associated with a significant improvement in naming performance and was significantly more effective than 1 Hz rTMS ($p = 0.043$).
Spagnolo et al.[130]	HPAR	10 Hz, 90% hand MT (motor cortex) and 100% MT (PFC), 3 tx/wk for 4 weeks.	Parkinson's disease	Bilateral motor cortex and PFC	27	Repeated measures ANOVA revealed significant improvement in total motor UPDRS after the last session (10.8 ± 6.6, $p < 0.0001$).
Klein-Dinur et al., submitted	HADD	10 Hz or 1 Hz or sham, 120% hand MT, 13 txs in 3 weeks. Each group was divided to subgroups who received/did not receive provocative cue increasing craving for cigarettes prior to each session.	Smoking addiction	Bilateral insula and PFC	115	Response rates: 10 Hz +cue group—81% 10 Hz no cue group—67% 1 Hz and sham groups—12%–29% Complete abstinence rates: 10 Hz +cue group—44% 10 Hz no cue group—25% 1 Hz and sham groups—0%–14%. Cotinine levels in urine showed significant reduction at the end of treatment in the 10 Hz + cue group, compared to baseline and to the other groups. Follow up 6 months after end of treatment found complete abstinence rates of 33% in the 10 Hz + cue group.

Note: PFC: prefrontal cortex; SAPS: scale for assessment of positive symptoms; AHRS: auditory hallucinations rating scale; rTMS: repetitive transcranial magnetic stimulation; ToM: theory of mind; PTSD: post-traumatic stress disorder.

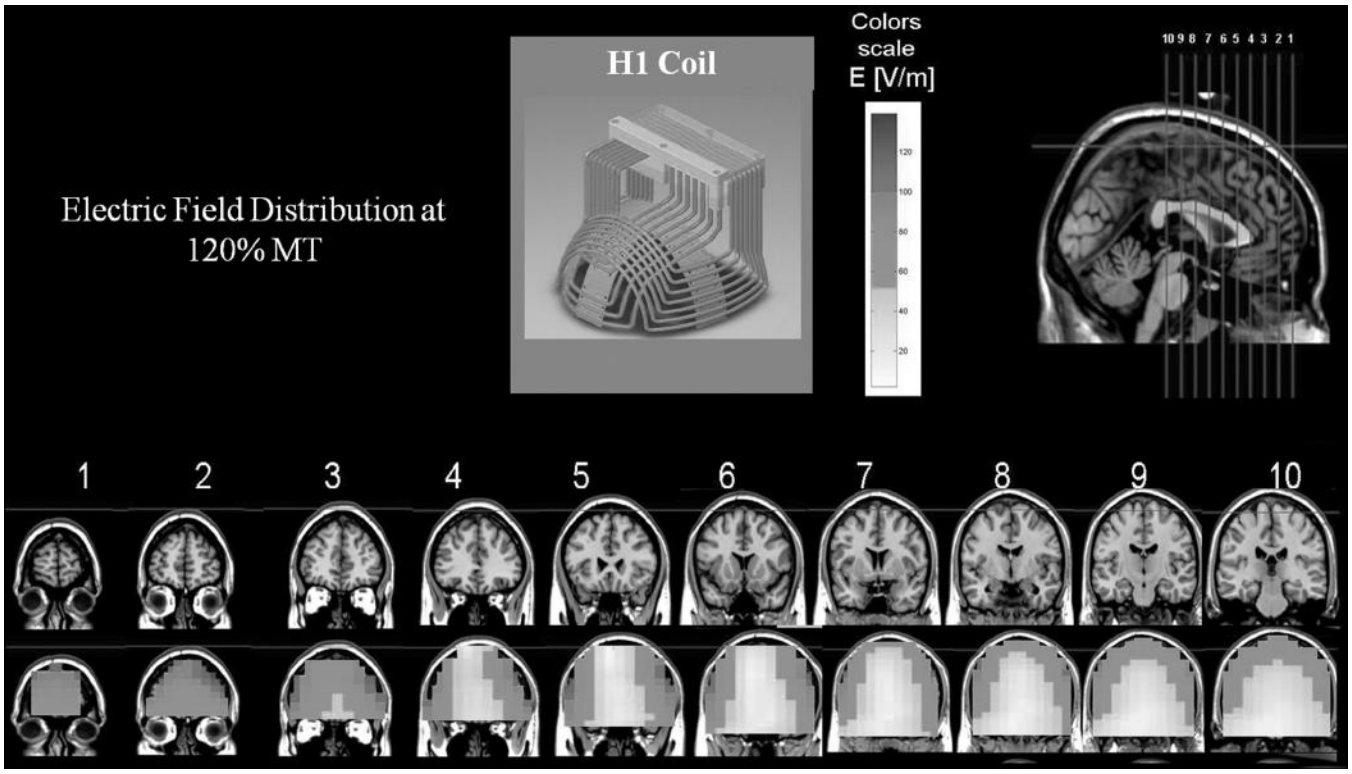

FIGURE 21.1 **(See color insert.)** Colored field maps for the H1 coil indicating the electric field absolute magnitude in each pixel over 10 coronal slices 1 cm apart. The red pixels indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output level required to obtain 120% of the hand motor threshold, at a depth of 1.5 cm.

The response was defined as a decrease of 50% or more in the HDRS-24 score from baseline (visit 1) to visit 21; remission was defined as an absolute HDRS-24 score of 10 or less. Response rates on week 5 were 47% (H1), 30% (H2), 60% (H1L-120%), and 0% (H1L-110%) with significant differences ($p = 0.0331$). Remission rates on week 5 were 42% (H1), 10% (H2), 50% (H1L-120%), and 0% (H1L-110%) with significant differences ($p = 0.0092$). Mean percentage HDRS improvement of patients from the four treatment groups were 52%, 42%, 49%, and 12% for the H1, H2, H1L-120%, and H1L-110%, respectively. The self-rated BDI-II questionnaire was used to assess the subjective evaluation of patients. Analysis of these scores revealed a similar pattern to that obtained by the HDRS scores; the three high-intensity treatments (H1, H2, and H1L-120%) yielded significant improvements (with the H2 group yielding smaller improvement), whereas the low-intensity H1L-110% treatment did not. There was significant positive correlation between the BDI-II and HDRS scores ($p < 0.0001$). The clinical effect as evaluated in a 3-months follow-up was sustained.

The study results found an advantage of activating left PFC over bilateral PFC activation. Moreover, the striking difference between the H1L-110% group and the other groups, where this group showed significantly worse results, accentuated the importance of direct activation of deeper neuronal structures in the left PFC. The H1L coil at 110% MT stimulation intensity induces direct effective stimulation up to 1 cm within the brain tissue below the skull (quiet similar to a standard figure-8 coil[7]), while the same coil at 120% MT induces direct stimulation up to 3 cm in depth.

Isserles and collegues[24] studied the effect of DTMS as an adjuvant to antidepressant medications. Fifty-seven MDD patients who did not respond to at least two antidepressant medications were enrolled and they received H1 coil treatment. Sessions were conducted in a 5-day sequence for four consecutive weeks, followed by a maintenance phase of one session per week for an additional 4 weeks.

Stimulation parameters were 120% MT, 20 Hz frequency, train duration of 2 s, inter-train interval of 20 s and 42 trains. Response rates at the end of 4 weeks were 46%. Remission rates at the end of 4 weeks were 28%. Mean improvement of 13.4 points in HDRS24 slope across 4 weeks was found. The results of the BDI-II self-questionnaire corroborated the HDRS scores. The clinical improvement was maintained after the 4 weeks of maintenance phase.

The effects of guided cognitive-emotional manipulation on the antidepressant outcome were explored. It was found that in patients instructed to concentrate on negative emotions during the DTMS session the improvement in depression rating scales was significantly smaller.

Another study[25] investigated the long-term antidepressant effect of DTMS. Twenty-nine MDD patients who did not respond to at least one antidepressant medication, or did not tolerate the side effects of at least two medications in the current episode, were enrolled and treated with the H1 coil. The treatment period lasted 22 weeks and included three phases:

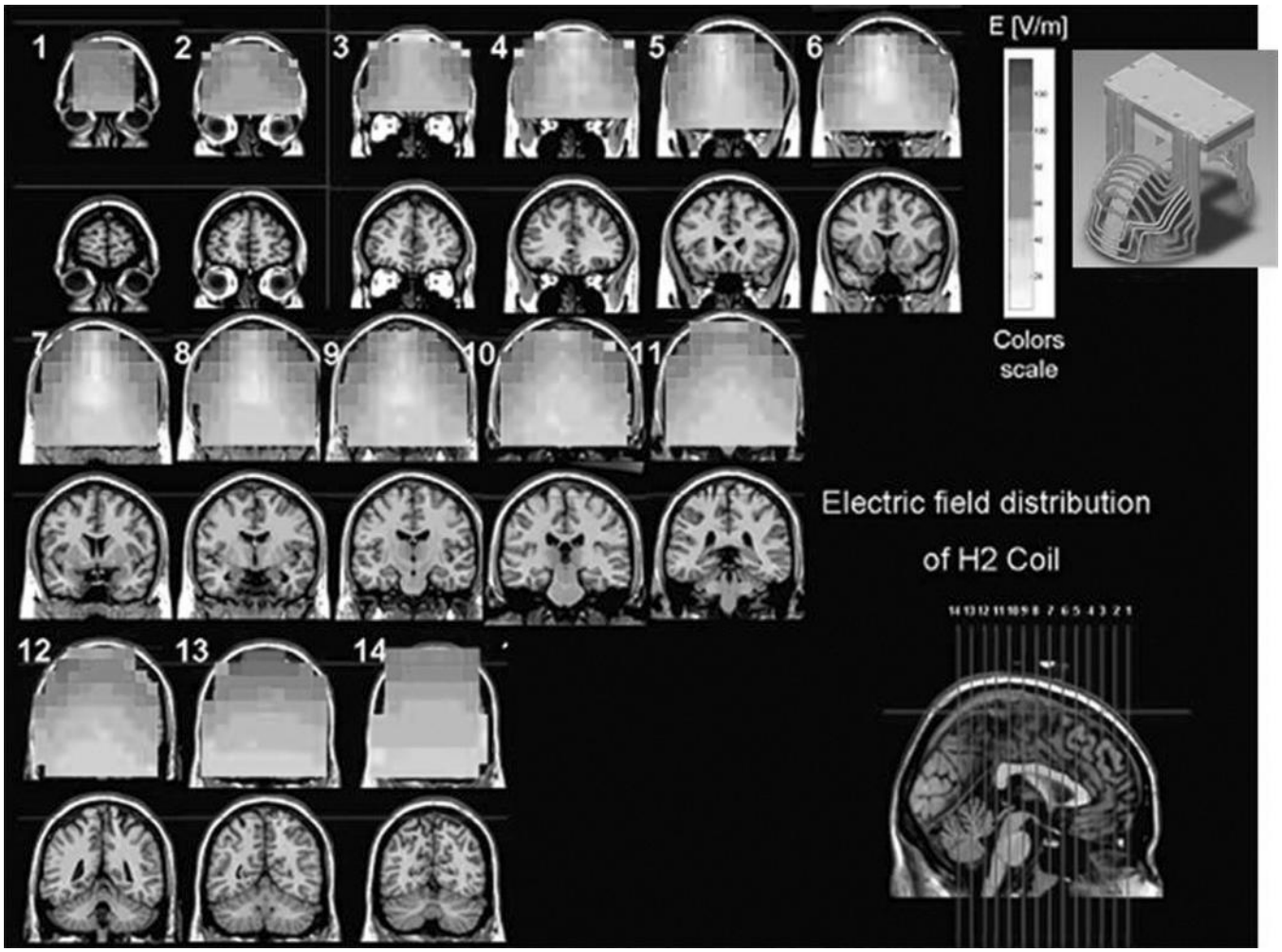

FIGURE 21.2 **(See color insert.)** Colored field maps for the H2 coil indicating the electric field absolute magnitude in each pixel at 120% of hand motor threshold, for 14 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

(i) acute phase of 4 weeks, with five sessions per week; (ii) continuation treatment I (CT-I) of 8 weeks, with two sessions per week; and (iii) continuation treatment II (CT-II) of 10 weeks, with one session per week. The DTMS treatment was add-on to antidepressants. Stimulation parameters were 120% MT, 20 Hz frequency, train duration of 2 s, inter-train interval of 20 s and 42 trains.

Response and remission rates at the end of the 4-week acute phase were 46% and 27%, respectively. Response and remission rates after 22 weeks were both 31%.

Mean improvement in HDRS21 was 9.48 points after 4 weeks and 10.12 points after 22 weeks. The study results indicate that antidepressant effect is preserved by maintenance DTMS treatment of biweekly treatment for 8 weeks followed by once a week for 10 more weeks. Kaplan-Meier estimated probability of response by the end of the study was 81.12% and 71.45% for remission.

Rosenberg and colleagues[26] studied the effect of DTMS on six MDD patients who previously did not respond to electroconvulsive therapy (ECT). Subjects were treated with the H1 coil with five sessions per week for 4 weeks, using the same parameters as in the previous studies.[24,25] Based on the HDRS scores, at the end of study response rates were 33% (two out of six), and remission rates were 17% (1/6).

In another study by the same group[27] seven MDD patients who failed to respond to at least two trials with antidepressants from different pharmacologic classes in the current episode, were enrolled and treated with the H1 coil using the same stimulation parameters as in the previously-described studies, in an add-on design. The response rates based on the HDRS24 scale were 57% (four out of seven), and remission rates were 14% (1/7). Mean improvement of 14.8 points in HDRS24 slope across 4 weeks was found.

Another study[28] addressed the efficacy of a second DTMS course in MDD. Eight MDD patients who relapsed within 4 months after a successful DTMS treatment were treated by the H1 coil with five sessions per week for 4 weeks. Mean improvement of 13.2 points in HDRS slope across 4 weeks was found. Yet the improvement was smaller than that observed following the first DTMS course (mean

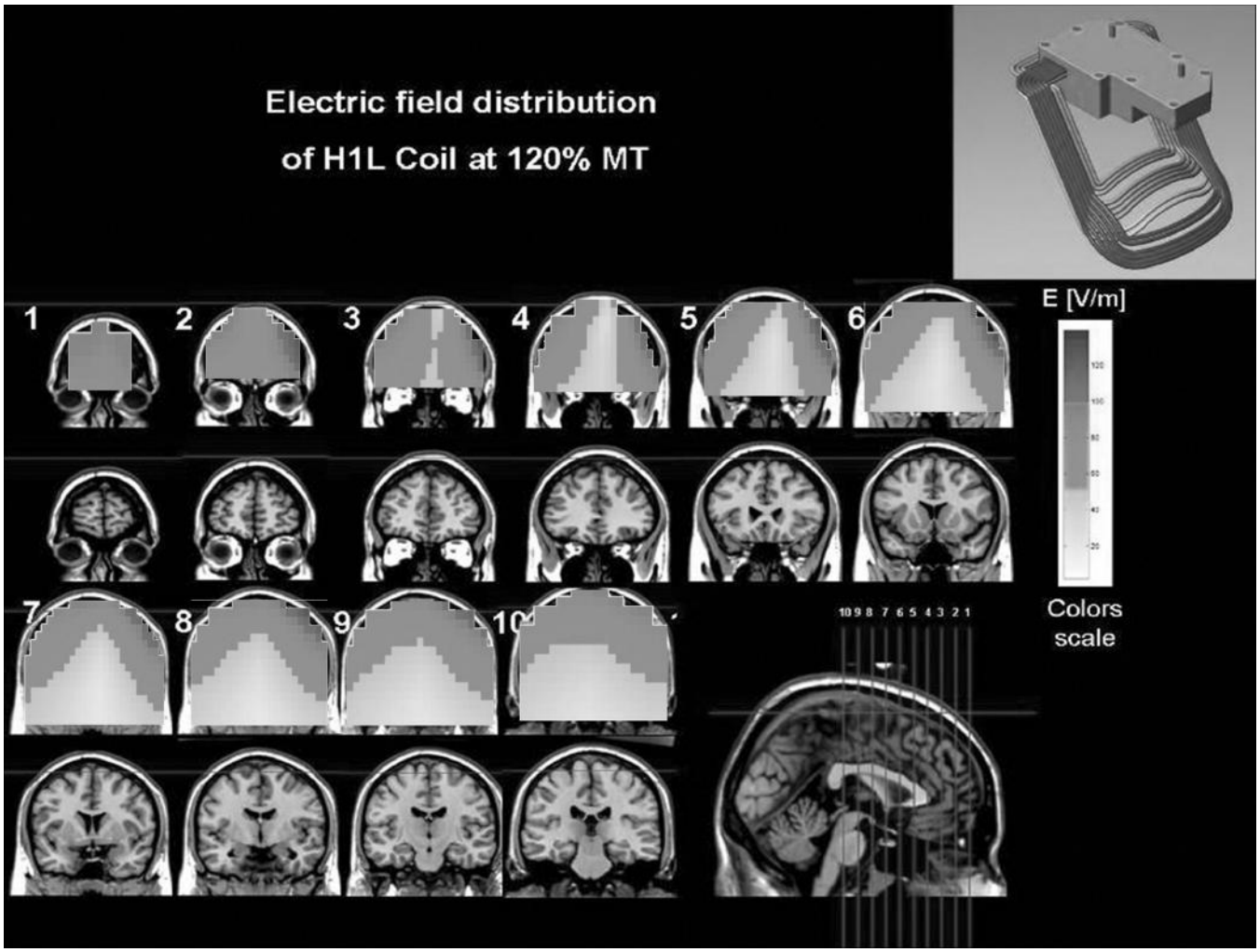

FIGURE 21.3 (See color insert.) Colored field maps for the H1L coil indicating the electric field absolute magnitude in each pixel at 120% of hand motor threshold, for 10 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

improvement of 19.0 points). The results indicate that a second DTMS treatment after relapse can be effective, yet they may imply that in some patients the efficacy may be reduced compared to a first treatment.

A large prospective multicenter DBPC study evaluating the safety and efficacy of dTMS in MDD was completed recently (Levkovitz et al., submitted); 212 MDD patients who failed 1–4 antidepressant treatment trials within the current episode were enrolled in 20 worldwide sites. Patients were randomized to receive either active or sham dTMS H1 coil treatment, applied as a monotherapy after patients had tapered off antidepressant medications. Treatment duration was 16 weeks, including an acute phase of five sessions per week for 4 weeks, followed by a maintenance phase of biweekly treatment for additional 12 weeks. Stimulation parameters were 120% MT, 18 Hz frequency, train duration of 2 s, inter-train interval of 20 s and 55 trains, leading to a total of 1980 pulses in 20 min.

The primary end point was the change in HDRS21 up to week 5. The estimated slope in the active dTMS group was −6.39 compared with −3.28 in the sham group. This difference was statistically significant ($p = 0.008$).

At week 5 the response rates were 38.4% for active dTMS versus 21.4% for sham treatment ($p = 0.0138$). Remission rates were 32.6% and 14.6% for dTMS and sham TMS, respectively ($p = 0.0051$).

At 16 weeks, the change in HDRS in the active DTMS group was −8.55 compared with −6.07 in the sham group. This difference was statistically significant ($p = 0.0259$). The response rates at week 16 were 44.3% after dTMS versus 25.6% after sham treatment (statistically significant difference, $p = 0.0086$). The week 16 remission rates were 31.8% and 22.2% in the dTMS and sham groups, respectively, and this difference was not significant ($p = 0.1492$).

The majority of patients who achieved remission at the primary endpoint (32.6% in the dTMS and 14.6% in the sham group) did not relapse (i.e., HDRS-21 > 17) until the end of the study. A total of 8/28 (28%) and 3/13 (23%) patients who achieved remission at the primary endpoint, relapsed at any time point before the end of the study in the active and

sham groups, respectively. Out of these eight patients in the active group, only three were at relapse at their last evaluation, while the rest improved before the end of study. An additional measure of clinical efficacy is the total amount of time (in weeks) during which subjects satisfied HDRS-21 criteria for response and remission. The highest obtainable result was 16 (for patients who remitted or responded already in the first week of treatment and remained in remission or response until the end of the study, without leaving the study) and the lowest 0 (for patients who did not achieve remission or response at all). The mean time in response in the dTMS group was 4.9 weeks versus 2.8 weeks in the sham group ($p = 0.0011$). The mean time in remission in the dTMS group was 3.7 weeks versus 2.1 weeks in the sham group ($p = 0.0031$). The mean percentage of time in response in the dTMS group was $36 \pm 4\%$ (mean ± standard error) versus $22 \pm 3\%$ in the sham group ($p = 0.0018$). The mean percentage of time in remission in the dTMS group was $26 \pm 3\%$ versus $16 \pm 3\%$ in the sham group ($p = 0.0050$).

An interesting question is the dependence of clinical response on depression resistance, that is, the number of failed medications. Remission rates in patients who failed to respond to one or two meds were 36.6% for the dTMS group and 16.7% for the sham group ($p = 0.032$). Remission rates in patients who failed to respond to three or more meds were 28.9% for dTMS group and only 12.2 for the sham group ($p = 0.057$).

dTMS induces significantly deeper and wider stimulation in the PFC compared to a standard figure-8 coil. This represents additional hundreds of millions of neurons and many more connections in the PFC, which is a key region in the manifestation of depression.[18–23] Moreover, recent studies suggest that stimulation of prefrontal cortical regions with extensive connections to the subgenual cingulate may be crucial for the antidepressant action of standard rTMS.[29] As the exact location of these cortex regions varies greatly between individuals,[30] and standard (figure-8) TMS coils exert a more focal and superficial stimulation, optimal stimulation targets may be easily missed with standard coils. This might contribute to the large efficacy differences seen in studies with dTMS compared to standard TMS coils when large double-blind multicenter trials are compared. O'Reardon et al. reported HDRS-24 response and remission rates of 19.4% and 9% in subjects treated with the Neurostar device for 4 weeks.[31] In a duration-adaptive study (3-week acute treatment phase with a 3-week extension for clinical improvers), George et al. reported remission rates of 14.1% following Neurostar rTMS treatment.[32] As noted above, in the large prospective DBPC multicenter study using H1 coil for the treatment of MDD, the response and remission rates were 38.4% and 32.6%, respectively, after 5 weeks (Levkovitz et al., submitted).

The vast difference in the efficacy results is reflected in the indications for use approved by the Food and Drug Administration (FDA) for the deep TMS and superficial TMS devices. The multicenter trial described above (Levkovitz et al., submitted) resulted in FDA approval for the dTMS H-coil device for the treatment of MDD in the United States, given in January 2013. The indications for use include the treatment of depressive episodes in adult patients suffering from MDD who failed to achieve satisfactory improvement from any number of previous antidepressant medication treatment in the current episode. In contrast, the indications for use of the standard TMS Neurostar device, approved by the FDA on October 2008, include the treatment of MDD in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.

dTMS AS TREATMENT FOR BIPOLAR DISORDER

Bipolar disorder (BD) is a common condition with a lifetime prevalence of 1.2%–1.6%.[33,34] Three small randomized controlled trials[35–37] and one open study[38] have tested the efficacy of standard TMS in BPD, as have a few case studies.[39–40] Overall, these studies showed a moderate efficacy of standard TMS. Given the deeper electric field, it may be hypothesized that dTMS can be more effective in the treatment of this disease than standard TMS.

Currently, there is one published study that tested the efficacy of dTMS in the treatment of bipolar disorder.[41] Nineteen bipolar patients with current depressive episode were treated with the H1 coil over the PFC. Stimulation parameters were 120% MT, 20 Hz frequency, train duration of 2 s, inter-train interval of 20 s and 42 trains. Patients received five sessions per week for 4 weeks.

A significant mean decrease of 12.9 points over 5 weeks in the HDRS-24 scale ($p = 0.001$) was found. Response rates were 63.2% and remission rates were 52.6%. Cognitive assessments revealed significant improvements in reaction time and spatial working memory, which were both significantly poorer at baseline in bipolar patients compared to matched healthy subjects, but after 2 weeks and 5 weeks, the performance of the two groups in these tasks was not significantly different. No deterioration was found in any cognitive task.

In a case report,[42] a BD patient completed a cycle of dTMS treatment consisting of five consecutive session days for four consecutive weeks. As the patient showed a significant response to treatment, the patient continued the treatment with fortnightly dTMS sessions for the first three months after the 20th session, with the same parameters used in the acute phase (18 Hz for 2 s for 55 trains, at 120% of the MT). During continuation sessions, the patient was free from depression. He showed no depressive relapses and no (hypo)manic switches. This case suggested that dTMS added to medication could lead to complete symptom remission, which can be maintained for a long term in a treatment-resistant BD episode.

dTMS AS TREATMENT FOR POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is a serious consequence that occurs in large numbers of trauma survivors. With a 3.5% estimated 12-month prevalence and about a third

of those affected presenting a severe form of the condition, this disorder poses a significant therapeutic challenge.[43–44]

Few DBPC studies used standard TMS over the right or left DLPFC to treat PTSD patients.[45–48] The results imply that high frequency more than low frequency rTMS may have therapeutic potential in PTSD.

In a recent study, Isserles and colleagues[49] tested the feasibility of deep TMS in conjunction with exposure to the trauma for the treatment of PTSD patients. Several imaging studies showed hypoactivation in the medial prefrontal cortex (mPFC) and hyperactivation in the amygdala in PTSD patients versus trauma exposed controls.[50–51]

The study hypothesis was that the ability to extinct fear response is impaired in PTSD patients due to malfunctioning of mPFC circuits that normally control the amygdalar fear response. Hence, the study rationale was to induce high frequency (excitatory) stimulation of the mPFC with dTMS in order to modulate the excitability of the mPFC impaired circuits, and thus, facilitate extinction of the fear response to the traumatic memory. The study also tested whether exposure to the traumatic memory just prior to stimulation can affect the clinical outcome.

Thirty subjects suffering from resistant PTSD symptoms who have failed to respond to antidepressant medication and/or trauma focused psychotherapy were treated with the H1 coil positioned above the medial frontal cortex. Electric field distribution induced by the coil at the treatment position is shown in Figure 21.4.

Patients were randomized to three groups

A. "EXP-STIM"—receiving dTMS after script-driven imagery of the traumatic experience
B. "NOEXP-STIM"—receiving DTMS after script-driven imagery of a positive experience
C. "EXP-SHAM"—receiving sham-DTMS after script-driven imagery of the traumatic experience

Patients received three sessions per week for 4 weeks. Subjects in groups B and C were offered an open crossover treatment with traumatic exposure followed by active dTMS treatment

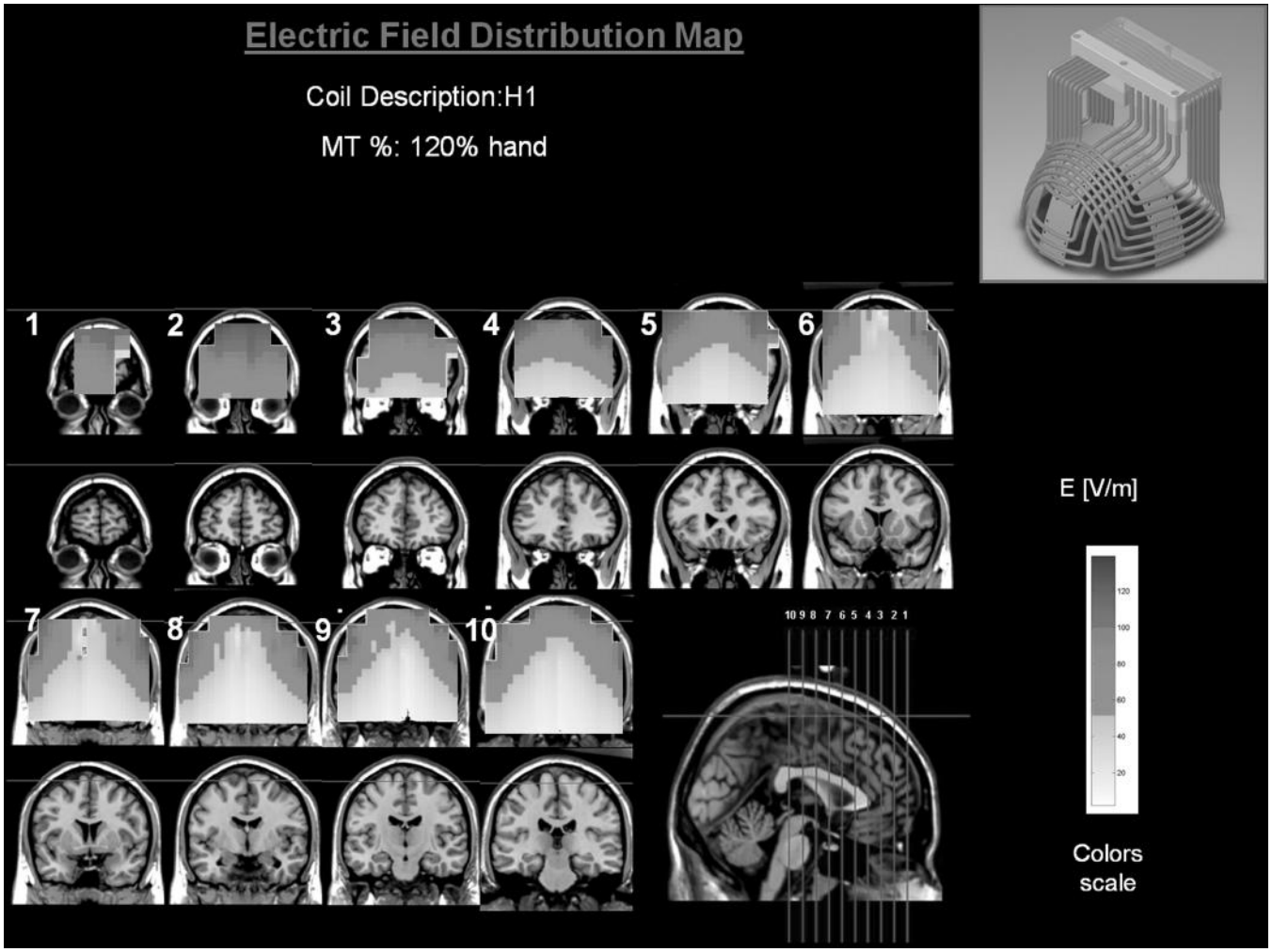

FIGURE 21.4 **(See color insert.)** Colored field maps for the H1 coil positioned above the medial frontal cortex for the treatment of post-traumatic stress disorder patients, indicating the electric field absolute magnitude in each pixel at 120% of hand motor threshold, for ten coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

after completing the 4 weeks of treatment. Stimulation parameters were 20 Hz, 120% MT, 2 s train duration, 20 s inter-train interval and 42 trains.

CAPS scores after 4 weeks improved by 27 pts in the active (EXP-STIM) group compared to 10 pts in the two other groups. Improvement compared to baseline was significant only in the EXP-STIM group ($p = 0.0003$) but not in the other groups. For the three CAPS components (intrusion, avoidance and arousal), analyses found significant improvement compared to baseline only in the EXP-STIM group. Significant improvement in CAPS scores was also found in subjects receiving open crossover EXP-STIM treatment.

Response was defined as an improvement of 50% or more in the CAPS total score after 4 treatment weeks compared to baseline. Response rates were 44% in the EXP-STIM group, 12.5% in the NOEXP-STIM group and 0% in the EXP-SHAM group.

Heart rate responses to the brief script-driven imagery of the traumatic exposure demonstrated a significant attenuation throughout the treatment only in the EXP-STIM group.

Follow-up assessments 2 weeks and 2 months post-treatment found that the therapeutic effect was still significant and maintained.

The results of this study indicate that high frequency dTMS stimulation of the mPFC following a brief exposure to the traumatic experience can be effective in treating resistant PTSD patients and that the therapeutic effect is sustained for at least 2 months.

dTMS AS TREATMENT FOR NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Negative symptoms are considered core symptoms of schizophrenia.[52] The term negative symptoms refers to decline or disappearance of some skill or experience of the normal subject, which may include emotional and affective flattening, lack of energy, apathy, anhedonia and asociality. The introduction of second-generation antipsychotics (SGAs) during the 1990s was accompanied by reports suggesting that these agents comprised a breakthrough in the treatment of negative symptoms.[53] Yet, only a few SGAs have been demonstrated to be moderately efficient in the treatment of negative symptoms, and currently available treatments for negative symptoms appear to have modest benefits.[54–55] Although positive symptoms are the most striking manifestation of the disease, the negative symptoms are often more intrinsically linked to the social and functional disability of schizophrenic patients and continue to disproportionately limit patient recovery.

Studies have identified hypoactivity in the frontal cortex[56] that correlates with negative symptoms in schizophrenic patients. Several trials have attempted to alleviate negative symptoms using high frequency (excitatory) repetitive TMS over the dorsolateral prefrontal cortex. Recent reviews reported moderate improvement of negative symptoms following treatment with standard TMS.[57–59]

One published study tested the use of deep TMS to treat negative symptoms in schizophrenia.[60] The H1 coil was used to treat 15 patients diagnosed as having schizophrenia and displaying predominant negative symptoms.

Stimulation parameters were frequency of 20 Hz, intensity of 120% of MT, 2 s train duration, 20 s inter-train interval, and 5 sessions per week for 4 weeks.

A mean decrease of 17% in SANS score (11.8 ± 3.3 points) was found after 4 weeks ($p = 0.0025$). Response was defined as a change from baseline SANS score of at least 20% at 4 weeks. Seventy percent of the subjects who completed the entire course of treatment responded to the treatment. Inclusion of subjects who dropped out into the calculation yielded response rate of 47%. In all SANS subscales except "alogia" the scores after 4 weeks were significantly improved compared to baseline. Significant improvements were also found in PANSS, SOFAS, and CDS scores at the end of the study, and maintained for all scales in the 2-week follow-up. Cognitive improvement was found in executive functions and sustained attention.

dTMS AS TREATMENT FOR AUDITORY HALLUCINATIONS OF SCHIZOPHRENIA

Auditory hallucinations (AHs) are present in 50%–70% of patients diagnosed with schizophrenia; although the typical and atypical antipsychotic medications work effectively on this disorder, about 25% of patients are refractory to treatment,[61,62] and therefore patients suffer associated distress, functional disability, lack of behavioral control, and violent behavior. It has also been known to be a contributing factor in up to 25% of cases of serious suicide attempts.[61]

Imaging studies of patients with of auditory hallucinations demonstrated increased activity of brain regions involved in speech perception, such as the left and right superior temporal gyrus, and also in the anterior cingulate cortex, Broca's area, amygdale, the left middle frontal gyrus, and inferior parietal cortex.[63,64] Hyperactivation of the left temporoparietal cortex, which is critical to speech perception has been implicated to be involved in the onset of auditory hallucinations.[65]

Several studies have been published about the use of standard TMS to treat schizophrenic patients with auditory hallucinations. Hoffman et al.[66] applied rTMS over the left temporoparietal cortex of three patients over 4 days and reported an improvement in auditory hallucination severity in those patients, as rated on a visual analogue scale (VAS). In a later study, Hoffman et al. detected improvement primarily in frequency and attentional salience of hallucinations, which were associated with modest overall clinical improvement, but with no negative effects of rTMS on cognition.[67] Another DBPC study[68] found significant improvement in verbal AH following 5 days of rTMS over the left temporoparietal cortex. A DBPC study[69] with 39 patients revealed improvement in frequency of AH following two weeks of 1 Hz rTMS over the left or right temporoparietal cortex. Yet, the results in both active groups were not superior to the sham group.

To date, one open study[70] and one DBPC study[71] tested the use of deep TMS to treat auditory hallucinations in schizophrenia. The H1 coil was placed over the left temporoparietal

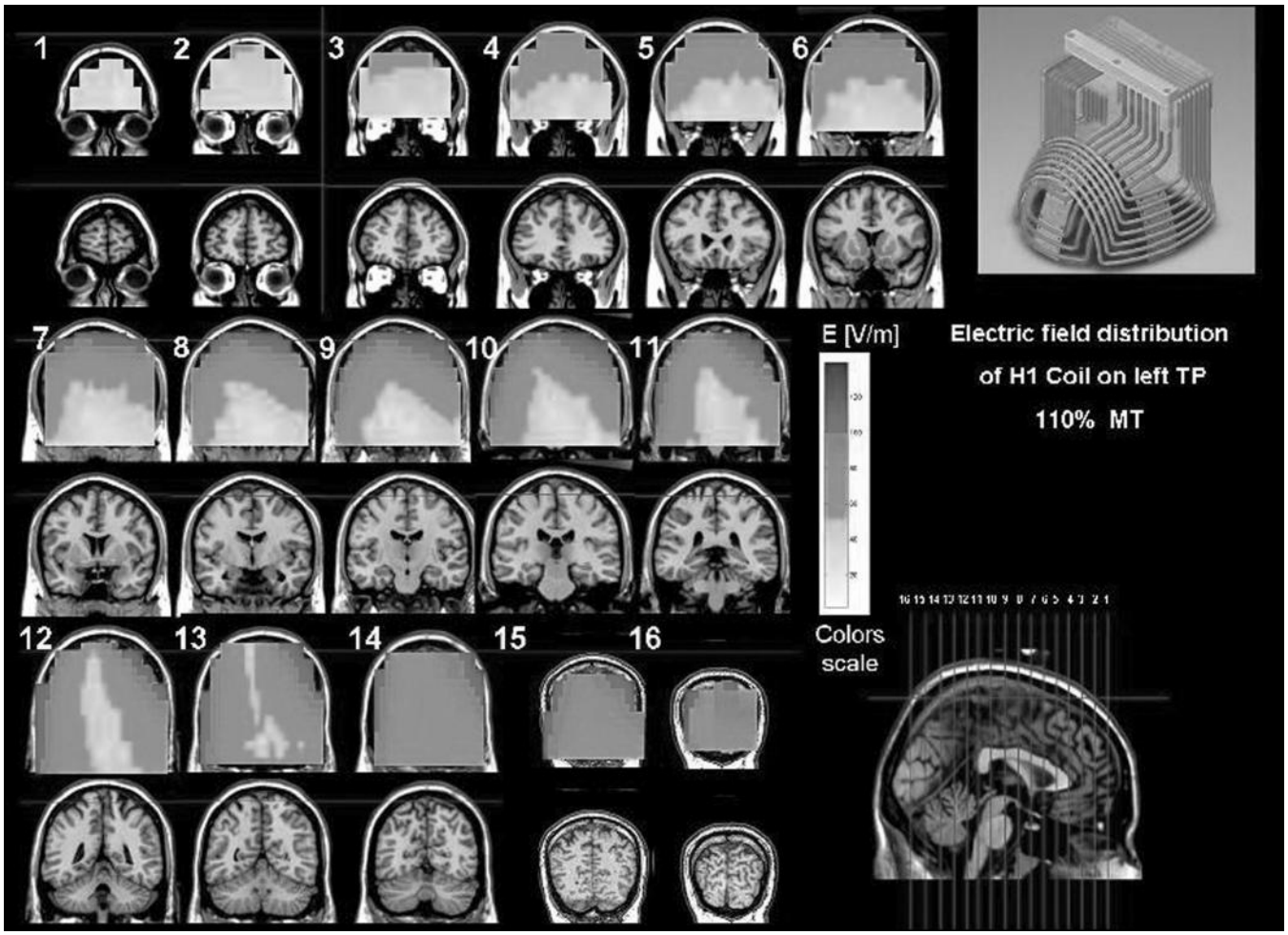

FIGURE 21.5 **(See color insert.)** Colored field maps for the H1 coil positioned above the left temporoparietal cortex for the treatment of auditory hallucinations in schizophrenic patients, indicating the electric field absolute magnitude in each pixel at 110% of hand motor threshold, for 16 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

cortex. An electric field distribution map of the H1 coil at this location is shown in Figure 21.5.

In the open study,[70] eight schizophrenic patients with refractory AH at least five times a day and under treatment with antipsychotic drugs for at least 1 month were enrolled. Stimulation parameters were 110% MT, frequency of 1 Hz for 10 min. Patients received five sessions per week for either 2 weeks (five patients) or 4 weeks (three patients).

For the five patients who received 2 weeks of daily dTMS, auditory hallucinations rating scale (AHRS) scores improved on average by 34.5% and average scale for assessment of positive symptoms (SAPS) scores improved by 23.1% after 2 weeks compared to baseline. Yet, at 1-month post-treatment, the values returned to baseline levels. For the three patients who received 4 weeks of daily dTMS, AHRS scores improved on average by 27.8% and average SAPS scores improved by 13.8% after 4 weeks compared to baseline. One subject did not improve and was lost to follow-up. However, in the remaining two patients, symptom scores kept improving, such that at the 1-month follow-up the average change in AHRS and SAPS scores reached a reduction of 42.6% and 17.9%, respectively. The overall improvements in AHRS for all eight subjects at 1 week and 1 month post-treatment follow-up compared to baseline were statistically significant.

Considering the resistance of AH to treatment in the eight patients treated in this study (failure of 4.75 trials of antipsychotic medications on average), this study may indicate a potential efficacy of dTMS for the treatment of AH in schizophrenia.

In the DBPC study[71] performed by the same group, 18 schizophrenic patients with refractory AH were treated by ten daily sessions of 1 Hz for 10 min at 110% MT with either active or sham coil. AHRS scores post-treatment improved by 12% in the active group and 13.5% in the sham group, with no statistical difference in any of the scales between the groups. The results of the DBPC study[71] are in contradiction with those of the open study,[70] and future studies with larger sample size will have to address this issue.

dTMS AS TREATMENT FOR AUTISM SPECTRUM DISORDERS

Autism spectrum disorder (ASD) is a neurodevelopmental condition of high prevalence, with recent data suggesting that one in 88 children are affected. Autism and Asperger's disorder are life-long neurodevelopmental disorders that involve significant social, communicative, and behavioral abnormalities. Social impairments are arguably the most debilitating aspect of these disorders, and persist into adulthood, creating difficulties in various domains including employment, education, and interpersonal relationships.

It has been suggested that the core deficit underlying social dysfunction in autism and Asperger's disorder is impairment in "theory of mind" (ToM).[72–74] ToM refers to the ability to represent and understand another person's psychological perspective by attributing mental states such as beliefs, intentions, emotions, and desires. Researchers differentiate between cognitive ToM, which involves understanding others' cognitive mental states, such as beliefs and intentions, and affective ToM, which involves comprehending others' emotional states. Neuroimaging studies have identified a number of brain regions activated during the performance of ToM tasks.[75] Studies have indicated that during cognitive ToM tasks a dorsal region within the medial prefrontal cortex (mPFC) is activated,[76] while affective ToM tasks appear to activate more ventral mPFC regions.[77,78] Individuals with ASD consistently demonstrate delayed or impaired performance on both cognitive and affective ToM tasks,[72,79,80] and these deficits seem to contribute to social relating impairments in ASD. Indeed, neuroimaging studies have found reduced dorsomedial PFC activity during ToM tasks in ASD.[81,82]

A recent study[83] tested the effect of 1 Hz dTMS over the mPFC on ToM functioning in healthy volunteers. The H-coil used was the HAUT, which is designed for effective activation of neuronal structures in the medial prefrontal and orbitofrontal cortex, with hemispheric symmetry.

A sketch of the HAUT coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.6.

Sixteen healthy subjects were treated with the following parameters: intensity of 100% hand MT, frequency of 1 Hz for 15 min (900 pulses). Each participant received an active and a sham session at least one week apart. Subjects completed tasks assessing cognitive and affective ToM following each session. It was found that dTMS had no effect on either cognitive or affective ToM performance. Yet when examining self-reported empathy, dTMS disrupted affective ToM performance for those with high self-reported empathy, but improved affective ToM performance for those with low self-reported empathy.

The same group studied the effect of dTMS over the mPFC on ASD subjects.[84] Twenty-eight adults diagnosed with either autistic disorder (high functioning) or Asperger's disorder were randomized to either active or sham treatment with the HAUT coil. Stimulation parameters were intensity of 100% hand MT, frequency of 5 Hz, 10 s train duration, 20 s inter-train interval and 30 trains. Treatment was administered at five sessions per week for 2 weeks.

From pre-treatment to 1 month follow-up, subjects in the active but not sham group showed a significant reduction in self-reported social relating symptoms ($p = 0.019$), the self-oriented anxiety during difficult and emotional social situations ($p = 0.004$), and the fantasy subscale ($p = 0.026$). The fantasy subscale provides a measure of the tendency to imagine oneself as a fictional character in a book or a movie. In all these measures, the improvement increased from the post-treatment assessment to 1 month following treatment. This may indicate that the improvements are not consolidated until a period after the end of treatment, and that dTMS of the mPFC may induce long-lasting neuroplastic alterations in associated neuronal network that are hypoactive in ASD subjects.

In a case report by the same group,[85] an Asperger disorder woman received nine sessions of 5 Hz dTMS over the mPFC. Self-reported assessments at the end of treatment and after 1 month revealed a number of improvements. These were primarily in the domain of social relating and interpersonal understanding and were corroborated by family members. The patient was interviewed approximately 6 months after the last dTMS treatment. She felt that dTMS had been associated with a number of improvements to her social functioning. The patient felt that she could now more easily make eye contact, was more aware of others' feelings, and was more comfortable in social situations. She also reported greater consideration for, and affection toward, family members. These improvements were corroborated by family members, who reported noticing marked changes beginning only around 2 weeks after the end of treatment. This might reflect that a social outcome takes longer to either consolidate or be noticed, again possibly indicating long-lasting neuroplastic modulations induced by dTMS in the relevant brain networks.

dTMS AS TREATMENT FOR CHRONIC PAIN

Chronic pain is a high prevalence problem. When defined as a pain lasting longer than 3 months, 10%–20% of the adult population suffer from clinically significant chronic pain.[86] Chronic pain is a heterogeneous phenomenon that may be divided into nociceptive pain, caused by activation of nociceptors (sensory neurons), and neuropathic pain, caused by damage to or malfunction of the nervous system.

Invasive brain stimulation techniques are already used successfully to treat drug-resistant neuropathic pain, including deep brain stimulation and epidural motor cortex stimulation.[87,88] Several studies used standard rTMS for the treatment of neuropathic pain with mixed results. In some studies no significant improvement in pain perception compared to sham was detected,[89–91] while, in other studies, rTMS was found to lead to significant relief.[92–101] Yet the analgesic effect seems to disappear after no more than 1–2 weeks.[92,97,98,101] In all these standard rTMS studies stimulation was limited to upper limb motor cortex representations.

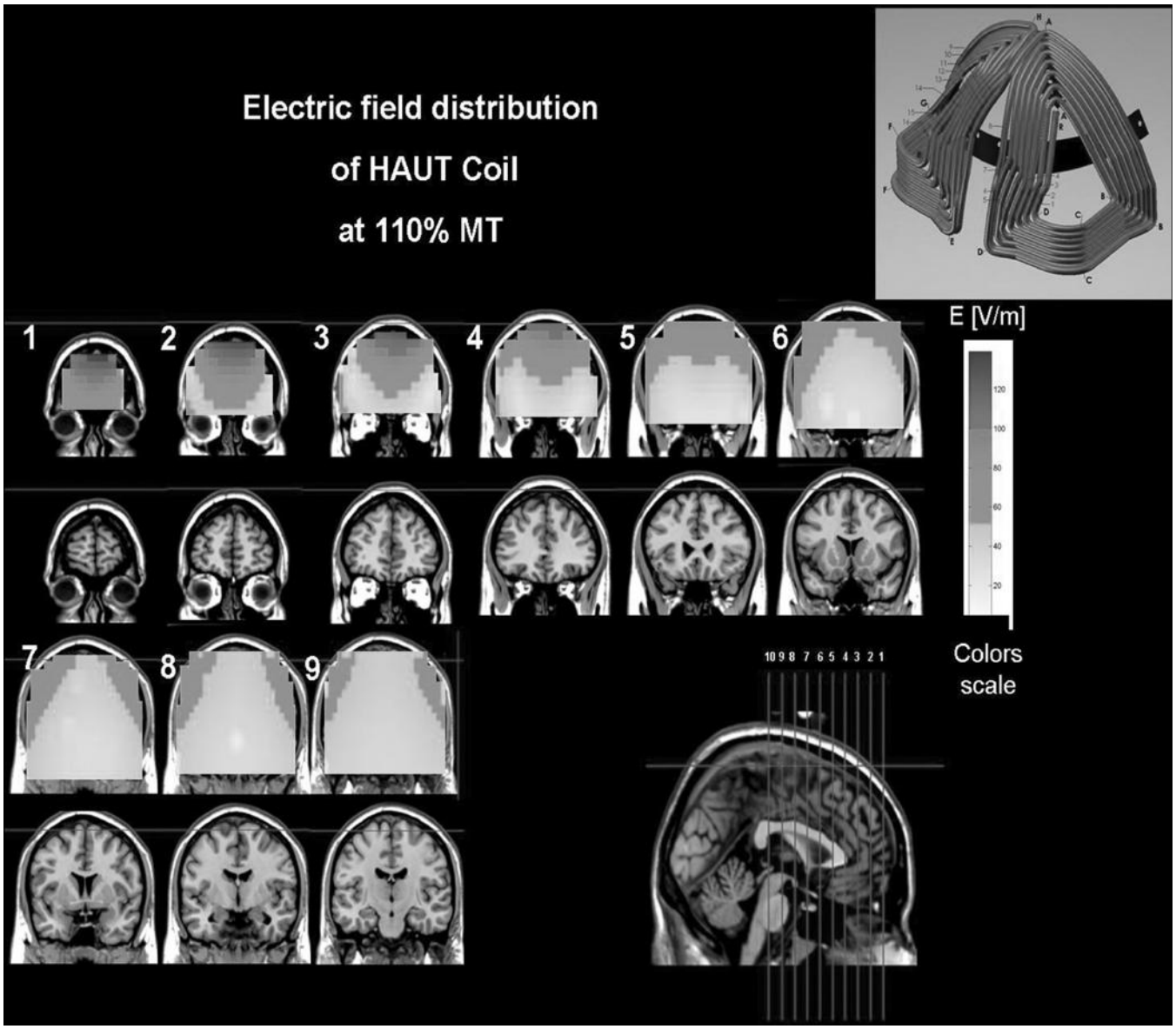

FIGURE 21.6 **(See color insert.)** Colored field maps for the HAUT coil indicating the electrical field absolute magnitude in each pixel at 110% of hand motor threshold, for nine coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

A recent study used deep TMS over the deeper leg motor cortex to treat patients suffering from diabetic neuropathic pain.[102] Twenty-five patients were enrolled and treated with the HMMC coil, which is designed for effective activation of neuronal structures in the motor cortex including the deeper structures of the leg motor cortex, with hemispheric symmetry.

A sketch of the HMMC coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.7.

Patients were randomly assigned to receive daily active or sham dTMS for five consecutive days. Sham/active treatment sessions were applied in crossover design with 5 weeks interval. Stimulation parameters were 30 trains with 2.5 s train duration, 20 Hz frequency, inter-train interval of 30 s, intensity of 100% of leg tibialis resting MT.

The analgesic effect of dTMS (real versus sham) on pain relief was evaluated by measurements of VAS and the nociceptive flexion RIII reflex (RIII reflex). The flexion reflex is a withdrawal reflex consists of an early response, the RII reflex, and a late response, the RIII reflex. Some evidence suggests that the RIII reflex area is related to the level of pain perception.[103] These observations led some to propose the RIII reflex as a valid tool for assessing the mechanisms underlying pain perception.[104] The sural nerve was electrically stimulated percutaneously through superficial electrodes and the RIII reflex was recorded.

Repeated measures ANOVA showed a significant decrease in VAS of subjective pain sensation in the active but not in the sham group ($p = 0.01$), and in the RIII reflex area ($p < 0.01$) following active but not sham treatments. The

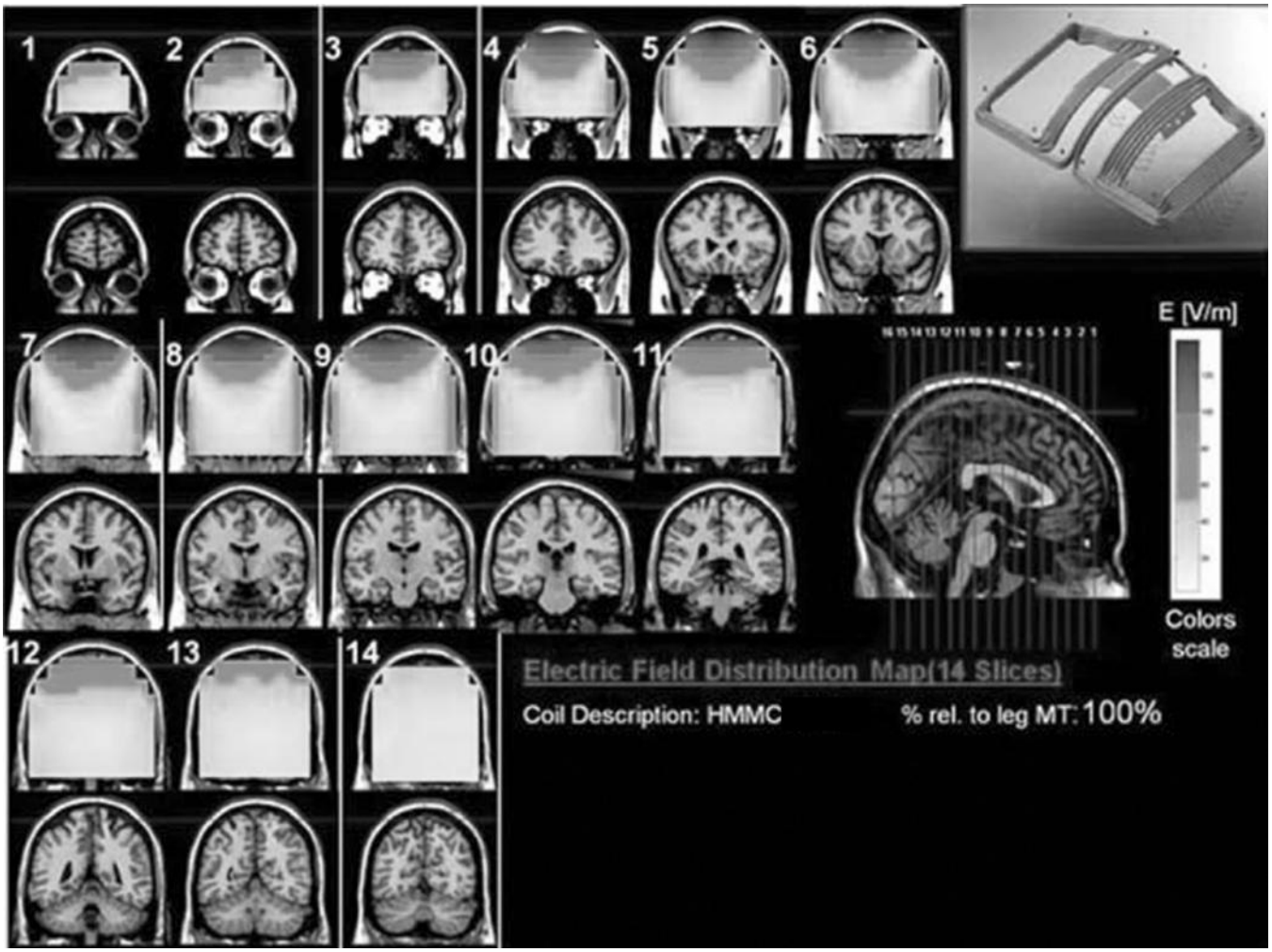

FIGURE 21.7 (See color insert.) Colored field maps for the HMMC coil indicating the electrical field absolute magnitude in each pixel at 100% of leg motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

improvements in both VAS scores and RIII reflex area were preserved 3 weeks after last active session, but disappeared after 5 weeks.

Future studies will have to evaluate whether longer and more intense stimulation periods will produce longer-lasting beneficial effects in neuropathic pain, and whether maintenance dTMS treatment can relieve pain for a long period.

dTMS AS TREATMENT FOR MIGRAINE

Chronic migraine (CM) is a disabling and common condition with a prevalence of 10%–15%.[105] A few pilot studies have explored the possibility of applying rTMS in migraine for acute or chronic treatment with controversial results.[106–108]

A recent study evaluated deep TMS efficacy and tolerability in chronic migraine (CM) subjects.[109] Twenty-two CM patients resistant to preventive pharmacological therapies were treated with the H7 coil over the medial prefrontal cortex. The H7 coil is designed for effective activation of neuronal structures in the medial prefrontal cortex including the anterior cingulate.

A sketch of the H7 coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.8.

Three dTMS sessions per week were performed for 6 weeks with a follow-up visit at 4, 8, 12, and 24 weeks after the end of treatment. Stimulation parameters were intensity of 110% of MT, a frequency of 20 Hz, 20 trains of 2 s train duration with 30 s inter-train interval.

No side effects were evident during the study. Ten patients presented with a significant reduction (50%) in headache days ($p < 0.0001$) and attacks ($p = 0.02$), and pain intensity ($p = 0.005$). A parallel decrease in the number of acute medications ($p < 0.01$) was evident, together with improvement in quality of life items ($p < 0.01$). A partial response to treatment (20%–40% attacks reduction) occurred in seven other patients. Five patients reported no modification in their headache. These results indicate that the use of dTMS could give significant

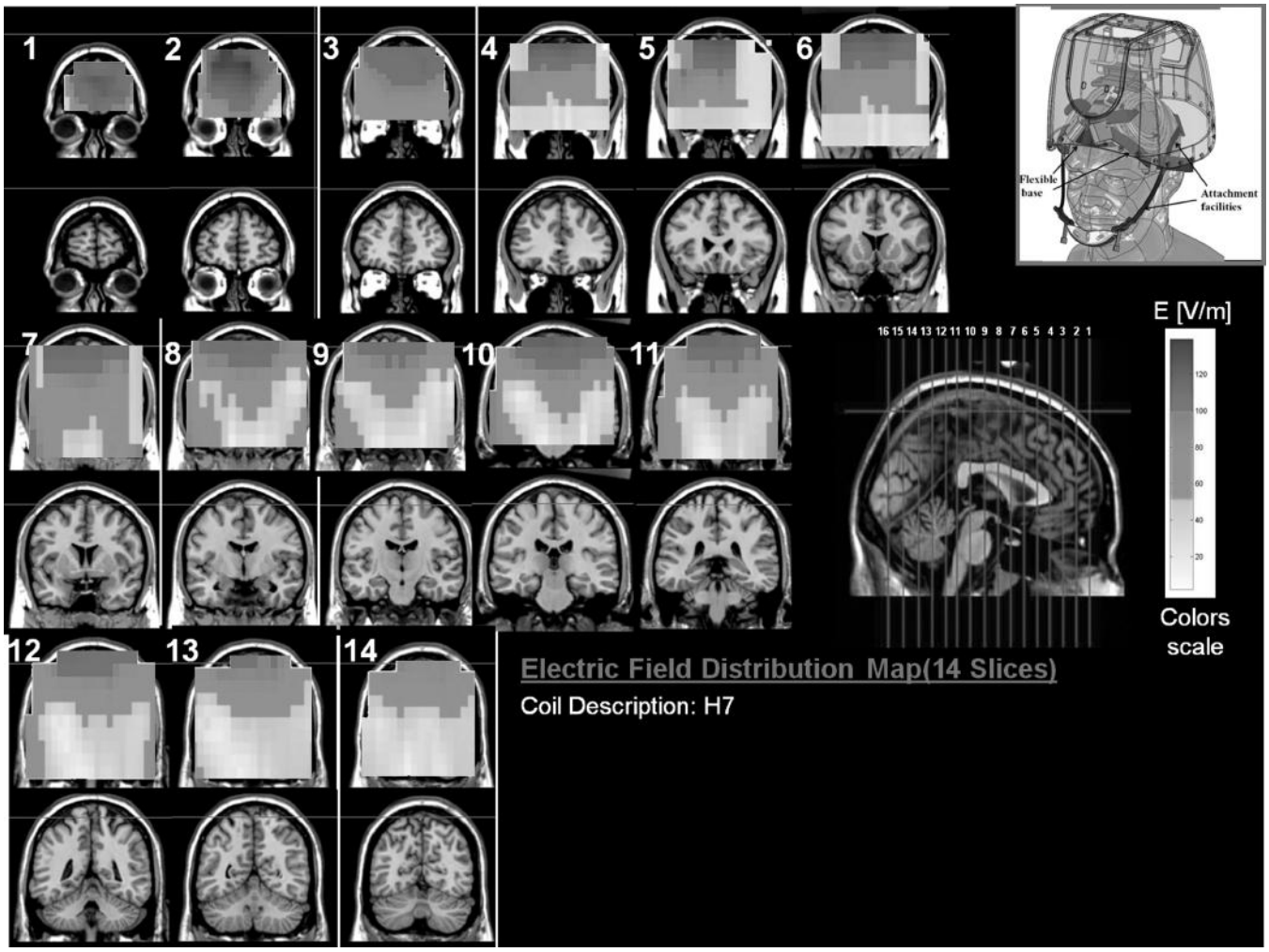

FIGURE 21.8 **(See color insert.)** Colored field maps for the H7 coil indicating the electrical field absolute magnitude in each pixel at 110% of motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

benefit to CM patients, particularly in patients where available drugs are ineffective, poorly tolerated, or contraindicated.

dTMS AS TREATMENT FOR BLEPHAROSPASM

Benign essential blepharospasm (BEB) is a common form of focal dystonia involving involuntary and sustained contractions of the muscles around the eyes and closure of the eyelids.[110] PET studies have shown increased glucose uptake in the right posterior and left anterior cingulated cortex (ACC),[111,112] and a functional magnetic resonance imaging study demonstrated eye-closure-related brain activity in the rostral ACC.[113] A standard rTMS study applied inhibitory low frequency rTMS over several brain regions, and found that rTMS over the ACC had the best clinical effects.[114]

A recent study tested the effects of low frequency rTMS over the ACC on BEB symptoms, using a deep TMS coil (HBL coil), a 9 cm circular coil, and a sham coil.[115] The HBL coil is similar to the H7 coil used by Dalla Libera et al.[109] A sketch of the HBL coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.9.

Twelve BEB patients received all three stimulation procedures at three visits separated by at least 2 days, in a randomized order. For all three coils the session included pulses at 0.2 Hz frequency for 15 min (180 pulses), at 100% of leg tibialis active MT. It was found that blink rate (number of spasms rated by a blinded physician and by the patient) and blink reflex recovery significantly improved after the session for the HBL and the circular coils but not following sham session. For the two former measures, the improvements were significant at 1 h post-session. The active motor threshold was significantly lower for the HBL coil compared to the circular coil.

dTMS AS TREATMENT FOR POST-STROKE REHABILITATION

Stroke is the most frequent cause of disability in adults in the industrialized world.[116] About 750,000 individuals in the United States and 1 million individuals in the European Union are affected each year.[117]

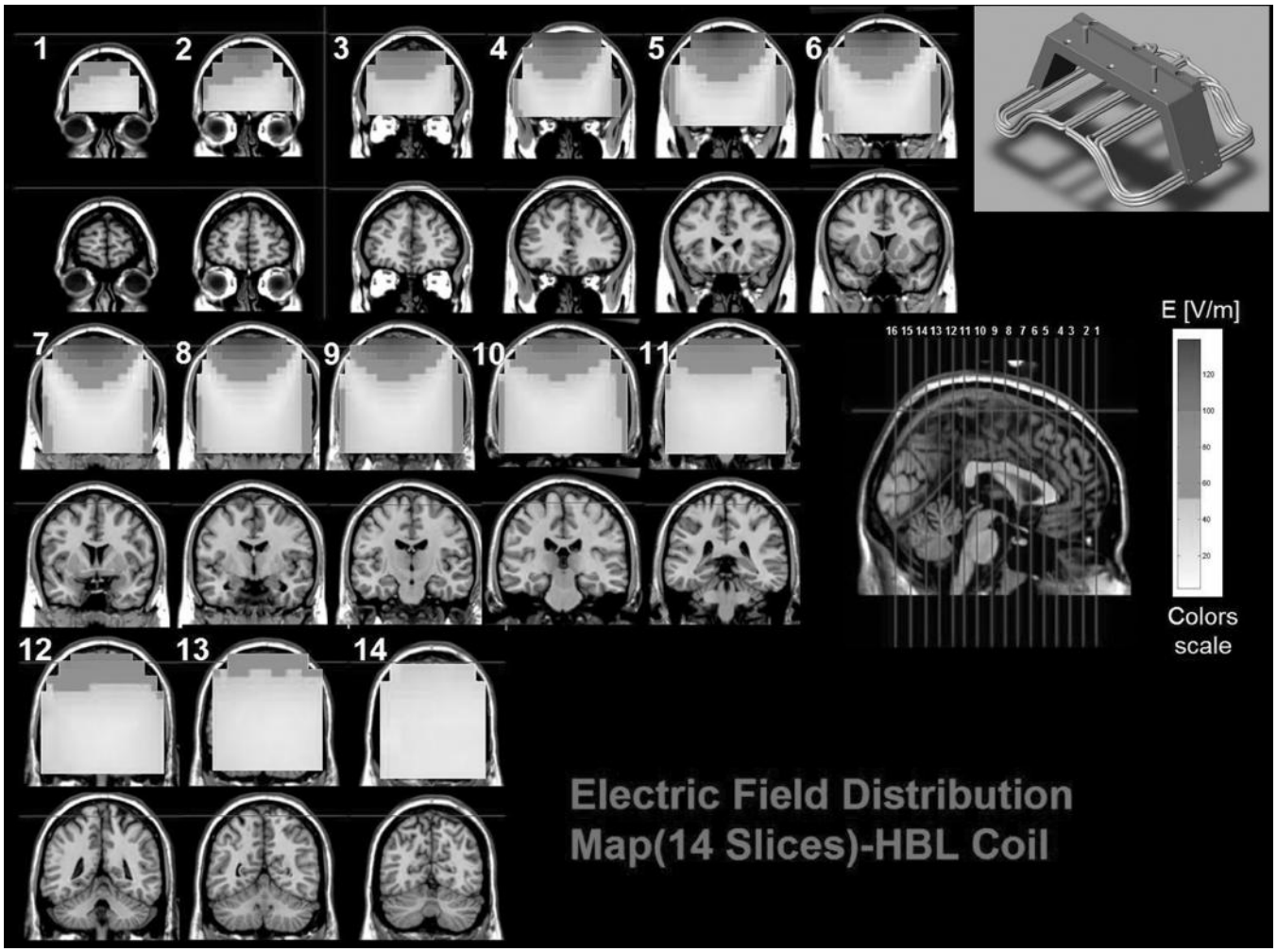

FIGURE 21.9 **(See color insert.)** Colored field maps for the HBL coil indicating the electrical field absolute magnitude in each pixel at 100% of active leg motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

Aphasia is a frequent consequence of stroke to the language-dominant hemisphere, associated with high mortality and reduced global functional recovery.[118]

Standard rTMS over the pars triangularis, a specific portion of the right homologue language region was shown to induce improvements in naming.[119–123]

A recent study[124] used the HMMC coil (used also in the previously reported study by Onessti et al.[102]) over the right inferior frontal gyrus to test the efficacy in five post-stroke patients suffering from aphasia. Each patient received a single session of each of three procedures: high frequency dTMS, low frequency dTMS, and sham. The three sessions were separated by at least 6 days. High frequency dTMS consisted of 10 Hz trains at 100% hand MT with train duration of 2 s, inter-train interval of 20 s and 40 trains. Low frequency dTMS consisted of 1 Hz stimulation at 100% MT for 15 min (900 pulses).

Evaluations of naming task performance revealed significant improvement only after the 10 Hz dTMS compared to baseline ($p = 0.042$), and also in comparison with the performance after the 1 Hz session ($p = 0.043$).

The results of this study provides evidence that high frequency dTMS over the right inferior frontal gyrus improves naming performance in patients with chronic post-stroke aphasic deficits. Future studies should test the efficacy of repetitive sessions and duration of the effect in aphasia and other post-stroke deficits.

dTMS AS TREATMENT FOR PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disease belonging to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells. PD is the second most common neurodegenerative disorder after Alzheimer's disease with a prevalence of about 0.3% in the whole population and of 4% in the population over 80 in industrialized countries.[125] The disease affects approximately 7 million people globally and 1 million people in the United States.[125]

The four primary symptoms of PD are: tremor, or trembling in various organs; rigidity, or stiffness of the limbs and

trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination. PD is both chronic and progressive.

Medication treatments are effective at managing the early motor symptoms of the disease, mainly through the use of levodopa and dopamineagonists. As the disease progresses and dopaminergic neurons continue to be lost, the response to these drugs decreases, and motor fluctuations and levodopa-induced dyskinesias become problematic. In such cases, surgical therapy of deep brain stimulation (DBS) may be considered, where electrodes are implanted into the basal ganglia nuclei and connected to a small electrical device called a pulse generator that can be externally programmed. DBS improves motor symptoms of PD and can reduce the need for levodopa and other drugs, which in turn decreases the dyskinesias. Yet, DBS is an invasive device that requires brain surgery in order to implant the DBS electrodes. Additionally, DBS requires careful, and at times frequent, programming of the stimulator device in order to work both effectively and safely.

Improvements in PD motor symptoms especially after high frequency rTMS over primary motor cortex and PFC has been reported in several standard TMS studies.[126–129] It may be assumed that the deeper and wider activation of deep TMS could increase the clinical benefit. A recent study[130] used the HPAR coil to test the efficacy in 27 PD patients. The HPAR coil is designed for effective activation of dorsal and ventral neuronal structures in the motor cortex and the PFC bilaterally with hemispheric symmetry.

A sketch of the HPAR coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.10.

Each patient received three treatments per week for 4 weeks. Each treatment consisted of two sessions in sequence, one over the motor cortex and one over the PFC. The stimulation parameters over the motor cortex were 90% of hand resting MT, 42 trains at 10 Hz with 2 s train duration and 22 s inter-train interval. For the PFC session, the parameters were the same except the intensity, which was 100% of MT.

Evaluations of motor UPDRS III were done at baseline and after the last treatment, all in OFF state. Repeated measures ANOVA revealed significant improvement in motor UPDRS after the last session compared to baseline (10.8 ± 6.6, $p < 0.0001$). A significant correlation was found between the motor UPDRS score at baseline and its absolute improvement after dTMS ($p = 0.035$).

These results indicate a potential efficacy of dTMS in PD, which should be investigated in further randomized, placebo-controlled studies.

dTMS AS TREATMENT FOR SMOKING ADDICTION

Smoking is the leading cause of preventable deaths in the world. Tobacco use causes more than 5 million deaths per year worldwide.[131] The physiological effects of smoking addiction arise from neuroplastic changes induced by nicotine psychoactive constituents on the brain reward system,[132,133] which includes structures in the PFC.

Several standard TMS studies demonstrated a direct effect of single rTMS sessions targeting the DLPFC on cigarette consumption,[134] general craving,[135] and cue-induced craving.[136] Amiaz and collegues[137] found that 10 days of high frequency rTMS over the left DLPFC reduced cigarette consumption and nicotine dependence. However, this effect tended to dissipate after the acute treatment. In a follow-up 6 months later, the reduction in cigarette consumption did not remain and only 12.5% of smokers who responded to the treatment remained in full abstinence.[137]

The insula was shown in several recent studies to have a crucial role in craving in several types of addictions, including smoking.[138–141] Deep TMS can directly stimulate the insula as well as deeper PFC structures, which are not directly affected with standard TMS.

A recent study[142] tested the efficacy of deep TMS over the PFC and the insula bilaterally on smoking addiction in 115 subjects who smoke at least 20 cigarettes per day and failed previous treatment. The HADD coil was used, which is designed to stimulate neuronal structures in the ventral and dorsal PFC and in the insula bilaterally with hemispheric symmetry. A sketch of the HADD coil and color maps of the electric field distribution induced by the coil in the brain are shown in Figure 21.11.

Subjects were randomized into six groups forming three dTMS stimulation conditions (10 Hz frequency, 1 Hz, and sham) with or without presentation of smoking cue prior to dTMS session. The six groups are denoted accordingly as 10+, 10−, 1+, 1−, S+, and S−. High frequency sessions consisted of 33 trains of 10 Hz each lasting 3 s with an inter-train interval of 20 s. Low frequency sessions consisted of a continuous 600 s 1 Hz stimulation. Stimulation intensity was 120% hand MT in all groups. Each participant received five sessions per week for 2 weeks followed by three sessions on the third week.

Response rates: 10 Hz +cue group—81%; 10 Hz no cue group—67%; 1 Hz and sham groups—12%–29%. Complete abstinence rates at the end of treatment: 10 Hz +cue group—44%; 10 Hz no cue group—25%; 1 Hz and sham groups—0%–14%.

Cotinine levels in urine were measured and showed significant reduction at the end of treatment in the 10 Hz +cue group, compared to baseline and to the other groups. These results correlated well with self-reported cigarette consumption.

Follow-up at 6 months after the end of treatment found complete abstinence rates of 33% and 23% in the 10+ and 10− groups, respectively. Abstinence rates in the 1 Hz and sham groups were between 0% and 14%. The results of this suggest high frequency dTMS of the PFC and insula in combination with presentation of smoking cue as an effective treatment for smoking cessation with long-term effects.

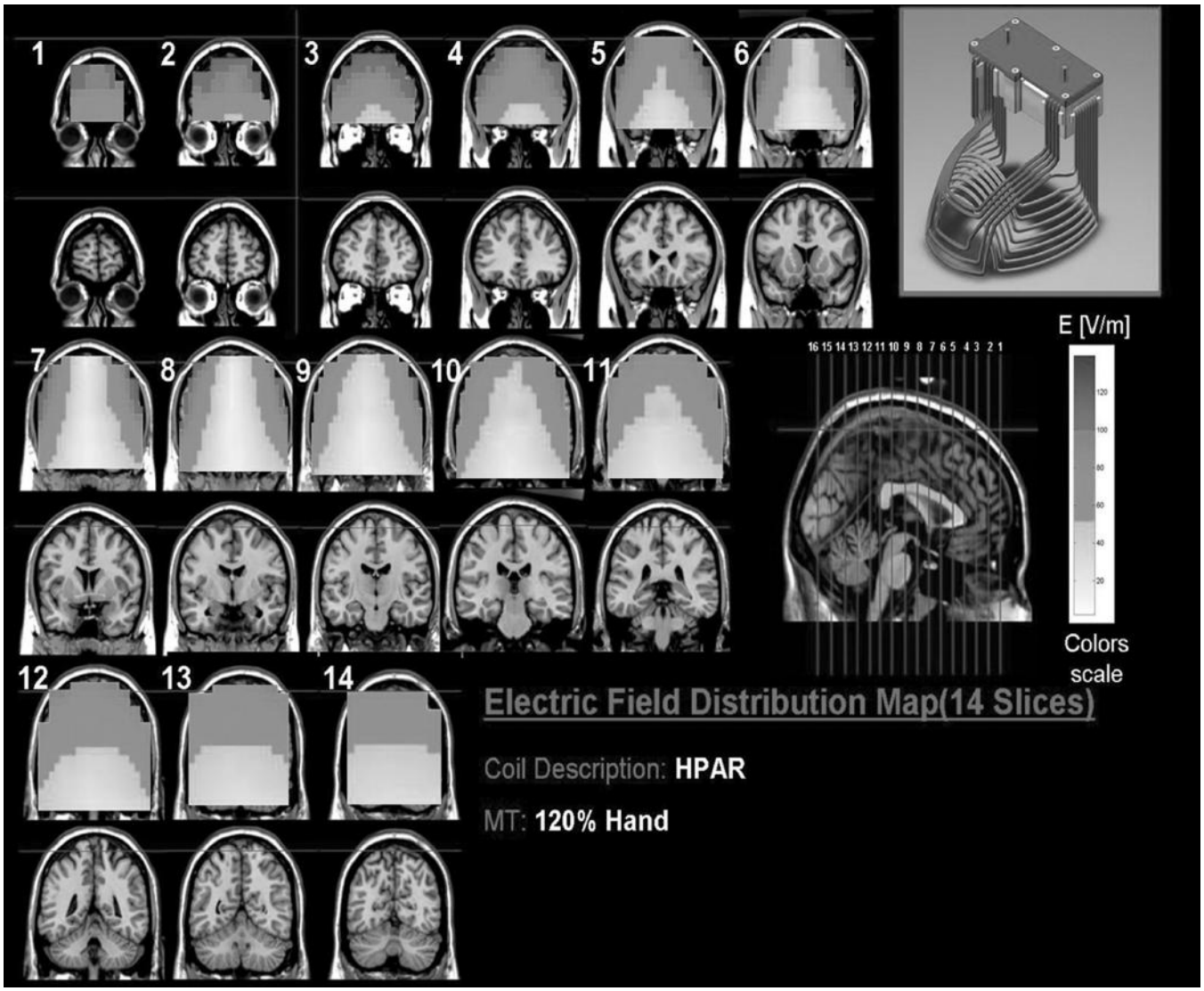

FIGURE 21.10 **(See color insert.)** Colored field maps for the HPAR coil indicating the electrical field absolute magnitude in each pixel at 120% of active hand motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

SUMMARY

The safety and efficacy of deep TMS in various psychiatric and neurological disorders was tested in several studies. Deep TMS has been shown to be safe and tolerable, with minor side effects, such as application site pain or discomfort during session. The most serious reported adverse event was self-limiting seizure, which occurred in a few subjects, usually having additional risk factors that lowered the epileptic threshold. It seems that the risk of seizure is quite similar between dTMS and standard TMS.

The indication with the most extensive clinical data is MDD. From the various clinical trials, including the large prospective multicenter study, which was the basis for the FDA approval for dTMS as a treatment for depression, emerges a consistent picture.

Deep TMS can achieve high remission and response rates in MDD patients, including patients who did not respond to various numbers of antidepressant medications and patient who cannot tolerate the medications side effects. The therapeutic effect was found to be long lasting and stable, and it can be maintained for at least 4–6 months using a maintenance biweekly dTMS treatment.

In bipolar disorder and negative symptoms in schizophrenia, open studies found high efficacy of dTMS. These findings must be tested in future DBPC studies. Conversely, the clinical results in auditory hallucinations in schizophrenia do not point to a clinical benefit superior than a placebo treatment.

dTMS treatment over the medial PFC combined with brief exposure to the traumatic recollection was found to be a very promising novel therapy for PTSD, which can relieve

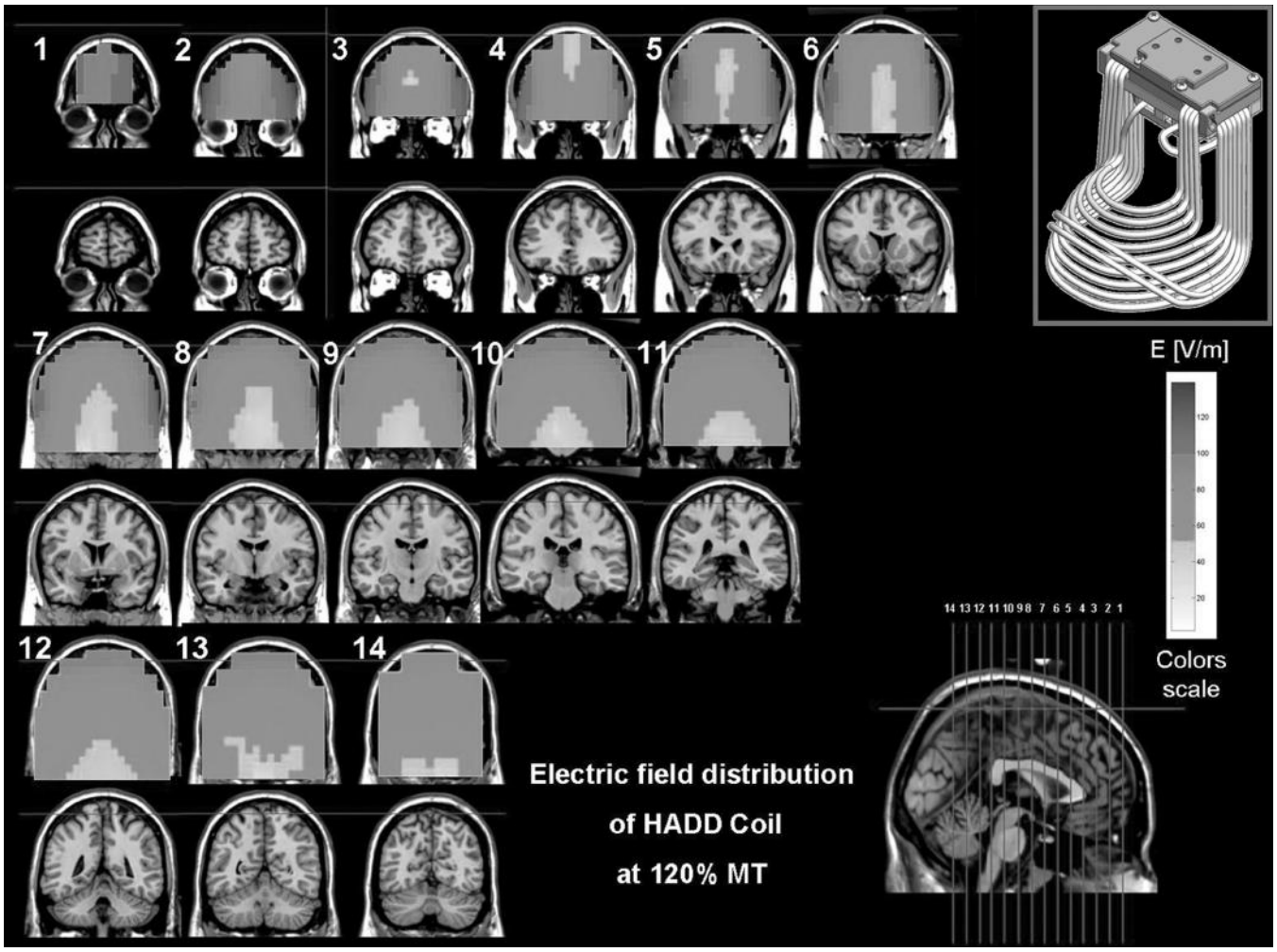

FIGURE 21.11 **(See color insert.)** Colored field maps for the HADD coil indicating the electrical field absolute magnitude in each pixel at 120% of active hand motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

post-traumatic symptoms in patients who did not respond to previous treatments. In the realm of smoking cessation, bilateral high frequency dTMS treatment over the insula and the PFC, especially when preceded by cue increasing craving for smoking, was found to lead to significant reduction in cigarette consumption and nicotine addiction, and even to high rates of abstinence, which were maintained 6 months after treatment. Future studies should test the efficacy of dTMS treatment for other types of addiction.

In the neurological area, very encouraging results were found in ASD subjects where significant improvements in social behavior and social-related anxiety were reported following dTMS over the medial PFC. Interestingly, these improvements were present in a 1-month follow-up, possibly indicating long-lasting neuroplastic changes induced by dTMS. The efficacy of dTMS in these and other ASD symptoms, as well as the duration of the clinical effects, should be addressed in future studies.

An open trial in Parkinson's disease found a significant improvement in motor symptoms following dTMS treatment over the motor cortex and the PFC. Future DBPC studies should investigate the potential of dTMS in this devastating disease.

Significant improvements in pain symptoms were found in a DBPC trial following dTMS treatment in patients suffering from chronic neuropathic pain, which was maintained for 3 weeks. The potential of dTMS for relief in this and other chronic pain types, and the ability to give benefit to the patients for long period, should be studied in future trials.

Significant improvements were also found in subjects suffering from migraine and from blepharospasm following dTMS treatment over the medial PFC.

A highly important area is post-stroke rehabilitation. A small DBPC study in stroke patients suffering from aphasia found significant improvement in naming performance following a single session of 10 Hz dTMS, but not after 1 Hz dTMS or sham sessions. Several studies indicated improvements in upper limb performance following standard TMS over the hand motor cortex in post-stroke patients. As dTMS can stimulate deeper neural structures including the deeper

leg motor cortex representations, it may have potential in improving post-stroke lower limb functionality including ambulation abilities. Further research is required to inquire the clinical potential of dTMS in various types of post-stroke deficits and the optimal temporal window for intervention.

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22 Advances in Stimulation of the Vagus and Trigeminal Nerves for the Treatment of Epilepsy

*Steven C. Schachter**

CONTENTS

INTRODUCTION

Despite an increase in the number of antiepileptic drugs (AEDs) that have become available since the publication of the first edition of this book, epileptic seizures in approximately one in three patients with epilepsy do not improve with appropriately selected and dosed AEDs (referred to as drug-resistant epilepsy [DRE]). Consequently, nonpharmacological options, such as vagus nerve stimulation (VNS), continue to be important treatment options.

VNS was approved in 1997 by the U.S. Food and Drug Administration (FDA) as an adjunctive therapy for reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures refractory to antiepileptic medications. The VNS Therapy™ system (VNS Therapy; Cyberonics, Houston, TX, USA) is also approved in numerous countries worldwide for use in patients with DRE. Over 60,000 patients worldwide have been treated with VNS Therapy for epilepsy (http://us.new.cyberonics.com/en/vns-therapy-for-epilepsy/healthcare-professionals/vns-therapy/about-procedure/; accessed December 30, 2013).

Transcutaneous trigeminal nerve stimulation (TNS) is a relatively new nonpharmacological approach to the treatment of epilepsy that uses another peripheral stimulation site as a portal to the brain, and which has undergone initial clinical testing.

This chapter provides an update to the first edition on VNS for the treatment of epilepsy and adds an overview of TNS as an emerging therapy for epilepsy. The term "VNS Therapy" is used when describing the device manufactured by Cyberonics, Inc., and "VNS" to refer more broadly to stimulation of the vagus nerve.

PROGRESS WITH THE VNS THERAPY DEVICE AND SURGICAL EXPERIENCE

Successive generations of VNS Therapy pulse generators have become progressively smaller with improved battery lives. The latest generator (Model 105; released in 2011) is 6.9 mm thick and weighs 25 grams. According to the September 2013 Physician's Manual (http://dynamic.cyberonics.com/manuals/index.asp; accessed December 30, 2013), the generator will provide in excess of 10 years of operation at clinically relevant settings. Because seizure frequency may worsen in patients who have clinically improved with VNS Therapy when their generator battery is depleted,[1,2] clinicians are advised to preemptively replace the battery for such patients when device interrogation with the supplied software indicates that end-of-battery life is forthcoming.

Accumulated clinical experience has shown that surgical complications, such as infection or vocal cord paralysis, occur infrequently, with the former responding to systemic antibiotics and removal or debridement of the device, and the latter often resolving with time.[3–6] While electrical stimulation of the left vagus nerve is generally used in order to avoid adverse cardiac effects, safe use of right-sided stimulation has been described.[7]

Clinicians determine the stimulation parameters for automatic, ongoing stimulation, as well as for on-demand stimulation using computer software. On-demand stimulation is accomplished by the patient or a companion by placing the supplied magnet over the generator for several seconds. Recommendations for magnet use have become available.[8]

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UPDATE ON PROPOSED MECHANISMS OF ACTION AND CLINICAL EFFECTS OF VNS

In the late 1990s, Krahl et al. provided evidence from animal studies that norepinephrine release from the locus coeruleus is related to the action of VNS in epilepsy.[9] This mechanism was further validated more recently by Raedt et al.[10]

Evaluation with transcranial magnetic stimulation in a small clinical study suggests that the therapeutic benefit of VNS for patients with DRE is associated with increased inhibition of cortical function.[11] This finding is further supported by the demonstration that a therapeutic response was associated with normalized, that is, increased, receptor density for gamma amino butyric acid, the major inhibitory neurotransmitter in the brain.[12]

Uncontrolled studies since FDA approval have evaluated the effectiveness of VNS Therapy in children with DRE,[6,13,14] the benefit for seizure types other than partial-onset, the effect on mood problems in adults with epilepsy,[5,6] and impact in patients with particularly severe forms of DRE, such as Lennox–Gastaut syndrome (LGS).[13,15–22] In 2013, a Guideline Development Subcommittee of the American Academy of Neurology published an evidence-based review of 216 reports published from 1996 to February 2012 and concluded that VNS "may be considered for seizures in children, for seizures associated with LGS, and for improving mood in adults with epilepsy."[23] The Subcommittee also recommended that children be carefully monitored for site infection after implantation of the device, and concluded, based on long-term, open-label studies in patients with DRE, that seizure control may progressively improve over time.[24–28]

There have been few new side effects or other safety issues described since the publication of *Bioelectromagnetic Medicine*. Bradycardia and transient asystole have been typically noted in association with the VNS lead test during surgical implantation of the VNS Therapy generator in approximately 1 in 1000 cases.[29,30] They have also now been described in two case reports in which the VNS device had been implanted 2 and 9 years, respectively, before the cardiac arrhythmia was documented.[31,32] In addition, paradoxically aggravated seizures, though generally not seen with VNS, was described in one patient.[33]

UPDATE ON VNS TECHNOLOGY

A variety of new technologies are either available or under development to augment the effectiveness of VNS for epilepsy or to address challenges with the currently available equipment. For example, new methods to trigger on-demand stimulation of VNS Therapy that do not require manual use of the magnet by the patient or a companion are under evaluation, such as those based on seizure detection using algorithms that either monitor brainwave activity[34,35] or heart rhythm (http://ir.cyberonics.com/releasedetail.cfm?releaseid=573501; accessed December 30, 2013).

Current limitations in optimizing the VNS parameters other than by titrating to clinical response are the focus of the ADNS-300 VNS system[36] (Neurotech, Louvain-la-Neuve, Belgium; http://www.neurotech.be/?page_id=73; accessed December 30, 2013). This system includes a stimulating cuff electrode that can also quantify the response of the vagus nerve to stimulation, and it received European CE Mark approval in 2012 for the treatment of refractory epilepsy.

Another investigational VNS system, called FitNeS (BioControl Medical Ltd, New Hope, MN, USA), may reduce some VNS-related side effects due to efferent stimulation such as shortness of breath, hoarseness, pain, dysphagia, and cough, which may thereby allow for potentially higher and more efficacious current strengths to be used. This system features a novel stimulating electrode that sends current along the vagus nerve only in one direction.

A third investigational device called NEMOS™ (Cerbomed, Erlangen, Germany) (http://www.cerbomed.com/Therapy-with-NEMOS-92.html; accessed December 30, 2013) is entirely noninvasive and provides stimulation of the auricular branch of the left vagus nerve transcutaneously. Scientific evidence that this cutaneous stimulation site can affect brain function[37,38] and a positive pilot study in ten patients with DRE support its further clinical development.[39]

THE EMERGENCE OF TRIGEMINAL NERVE STIMULATION FOR THE TREATMENT OF EPILEPSY

The trigeminal nerve transmits sensory information from the face via the trigeminal ganglion to the trigeminal nuclei in the brainstem. Similar to the central projections of the vagus nerve, the trigeminal nuclei then send projections to the thalamus, the locus coeruleus, and the nucleus of the solitary tract which, as described in *Bioelectromagnetic Medicine*, are considered necessary components of the anticonvulsant effect of VNS.[40,41]

Consequently, Fanselow et al. evaluated TNS in the pentylenetetrazol-induced acute seizure model in awake rats and found a reduction in seizure severity and duration that was proportional to frequencies >100 Hz.[42] Bilateral stimulation was more effective than unilateral stimulation.

The shared central projections of the trigeminal and vagus nerves and the proof-of-validation in a standard animal model of epilepsy[42] provided the scientific rationale for proceeding to clinical studies of TNS as a potential treatment for epilepsy. The first clinical trial was a pilot study of the feasibility, safety, and efficacy of transcutaneous stimulation of the infraorbital and supraorbital branches of the trigeminal nerve in seven patients with epilepsy.[43] TNS was well tolerated, and four (57%) of seven participants who completed ≥3 months of treatment had at least a 50% reduction in seizure frequency.

DeGiorgio et al. then conducted a phase II, double-blind, randomized, multicenter trial evaluating bilateral transcutaneous stimulation of the ophthalmic and supratrochlear nerves with the Monarch™ eTNS™ System (NeuroSigma, Los Angeles, CA, USA; http://www.neurosigma.com/tns.html; accessed December 30, 2013) in patients with DRE.

Enrolled participants were randomized to receive either active treatment (frequency = 120 Hz, pulse duration <250 μs) or a control treatment that used stimulation settings based on previous controlled studies of VNS.[44] After a 6-week baseline period, participants were monitored for tolerability, safety, and efficacy at 6, 12, and 18 weeks. The three primary outcome measures were change in seizure frequency, proportion of participants who experienced at least a 50% reduction in seizure frequency (the responder rate), and time to the fourth seizure.

Tolerability and safety were acceptable, with skin irritation, anxiety, and headache the most frequently reported side effects. There were no statistically significant differences between the treatment groups for any of the primary outcome measures, though further analysis showed a significant improvement in responder rate within the active treatment group over the duration of the trial.

The Monarch eTNS System received CE certification in Europe in 2012 for the adjunctive treatment of epilepsy and major depressive disorder for adults and children 9 years and older, and a Class 2 medical device license in Canada in 2013 for treatment of DRE, major depressive disorder, and treatment-resistant depression. A multicenter phase III trial of the Monarch eTNS System is planned for sites in the U.S., Europe, and Canada (http://www.prnewswire.com/news-releases/neurosigma-announces-fda-approval-to-commence-phase-iii-trial-217368281.html; accessed December 30, 2013).

SUMMARY

Since the publication of *Bioelectromagnetic Medicine*, VNS has remained an established nonpharmacological treatment for epilepsy, including patients whose seizures have not improved from intracranial epilepsy surgery.[24,45,46] Published evidence supports the use of VNS Therapy for seizures in children, for seizures associated with LGS, and for improving mood in adults with epilepsy. New technologies under development for stimulation of the vagus nerve and closed-loop systems that turn on VNS at seizure onset offer the potential for improved tolerability and efficacy.

Trigeminal nerve stimulation is now emerging as another method for cranial nerve stimulation and appears promising as a treatment for epilepsy. Further studies will help to characterize its clinical profile in comparison to VNS and other epilepsy therapies.

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23 Vagus Nerve Stimulation and the Neurocybernetic Prosthesis
The Way Forward

*Jacob Zabara**

CONTENTS

The electric fish was probably the first bioelectric treatment. The experimental breakthrough by Galvani that led to the battery (Volta), the pioneering treatments of Benjamin Franklin, and the cardiac pacemaker have been the historical foundations of the neurocybernetic prosthesis (NCP). The NCP was invented and developed by Zabara utilizing the electrical properties of the vagus nerve as an entry channel into the brain.[1] Norbert Weiner derived the term "Cybernetics" from the Greek to mean regulation and control in man and machine. The NCP was an attempt to accomplish this in "man" through control of an electromagnetic "machine." The "machine" was, at least initially, to be based on the cardiac pacemaker; however, the goal of the NCP is very different. Whereas the cardiac pacemaker represents a driving function placed in or on the end organ (heart), the NCP is placed distal to the end organ (brain or body) and it communicates electromagnetically (vagus nerve stimulation [VNS], etc.) with cybernetic or regulatory functions.

The vagus nerve has been stimulated for over 100 years resulting in 1000s of papers (studies), but critical functions were unknown until Zabara undertook animal and patient studies resulting in the successful treatment of patients with epilepsy. The vagus nerve had been considered for 100 years as primarily motor (not sensory) and subserving autonomic functions (not somatic) and virtually unrelated to the striated muscle, which acted in correspondence to behavior and conscious states.

Epileptic patients can experience uncontrollable motor and conscious states, and VNS can re-establish regulation of these states by generating action potentials ending primarily in the solitary tract nucleus of the brain stem. The solitary nucleus acts as a gate or integrator-differentiator, sending impulses along tracts to many nuclei of the brain.

There are about 90,000 neurons in the vagus nerve and the ability to discharge specific groups of neurons is called spectral discrimination (Zabara). The predominance of afferent neurons led to the next step of determining their function. A relatively small number were involved in apparent reflex effects, primarily from the lungs and heart. Zabara concluded that the majority were feedback loops involved in regulations in both autonomic and somatic systems, and became apparent in his studies in epilepsy. Even today, the vagus nerve is not considered as being an integral component of epileptic seizures. Thus, the problem became not to "stimulate" the vagus nerve but rather to modulate it, and in this sense, vagus nerve stimulation is a misnomer and may lead to problematic results and conclusions.

The regulatory function led to what was to many investigators a surprising observation: that the patients' seizures decreased over a period of weeks or months. This was very different with anti-epileptic drugs where the efficacy of the drug decreased with time (and side effects increased). Therefore, even though the vagus nerve has no reflex connection with striated muscle (behavior) or cortical conscious states, it has a powerful effect on both of these by modulation of the brain's regulatory system. It is important to keep in mind that this is a self-regulating system so that the modulation is among a range of set points, which, if exceeded, results in instability, which the vagus nerve is able apparently to reverse. This is a dynamic effect, dependent on the specific neurons and the pattern (frequency, etc.) of action potentials reaching the solitary nucleus (nucleus of the tractus solitarius) and the state of the nucleus. The range of set points includes those represented by the electroencephalogram (EEG): alert (beta rhythm), relaxed (alpha rhythm, etc.), whereas instability is represented by the EEG of the seizure state including high voltage and high frequency, which is beyond the "normal" rhythm.

Another observation supporting the conclusion that vagus nerve modulation acts primarily on the regulatory system is that it does not change the "normal" EEG in the patient with epilepsy. That the vagus modulation relates to a regulatory system rather than a reflex system opens the way forward to new treatments and even new technology, which will be described further on. The animal experiments supporting

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these hypotheses have been reported by Zabara[2–5] and in other publications. However, the major testing occurred in a clinical trial in several hundred patients with epilepsy under the aegis of the U.S. Food and Drug Administration (FDA), which is difficult to achieve by an individual scientist requiring patents, investment in many millions (mainly for the FDA clinical trial), and founding of a company (Cyberonics, Houston, TX, USA). As this is not considered basic research, there is very little support in an academic environment. The period for the clinical trial was almost 10 years, but finally, there was FDA approval for refractory epilepsy.[6] The FDA approval is based on a statistical analysis in a double-blind study, where physiological mechanism is usually ignored. This means that the FDA only determines the potential of the NCP-VNS system one treatment application at a time requiring hundreds of millions (dollars) and a period of time far exceeding the lifetime of the scientist.

A major drug company does not face the same, or as difficult, obstacles as the individual scientist. Zabara's way forward has been to develop a series of scientific premises framed as patents that may lead to innovative physiological and medical insight, extending both realms. The first step in this direction was in clinical depression, which approaches a population of 20 million and a suicide death rate of 40,000 a year in the U.S. The problem is that all are reflexes, instincts appear to act solely for survival, and yet, by a conscious determination, they can be overcome. This appears in opposition to the epileptic state where consciousness lapses in the presence of unconscious motor behavior and the EEG can almost disappear in clinical depression during sleep (some patients). Can this compulsion for death be prevented or overcome by vagus nerve modulation even though clinical depression appears, in some important characteristics, to be the opposite of epilepsy?

Zabara developed several animal models combining epilepsy and depression characteristics, although conscious expressions could only be measured indirectly. In these models, vomiting was considered as a "physiological seizure" and it was also related to nausea as a model of clinical depression. Vomiting is initiated by modulation (or stimulation) of the sub-diaphragmatic vagus and prevented by almost simultaneous modulation of the cervical vagus (anesthetized dog). Vomiting is associated with most illnesses and some psychological states. At this time, it was not clear how, once initiated, vomiting (or seizures) were stopped. Zabara's hypothesis was that vagal afferent neurons from the lungs and heart inhibited those (vomiting afferents) from the gastrointestinal tract and hyperpolarized neurons or synapses in the vomiting center. This apparently operates, not only to inhibit vomiting, but also to prevent aspiration of vomitus that could lead to suffocation. The regulatory function involves another vagal afferent loop, which can determine its set point, which at sufficient depolarization of the center's neurons can activate the appropriate musculature (diaphragm, etc.) to produce vomiting.

In the human, nausea usually proceeds, and can continue during, vomiting, causing a lassitude that is depression-like. In the monkey (conscious), emesis is initiated as motion sickness by placing the monkey on a rotating platform and then modulating the vagus to prevent or decrease emesis. In the cat, xylazine acts on the chemoreceptor trigger zone to induce emesis where an important time factor emerges, similar to the one in epilepsy, due to vagal modulation. Experiments, like these, may be utilized in the scientific method as local, specific observations that can lead to general principles (similar to the observation of a tiny bending of light from a distant star by the sun supported Einstein's theory of relativity). The general principle, for our purposes, may be termed self-regulation, although this is different from machine regulation, and for the brain may be called neurocybernetics and the resulting treatments as based on the neurocybernetic prosthesis. However, the clinical trial is based on a statistical analysis (adjusted, because of the small sample) rather than the full scientific method or general principles.

In the clinical trial for VNS in clinical depression, the evaluation was mainly based on a standard questionnaire rather than in epilepsy on the absence or frequency of seizures, a direct observation. Although the FDA awarded approval, the outcome is not clear because VNS has not yet received reimbursement approval. This is a condensed, and perhaps incomplete, version of where VNS stands at present.

Now, the brain regulates the function of the internal organs, including the heart, but is it possible to say that the vagus, which is an important component of the brain's regulation of the heart, is also an important component of the brain's own self-regulation. The brain-heart regulatory system can serve as a model of brain self-regulation. The heart consists of an electrical function, which can be observed as the electrocardiograph (ECG), and a mechanical function that is represented by the pumping action of the heart. The electrical conduction activates heart muscle to contract (by depolarization) as initiated in the sinoatrial (SA) node. The ECG shows a rapid sequence of electrical events corresponding to atrial and ventricular contraction followed by repolarization. The frequency (and magnitude) of the ECG and corresponding contractions is based on the depolarization frequency-magnitude of the SA node, as mainly modulated by the vagus nerve (which also acts to a certain extent on the auricles and ventricles) and the sympathetic nerve innervation in these same structures. VNS treatment for the heart is based on this brain-heart self-regulation model. Although the heart has one main rhythm generator (SA node), the brain has many different rhythm generators lodged in many different nuclei (such as the respiratory center). Synchronization of cortical nuclei rhythms may result in the high voltage, low frequency EEG of deep sleep while asynchronization can cause the low voltage, high frequency EEG of the alert, conscious state. Instability is reflected in the very high voltage and frequency EEG of epilepsy.

Many studies have shown that stimulation of the cardiac branch of the vagus can cause a decrease in frequency (and magnitude) of the heartbeat, and even a temporary cessation. Physiologically, the heartbeat is a balance between the sympathetic (acceleration) and the vagus (deceleration). It is possible to stimulate both the sympathetic and vagus nerves

to regulate an unstable heart, where the beat may have a frequency or magnitude outside physiological limits or even be in fibrillation. The cardiac pacemaker is the main technology at present for controlling the heartbeat, which is done by a generator and electrodes placed in or on the heart (usually the ventricles). However, the cardiac pacemaker for many years had the serious limitation of a static heart rate that was not responsive to increases or decreases in physiological activity (exercise, etc.). This resulted from bypassing the brain-vagus-sympathetic regulation by the electrodes being placed directly in or on the cardiac muscle. Therefore, the action of the cardiac pacemaker is "stimulation," whereas that of VNS is "modulation," which sets the frequency and amplitude of the regulatory center's autorhythmic discharge. This approaches a mechanism for self-regulation but still requires an explanation, for instance, of the origin of the autorhythmic discharge.

Another important aspect that the cardiac pacemaker bypasses is heart rate variability (HRV). HRV is a noninvasive measure of vagus-sympathetic modulation of the heart that can predict morbidity and mortality (heart disease, coronary artery disease, post infarction, and sudden cardiac death). HRV is a result of the balance between vagus and sympathetic activity, but primarily due to changes in vagal action potentials on the SA node, originating in brain regulation (primarily the cardiovascular center). Further, HRV is related to EEG potentials during sleep. It is true that the rate cardiac pacer was introduced to respond to substantial changes in physiological activity, but this is by direct stimulation of the heart. It should be noted that VNS (Zabara) utilized the new technology (microchip) to program the generator (physician using an external wand connected to a computer) and allowing the possibility of customizing VNS to the individual patient. However, VNM allows brain regulation to continue to operate and enhances it by intermittent activation of both afferent and efferent vagal neurons. The afferent neurons prevent instability or reset regulation to correspond to circulatory and energy requirements. The brain-heart system can be structured as a rhythmic dipole where the heart normally has a dominant rhythm generated by the SA node and the brain has many nuclear rhythms may synthesize into a dominant rhythm, such as exhibited in the EEG. The two rhythms are functionalized by the afferent-efferent neurons into a self-regulating loop designated as a dipole-rhythm generator. The afferent and efferent neurons discharge periodically in almost synchrony with the heartbeat. The afferents end in stretch receptors, which sense the pressure change during systole and discharge action potentials conducted as a group to the brain and efferents emerge similarly in a similar grouped discharge with the same frequency as the heartbeat. Therefore, vagus and sympathetic nerve modulation can emerge as extending cardiac pacemaker therapy to enhance HRV, control tachycardia, prevent fibrillation, etc.

It is now possible to extend VNS to other cranial nerves, such as the trigeminal nerve that can be referred to as trigeminal nerve modulation (TNM). The trigeminal nerve has three branches corresponding to the upper (ophthalmic), middle (maxillary), and lower (mandibular) of the face. The ophthalmic and maxillary branches are sensory, the mandibular also includes motor functions, and these branches converge on the trigeminal ganglion where neurons emerge to end in the trigeminal nucleus. A neurons (low threshold) can subserve pain (instead of C neurons that are high threshold), which together with many connections of the nucleus with the reticular formation may account for the excruciating pain of trigeminal neuralgia. The reticular formation consists of many small groups of synapses (instead of large groups called nuclei) disbursed through the formation, which can result in a function resembling amplification. The nuclei have rhythms (electromagnetic oscillations) that can be observed as oscillations in synaptic potentials (or action potentials) and in the cortex represented by the EEG. The nuclear rhythms have spins that are more or less out of phase with each other, where the phase range can be from 0 to 360° but usually from 0 to 180°. The spins of the beta rhythm have maximal phase differences, which characterize it as high frequency and low voltage (alert, conscious state), and a high level of regulation. Here, the low signal to noise ratio also means a regulatory state level and not a reflex. In sleep, the phase differences decrease to produce a lower frequency and higher voltage EEG, resulting in a lower level of brain regulation and unconsciousness, muscle relaxation, low heart rate, etc. When the nuclear phase differences are zero, the nuclear rhythms are synchronized and brain regulation becomes erratic or absent, which can result in the very high voltage and frequency of the EEG in the generalized seizures of epilepsy. This is also reflected in heart regulation where a significant HRV (asynchronicity) represents a high level of regulation and heart competency.

The mechanism of vagus nerve and trigeminal nerve modulation now begins to be understood in terms of brain regulation and nuclear rhythms; it is to desynchronize the nuclear rhythms or prevent their synchronization. Trigeminal neuralgia is often treated with carbamezapine (Tegretol), which is also a treatment in epilepsy, indicating similarities, but over time, larger and even larger doses are needed, finally resulting in ineffectiveness and serious side effects. At this point, surgical alternatives may ensue, which include a dime size opening behind the ear through which a 2.7 mm endoscope is inserted and the trigeminal branch is encountered. The surgery is more serious than for the vagus nerve, therefore, at the University of California (UCLA), a study has been pursued to stimulate the supraorbital branch by placing electrode patches on the skin above the eyes. However, this study is limited by how much current can actually reach the nerve and the pain threshold at higher currents, but it is the first study attempting stimulation of the trigeminal nerve (branch) for the treatment of epilepsy. A number of other pilot studies have been completed or in process (VNS) including Alzheimer's and obesity.[7,8]

In obesity, a technical problem emerged in that the stimulation was at the abdominal vagus where the current was apparently not sufficient to activate the predominately C neuron population (much higher threshold than A fibers in the cervical vagus). In these pilot studies, a major problem

arose in terms of an individual scientist attempting to bring an innovative medical treatment from the laboratory to the clinic. As mentioned, the individual faces the same hurdles with the FDA as a major pharmaceutical or medical device firm, which for the individual can be just barely surmountable. Thus, the major firm can repeat the pilot study to overcome mistakes, whereas the individual may not have the resources to do so, or the investors may not want to take the chance. At this point, the individual or the treatment he or she invented and developed may become a target for serious negative criticism, as was the case with Jonas Salk, even after the polio vaccine was successful. The end result is that, at present, the new VNS (and NCP) treatments are on hold or not even begun. However, presently, it is difficult to overlook the success of VNS in the face of the hurdles encountered.

Chronic pain has become a very serious problem. A number of years ago, a peripheral control of pain was suggested whereby the C neurons conducting action potentials for pain could be inhibited by lower threshold A neurons at a common synapse in the spinal cord (Patrick Wall), and a series of investigations were supportive. Later, investigators demonstrated that stimulation of the vagus nerve could stop or prevent pain in animals (behavior linked to pain). A pilot study is pending in humans. At this time, it is should be emphasized that much of the confusion concerning mechanism and treatment procedure is due to regulation and not stimulation. Stimulation-response analysis is based on the reflex (Descartes) and involves an interaction between excitation and inhibition (depolarization and hyperpolarization), a temporal summation at the synaptic membrane. Regulation depends upon maintaining a range of set points in an ensemble of nuclei, similar to HRV maintenance. A suggestion would be to reserve stimulation for the reflexes of the vagus nerve, such as those that occur in cardiovascular and respiratory responses, or with the cardiac pacemaker, where the response is coincident with the stimulation. A regulatory response outlasts the stimulation; for instance, in the anesthetized dog, inhibition of seizures is four times longer than a single period of stimulation. This led to the conclusion that repetitive periods of stimulation would reset or re-initiate regulation and then should properly be termed modulation. This conclusion (hypothesis) was tested in an animal model involving the cat (conscious) and xylazine induced emesis (a "physiological" seizure).

Xylazine induces vomiting by activation of the chemoreceptor trigger zone in the brainstem. The cervical vagus nerve was modulated through implanted cuff electrodes utilizing an external generator producing pulses of 1–10 ma, 4–100 Hz, and 0.3–0.6 ms. Vomiting was prevented during modulation and latency was increased over control values. Repeated experimental trials could result in the complete absence of vomiting. This may be understood more clearly by describing a sequence of modulations in a single animal. When there was no modulation (control) the vomiting latency was approximately 4 min; at 16 min, latency was 25 min; at 25 min, latency was 90 min. At approximately 7 min, latency was approximately 7 min; at 25 min, no vomiting; at 16 min, no vomiting. At no modulation (control), latency was approximately 4 min; at 8 min, no vomiting; at 4 min, latency was approximately 11 min; at 6 min, no vomiting; at 5 min, no vomiting; at 4 min, latency was approximately 4 min; at 4 min 30 s, no vomiting. Each of these trial sessions occurred once a week over 12 weeks. A singularity is observed at approximately 4 min (latency), which may mean that the reflex response (by xylazine) can be maintained or is a fixed set point of the regulation. However, repeated modulations can delay the reflex response and eventually prevent it by acting on the regulatory centers. The reflex response seems to act in an on-off manner (digital) in a regulatory program. Thus, the synapses may be performing as quantum (or solid state) devices possessing memory, integration, and conditioning mechanisms.

A question arises here as to whether the modulation should be present during the latency for maximum effectiveness of a VNS treatment. In approximately 50% of epileptic patients, an aura precedes the seizure and patients with VNS can turn on their devices (with a magnet) on sensing the aura, but this still occurs on a basis of repetitive, periodic VNS action (often, 30 s on and 5 min off). A clinical trial is being performed to determine whether stimulation during a seizure will improve the effectiveness of VNS.

In 1985, experiments were performed in monkeys (conscious) with seizures to determine the effectiveness of VNS during a seizure, but at that time found little or no effectiveness over repetitive, periodic VNS (Zabara). However, the present clinical trial has an improved sensing system and generator that may offer a new answer. The answer may be unclear because with a 30 s on, 5 min off, a substantial number of seizures may occur during VNS action and the clinical trial may not show a definitive benefit because of this or due to the repetitive stimulation itself being optimal (as Zabara originally demonstrated but with limited technology). The significant delay (up to 90 min) in vomiting (to xylazine) may have a correlation to continued inhibition of a seizure beyond the termination of VNS action or the continued decrease of seizure frequency (VNS) over a period of many months.

A related question is why the seizures do not stop completely. In fact, in a small percentage of patients (perhaps 15%), the seizures do stop, but in the presence of continued repetitive stimulation (VNS). There is apparently a range of regulatory states or set points that can last beyond the direct modulation but it must be renewed periodically. This is observed in seizures where the range of regulatory states can vary from complete cessation of seizures to a decrease in seizure frequency. The explanation may be the spin of the nuclear rhythms where the spins and rhythms are desynchronized by VNS and the amount of desynchronization determines the effectiveness of seizure control. Effectiveness might be increased by changing the level of current in different patients. At the present time, the maximum current in VNS generators is approximately 3.5 ma, with most patients apparently at 2 ma or less, which accounts for 15%, or less, of the vagal neurons (approximately 90,000). These are the lowest threshold neurons, a subset of the A neuron group. The

largest group of neurons is the C neuron group, which are the highest threshold and apparently need 4.5 ma (Zabara) for initial excitation, and are apparently not activated by present VNS generators because of their high threshold.

The ability to produce VNS generators reaching 4.5 ma, and beyond, does not appear to be a problem, but there may be a difficulty for the patient in relation to side effects. The vagus nerve does not have pain neurons, but it does have neurons, which can initiate vomiting, and this has been seen, albeit rarely, in present VNS patients. It is possible vomiting would be increased with C neuron activation. However, it was observed that simultaneous activation of both A and C neurons in the cervical vagus did not result in vomiting because A neurons were able to inhibit the vomiting of C neuron stimulation (Zabara).

The second type of side effect is the escape of current into tissues surrounding the cervical vagus, such as the vocal cord, which can cause a temporary spasm of the chord during the stimulation, but often ceases after a period of repetitive stimulation (adaptation or habituation). When the vagus nerve is stimulated (30 s on, 5 min off), a volley of impulses is conducted to the solitary nucleus and, apparently, received as an ordinary physiological process causing synaptic potentials that summate (integrate) within the nuclear region of these neuron synapses. The individual synaptic potentials represent either depolarization (excitation) or hyperpolarization (inhibition), and the individual potentials summate (integrate) into a resultant depolarization (excitation) or hyperpolarization (inhibition) to open or close gates in the nucleus controlling access to the tracts leading to other nuclei in the brain. It is apparent that this is a physiological process and different mechanism from anti-epileptic pharmaceutical (drug) therapy.

Support for this conclusion also emerges from the fact that anti-epileptic drug effectiveness declines with time (and side effects increase), whereas VNS effectiveness can increase with time. Anti-epileptic drug therapy appears to be a simple blocking effect at the nuclei (synapses), whereas VNS can act on regulation to bring back stability. VNS has been disappointing in several therapeutic studies, including obesity, but this may be due to not considering carefully the physiological system or technology.

In obesity, the site of stimulation was moved from the cervical vagus (Zabara) to the diaphragmatic region where the vagus is predominately composed of C fibers. As mentioned, it is unlikely that the generator's current was sufficient to reach the threshold of the C neurons. In addition, the range of thresholds is much larger than for A neurons, which means that to discharge all these neurons requires a significantly higher current. However, the physiological principle of the study was sound in that appetite is reduced (saturation) by vagal feedback from stomach filling by primarily C neuron afferents. Nonetheless, several critical points were apparently missed in that the same C neurons course through the cervical vagus to reach the solitary nucleus, the A neurons in the cervical vagus may be reasonably expected to be sufficient, etc.

The holding pattern with VNS and clinical depression is very unfortunate, given the desperate need for a new therapy, the approval by the FDA, life-threatening potential of clinical depression, etc. But, here again, the physiological system and technology may not have been carefully considered leading to a problem with reimbursement. The inventor-developer (Zabara) was not able to remain close to these projects, but it is questionable if his input would have been considered with so many others present in the present world of biotechnology. There is not a definitive negative in any of these therapies with VNS (and many have yet to be tried) and there are about a dozen companies worldwide with studies on some of them, with about 2000 publications reporting research and studies. It appears that, in terms of medical treatment, this research is oriented towards the reflex response of VNS and not the regulatory state, which determines long-term effectiveness.

It may again be instructive to refer to the brain-heart model in describing the nature of this regulation. The brain and heart are connected by two sets of nerves, the vagus and the sympathetic. There is an ongoing impulse traffic in these nerves that modulate heart activity (frequency and magnitude). This is termed modulation because the heart beats autorhythmically (spontaneously) due to the SA node. Instability and illness result when the SA node loses this autorhythmic regulation and conditions, such as fibrillation, result when individual areas of the heart beat at their own rate where the pumping effectiveness of the heart is lost.

The SA node consists of about 400 neurons (human) that act autorhythmically to initiate a depolarization that propagates through the auricles and ventricles, initiating a rapid sequence of heart muscle contractions. There is a normal variability in the SA node's autorhythmic frequency (HRV), which is a function of vagus nerve modulation, and sympathetic modulation occurs when a substantial increase in heart activity (frequency and magnitude) is necessary (exercise, etc.). Vagal nerve afferents can conduct impulses, which reflect the physiological state of the heart to the regulatory nuclei (mainly in the cardiovascular center), and can be considered as either negative or positive feedback. The vagus can maintain the heartbeat below its "natural" frequency, and the regulatory system initiates an increase in heart rate by decreasing this vagal tone allowing the heart rate to increase. Thus, there is a loop of afferent and efferent neurons where impulse traffic goes back and forth between the brain's cardiovascular nuclei and the SA node, where both the nuclei and SA node are regulatory systems.

The main difference is the nuclei need to communicate with each other to modulate the SA node rhythm. The communication between the nuclei is similar to that in the brain-heart model in that the nuclei have different "natural" frequencies (rhythms) that interact to modulate each other. The natural frequencies are "out of phase" with each other and modulation can either increase or decrease this separation. A new model is introduced now that retains the cardiovascular center but substitutes the respiratory center for the SA node, so that the interaction is between two different nuclei clusters. Each of the nuclei clusters has its own natural

rhythm that modulate each other. The respiratory center acts similarly to the SA node in that it causes depolarization of respiratory musculature including the diaphragm resulting in contractions to expand the lungs. This expansion causes activation of stretch receptors in the lungs producing vagal afferent impulses and an action on the respiratory center to briefly terminate the rhythm allowing the lungs to deflate and be ready for the next respiratory cycle.

Respiratory sinus arrhythmia (RSA) represents an interaction between the cardiovascular and respiratory centers. RSA is a naturally occurring variation in heart rate in a breathing cycle corresponding to inhalation and exhalation. RSA is observed as changes in the R-R interval (ECG) in a respiratory cycle and can be used to determine the degree of vagal cardiac regulation. This demonstrates the relationship between nuclei in the brain and the interconnecting neurons that modulate their natural rhythms. A resultant rhythm can emerge from many different groups of nuclei as observed in cortical nuclei with the EEG. VNS can modify the EEG only in an abnormal state of the brain because it acts to restore regulatory stability. Based upon these observations and physiological mechanisms underlying VNS, it has become possible to develop a new treatment biotechnology that may include VNS (Zabara) and be a part of the neurocybernetic prosthesis.

VNS acts indirectly on brain nuclei and it was important to develop a technology, which could act directly on these nuclei without, physically or chemically, having to penetrate into the brain (causing side effects). The best technology for this appears to be based on electromagnetism and studies have been done on its safety.[9,10] For instance, magnetic resonance imaging (MRI) is safe as based on these studies to almost 4 T, and future studies may demonstrate an even higher threshold. The electromagnetic field acts here to depolarize or hyperpolarize neurons in a similar manner to the action of VNS; however, there is a fundamental difference. Whereas the solitary tract nucleus "sees" action potentials entering in the usual physiological manner, this is not the case with an electromagnetic field imposed on neurons in the brain that may be responded to as a foreign element. This would be similar to a pharmaceutical treatment where the efficacy decreases with time, therefore, a closer look at the technology and its effectiveness is warranted.

The electromagnetic field is developed by a current through a coil held over a scalp region overlying the brain area and its nuclei. The electromagnetic field is a function of the frequency and magnitude of the current and the diameter of the coil. The electric field produces a polarization or hyperpolarization of the nuclei at their synaptic membranes that can increase or decrease the synaptic potentials or their rhythmic oscillations. Stability in regulation can be achieved by a maintained depolarization or hyperpolarization of the membrane potential. Thus, regulation is related to a specific value of the membrane potential that can be varied over a range of values dependent on physiological requirements.

A form of magnetic therapy called transcranial magnetic stimulation (TMS) has been studied for many years for clinical depression and has recently been approved by the FDA (as premarket approval is not necessary), where a magnetic coil is usually placed over the scalp in the region of the left temporal lobe. In 1985, Barker et al.[11] at the Royal Hallbamshire Hospital demonstrated nerve impulse conduction from the motor cortex causing hand muscle contraction and it has been utilized as a diagnostic procedure. Single or paired TMS causes cortical neurons to discharge action potentials, repetitive TMS (rTMS) produce longer lasting effects that persist past the period of stimulation, which is a consequence of synaptic changes akin to long-term potentiation or long-term depression. TMS correlates with functional MRI or magnetic electroencephalography study results. TMS is relatively safe, but its main risk is the rare occurrence of an induced seizure. TMS current is limited to the cortex or slightly deeper. TMS studies appear to show that the antidepressant effect diminishes after the stimulation is terminated, and portable devices do not deliver sufficient current at present to continue the treatment, so that the question remains as to its effectiveness.

A solution is technology that combines vagal nerve modulation with magnetic modulation therapy (MMT) and may produce a long-term and more rapid effectiveness than with VNS alone (absence of seizures and sub-cortical treatment [Zabara]). There have been a number of studies of TMS for seizure treatment based on the observation that epilepsy is an altered balance between excitation and inhibition at the cortex and the hypothesis that rTMS can modulate the excitability of cortical networks.

Positron emission tomography (PET) blood flow studies demonstrated multifocal, bilateral activation from unilateral motor cortex activation, showing that changes in the nuclei rhythm of specific nuclei can affect other nuclei extending bilaterally, which would be an essential basis for a treatment modality. However, in a controlled study,[12] the effect of TMS on seizure frequency was mild and short-lived. A technology combining vagal nerve modulation with magnetic modulation therapy could substantially improve treatment effectiveness by amplifying and extending brain nuclei involvement (Zabara). This technology, vagus nerve stimulation with magnetic modulation, may be the next advance in the neurocybernetic prosthesis and increase its treatment potential appreciably.

It may be important to pause here to evaluate the potential of a cybernetic prosthesis because it takes a major effort and tens of millions of dollars for research and development; most of the cost is in relation to the clinical trial specified by the FDA, who usually considers the pharmaceutical approach as primary. The FDA mandated that the neurocybernetic prosthesis (for epilepsy) be used only after several anti-epileptic medications had been found to be ineffective (and surgery not indicated), so, in essence, only patients who had been refractory to other approved therapies. Is this sufficient for the stockholders of a company (Cyberonics) to maintain their investment allowing the treatment to go forward? There are approximately 70,000 patients at present with VNS, which represents about 10% of patients with refractory epilepsy after about 25 years of effort of Cyberonics and more of the inventor-developer (Zabara). By the criterion of number

of employees, Cyberonics has been successful, from six to about 600, although 10% appears to be a minimally successful result. This is not all due to an anti-epileptic medication being the primary treatment. There is also the question as to the management of the company, etc. Being the last approved therapy usually to be considered puts a higher burden for successful therapy on VNS. An argument is made that a patient who has experienced seizures for many years is more at risk for failure (VNS) than a relatively new patient. It is probably true that the most successful bioelectromagnetic therapy is the cardiac pacemaker, although there are several highly successful diagnostic electromagnetic technologies (MRI, etc.). From these considerations, and others, it appears that although the risk is high, the potential for a cybernetic prosthesis is also high and may be achieved in the near future.

These conclusions may be true for bioelectromagnetic therapies in general, but it is necessary to extend scientific proof into the arena of the FDA, National Institutes of Health (NIH), clinical societies, biomedical companies, etc., and different criteria of approval in each, all claiming to be scientific and rigorous. The new technology of the NCP should be evaluated with these factors in mind. Magnetic stimulation generally refers to nerve stimulation, and one well-known diagnostic technique is TMS.[13]

TMS can stimulate the human cortex (brain) noninvasively by using inductance to transmit electrical energy across the scalp and skull without the pain of direct percutaneous electrical stimulation. It involves placing a coil of wire (of various compositions) on the scalp and passing powerful and rapidly changing current through it. This produces a magnetic field that passes unimpeded and painlessly through the tissues of the head. The magnetic field, in turn, induces an electrical current, primarily limited to the cortex. The strength of the induced current is a function of the rate of change of the magnetic field, which is determined by the rate of change of the current in the coil. In order to induce a current in the cortex (which is effective), the current must start or stop or reverse its direction within a few hundred microseconds.

MMT comprises applying a magnetic field to the brain (cortex) to change the polarization level of at least one nuclei cluster (synapses). One or several magnetic coils may be applied to different nuclei clusters or focused on the same nuclei cluster. The magnetic coil(s) may be connected to a generator with switching elements, capacitors and sensing elements. This NCP includes both VNS and MMT, vagus nerve and magnetic modulation therapy (VNAMMT). An increase of effectiveness can be achieved because VNS acts directly sub-cortically, whereas MMT acts directly on the cortex. A magnetic field may be a pulsed magnetic field, an alternating magnetic field, or a steady magnetic field (for special purposes). The magnetic field may be concentrated on certain brain nuclei by orienting the magnetic coil(s) appropriately.

Applying a magnetic field can produce a positively directed induced current to cause a positive polarization (hyperpolarization). The hyperpolarization may cause a decrease in frequency in certain nuclei of the cortex, with a tendency to synchronization. Applying a magnetic field can also cause a negatively directed induced current to produce a negative polarization change (depolarization), initiating an increase in nuclei rhythm frequency and desynchronization. The depolarizations can be below threshold for neuron discharge and still produce the nuclei rhythm frequency changes.

MMT can incorporate VNS by including a computer-based subsystem that couples both for an integrated system programmed in terms of a specific treatment regimen. A plurality of magnetic coils arranged in different spatial planes can focus an increased current for specific nuclei. A central axis of a magnetic coil may be positioned perpendicular (or parallel) to an imaginary line defining a nuclei cluster.

The MMT subsystem includes a configuration of switches and storage capacitors. The switches may include solid state thyristors capable of switching energy stored in the thyristors. The VNS subsystem may include monitoring a physiological response of the patient to the electromagnetic modulations (EEG, heart rate, etc.) and a controller for parameters and operation of the system. The magnetic field is produced by charging the storage capacitors and discharging into the magnetic coil(s). The magnetic field may induce a biphasic, damped current that acts on the nuclei rhythms by synaptic polarizations. This effect is a function of the size (diameter), geometry, composition, and current parameters (coil). Focusing of the magnetic field may occur naturally by induced charges at the synaptic membrane (also produced by VNS effects). Focusing may be aided by placing magnetic or paramagnetic material at selected nuclei. The current in the coil can be increased by ferromagnetic substances.

The nuclei consist of synaptic areas including cell bodies, dendrites, and presynaptic terminals where there is a membrane potential but no action potential, therefore, no threshold exists, as it does for the action potential. Synaptic membranes are modeled as a resistor and capacitor in parallel. The product of the resistor value and the capacitor value determines the time constant of the synaptic membrane. A change in membrane voltage is proportional to the applied charges if the rise time is short enough and the duration is equal to or less than the time constant of the synaptic membrane. Each nucleus has its own average time constant that can determine the frequency and magnitude of the nuclei rhythms and MMT can address. The synaptic areas are more sensitive to induced currents than axonal regions; therefore, lower currents can be used during MMT than are necessary to activate axonal action potential. VNS and MMT may be administered to reach their polarization result almost simultaneously. Thus, VNS can be administered prior to MMT to take into account nerve conduction time, etc. However, there are instances where it is desirable to administer VNS and MMT with different temporal projections. One result of this would be to lengthen or shorten the polarization effect. In addition, it may be desirable to create a frequency effect by alternating VNS and MMT in a series of electrical and magnetic pulses.

There are many possible combination patterns for administering VNS and MMT that depend on the specific disease

and condition of the patient. Therefore, VNS and MMT can mutually augment the therapy to increase overall effectiveness. In some cases, it may be better to wait to initiate MMT until a certain clinical outcome is achieved and then initiate VNS for optimal effectiveness, or do the reverse. Using MMT in conjunction with VNS may not only increase effectiveness, but may reduce the time taken to reach effectiveness.

In epilepsy, it may take many months in some patients with VNS alone to achieve a maximal possible effectiveness. If a patient is observed to be slowly responding to VNS (or perhaps not responding), then a program of MMT in conjunction with VNS can accelerate therapeutic effectiveness. MMT and VNS offer a much better side effect profile than electroshock therapy in clinical depression. MMT may be provided to produce a rapid effect, which then can be prolonged by VNS in combination. The balance between VNS and MMT can be adjusted depending on the patient and the nature of the illness.

It is possible to extend research, development, and treatment beyond the nervous system, where a more general designation is appropriate, that is, the biocybernetic prosthesis (BCP) and the treatment as biocybernetic modulation (BCM). Research on BCM is beginning to reveal what might be called a bioelectromagnetic basis for cancer (Zabara). This sounds somewhat dubious, as the overwhelming effort has been to develop anticancer drugs that represent a chemical reaction, but please note that a chemical reaction is essentially an electrical action between molecules. The question is whether it is possible to directly determine an electrical effect in cancer cells, or, more specifically, to kill cancer cells or reset regulation to that of a normal cell.

The discussion here will be limited to a statement of the problem and a description of the experimental model. The problem of cancer is related directly to cell regulation or differentiation. A normal cell during its differentiation can undergo a fundamental change that converts to a malignant state of regulation. It is released from various restraints that held cell division in check and proliferates wildly to produce billions of altered cells that constitute the tumor. Uncontrolled growth is just one feature the cell acquires when its regulation transforms the cell into malignancy. The cell also gains immortality in that it can multiply indefinitely in cell culture, unlike normal cells that lose the ability to divide after about 50 cell generations and then die. Cancer cells also become less responsive to feedback mechanisms in normal cells.

In culture, normal cells form a neat, single cell layer, but cell division shuts down when the entire surface of the dish is covered. Conversely, malignant cells are not confined to the orderly single layer, but they grow on top of one another in disordered piles, so that cell division is not shut down in the presence of other cells. The cancer cell has lost this property of contact inhibition that is based on the extent to which cells can spread. A cell that is able to spread out on a surface has a shorter growth cycle. The rate of protein synthesis decreases in the more rounded cell (even in the absence of contact). Cancer cells, even when they cannot spread, still appear unaffected and continue to proliferate. This may be related to the membrane potential whose value may have been changed from that required for normal growth. The membrane potential is partially dependent on the membrane protein configuration and charge. It appears reasonable to conclude that restoration of the normal membrane potential would at least be one basis resetting normal regulation (and contact inhibition). Such a partial list of changes accompanying the malignant transformation indicates that the cellular control mechanism has been altered profoundly in the transition from the normal to the cancerous state.

There is reason to suspect that the membrane potential is an important component of the control mechanism and the return of the normal membrane potential would signal a reversal in the malignant process. The side effects of the major cancer treatments (chemotherapy, radiation, surgery) at present cause strict limitations on the use and scope of these treatments. The American Cancer Society data of 1986 indicated that in the USA, the incidence of new cases of cancer was 956,000 and 478,000 cancer deaths, a worldwide incidence of new cases of about 7.2 million and 4.9 million cancer deaths, while the worldwide prevalence of cancer is about 15.1 million. Approximately, one of three persons in the United States will contract cancer.

The major approach to viral infection (HIV or AIDS, etc.) is vaccination that is specific and allows very little defense against a sudden epidemic. Similar to cancer, a component of the disease mechanism is a change in the membrane potential. It is important to have an experimental model to demonstrate changes in the membrane potential and how it is possible to proceed in the development of the biocybernetic prosthesis. Thus, an animal tissue model may be utilized to demonstrate the electrical manifestations of a cancer cell or viral infection, and the difference from the normal cell. This is important because, with the exception of nerve and muscle cells, there is virtually little that is known, studied, or investigated with regard to the electrical differences between normal and cancer cells or viral infection. The experimental model is structured to measure electrical properties of the cancer, or infected, cell and compare these to the normal cell, and provide the observations necessary for the development of the biocybernetic prosthesis.

To begin, a viral infection (and cancer process) is initiated in a cellular population of several thousand cells by the virus pseudorabies (herpes simplex). Specifically, the superior cervical ganglion of the rat is infected by inoculation (the eye), and at the sign of symptoms (scratching around the inoculation site) the superior cervical ganglion may be removed with lengths of its presynaptic and postsynaptic nerves and placed in a controlled environment. Electrical potentials are recorded as a result of aggregate membrane potential changes that are observed as pre- and postsynaptic potentials. The mammalian ganglion does not initiate these synaptic potentials under any other condition but this infection. Replication is that of viral entities (the neuron does not replicate), and the progress of the replication is observed in the changes in the synaptic potentials. There is also a glioma of the glial cells in the synaptic area. There is a ganglionic

synaptic rhythm similar in some respects to the seizure rhythm of the patient's EEG. For instance, the ganglionic synaptic rhythm is synchronous and of relatively high voltage. The frequency and voltage increase with time in correspondence to viral reproductive rate. A single component of the rhythmic oscillation lasts about 250 ms and represents a large membrane potential, essentially equal to the resting membrane potential, followed by repolarization and hyperpolarization (lasting about 30 ms).

The observation that this cellular and membrane activity is from isolated tissue indicates it is not initiated by the environment, but is due to the cancerous or infective process. This electrical activity is not present in the normal cellular tissue, even if the normal tissue is isolated in the same way (*in vitro*). This indicates that the regulatory system of the cancer or infected cell no longer relies upon an external component and can be independent of external influence.

It is commonly believed that the cancer cell proliferation is a chaotic event and free of regulation, but the genetic mutations appear to be the basis of a regulation, which, although pathological in effect, still determines the proliferation of the cancer cell. If the infected tissue is left in place in the animal, but simply isolated chemically or surgically, the synchronized membrane potential oscillations appear after a lag time of approximately a minute. This allows an input from the brain or spinal cord (in this tissue model) to prevent the appearance of these oscillations. However, over an extended period, the oscillations will emerge (after several hours or more) even in an intact preparation, indicating eventual dominance of the pathological regulatory system.

The initial phase in the cancer cell's development is called promotion and is generally accepted to be reversible. Thus, it appears that the initial phase represents the brain's control by hyperpolarization (or other electrical means) of the synaptic membrane potential until genetic control in the synaptic region (where the DNA resides in the cell body) is fully achieved by viral action. The remaining phase of the cancer cell's development is called progression and id considered to be irreversible. In the superior cervical ganglion model, this phase is correlated with an increase in the frequency and voltage of the synchronized synaptic oscillations. Significantly, the hyperpolarization indicated at the termination of the single oscillatory potential in the early phase is absent in the late phase of multiple oscillations. This observation supports the hypothesis that synaptic membrane hyperpolarization can help maintain the cell's normal regulatory system during a challenge from a cancerous or infective process. Obviously, more must be involved and this will be pursued in further studies with this experimental model.

The neurocybernetic prosthesis (and VNS) has presented a number of new insights into the nervous system and possible conclusions. Langley concluded over 100 years ago that the autonomic nervous system was separate in structure and function from the somatic-motor system and dealt exclusively with the internal environment of organs and tissues, whereas the somatic-motor system dealt with the external environment of stimulation and behavior.

Results with the NCP (VNS) indicate that in relation to regulatory systems there is virtually no difference between the autonomic and somatic-motor nervous systems. The neurons of the vagus nerve (approximately 90,000) are involved primarily with regulation and to a much smaller extent with stimulus-response (reflex).

Many years ago, Lashley demonstrated a mass effect in the brain, but the primary concept of brain centers still prevails. The NCP (VNS) indicates that Lashley had the better approach in that regulation is based on brain nuclei interaction and is the prevalent process with stimulus-response secondary. Wilder Penfield electrically stimulated specific points in the motor and sensory cortex eliciting rudimentary responses, such as a muscle twitch, which elicited the conclusion that these points were centers controlling complex motor and sensory responses and were fixed regions. Although this is possible in terms of stimulus-response, it is apparently not possible with a complex regulatory system with a range of set point interactive dynamics.

Another insight, which is perhaps the most novel, is that the autonomic nervous system (VNS) can affect and stabilize the conscious state. This was observed in both epileptic and clinically depressed patients. In an epileptic patient becoming unconscious (seizure state), it is possible to return the patient, within a minute or two, to an alert, conscious state by VNS. Some patients will perform a complex behavior without being aware or remembering it. Were these patients conscious while they were performing this behavior? They were not in an alert, conscious state, so their regulation had shifted, possibly into a state where memory was not possible (sleepwalking). It is possible for VNS, by acting almost simultaneously, to reverse this state to alertness (Zabara). These observations may begin to explain why VNS can be effective in both epilepsy and clinical depression. For instance, the EEG magnitudes appear to be the reverse of each other, high in epilepsy and low in clinical depression. However, the brain states may be almost the same under similar conditions of unconsciousness (and instability). Again, the conclusion appears to be that VNS acts to restore stability in brain regulation.

However, it may be important to report another observation in this regard. In patients with epilepsy, it is possible to elicit a seizure (either overt or EEG) by rapid flashes of light (strobe lamp) at a certain frequency. The nuclei in the visual cortex are driven at a frequency (synchronously), which then drive the unstable nuclei rhythm (motor cortex, etc.) precipitating the seizure. The neural receptors are tuned to specific types of physical energy and may provoke a corresponding sensation, which appears to play out on a conscious state. It in this relationship of sensation to the conscious state that VNS may prove to be helpful in certain patients.

Substance addiction, including drugs and alcohol, is an illness. Addiction generally begins with the voluntary use of one or more of these substances. With extended use, the ability to abstain from the substance becomes very difficult and withdrawal symptoms occur that might, in certain cases, be life threatening. The symptoms can include nausea, vomiting, fever, dizziness, morbidity, etc., and decreased ability to

obtain recovery, resulting in serious health problems. VNS may be able to treat both the health problems and the withdrawal symptoms. Various nuclei clusters appear to be associated with specific addictions: a mesolimbic system with stimulants and cocaine; the locus coeruleus with opioids; the basal ganglia with compulsive problems; the orbitofrontal cortex with high-risk behavior; the amygdala with relapse; and the prefrontal cortex with stress.

The circadian rhythm appears to be directly related to these problems in that it appears to become disturbed or unstable. VNS may be able to reset the rhythm again to the light-dark cycle of about 24 h. Tracts from the solitary tract nucleus project to the amygdala, locus coeruleus, orbitofrontal cortex, and basal ganglia and VNS can open up the gates in the nucleus for these tracts. The circadian rhythm links these nuclei with others in a sequential regulation of organs and tissues. At present, most substance addictions cannot be cured, and relapses may remain a constant problem.

In summary, VNS (and cranial nerve stimulation) and NCP have been used to treat a number of illnesses and health problems involving brain nuclei, including epilepsy, movement disorders, neuropsychiatric disorders (clinical depression), dementia, migraine, obesity, eating disorders, sleep disorders, cardiac conditions (congestive heart failure and atrial fibrillation), hypertension, endocrine disorders (hypoglycemia and diabetes), and chronic pain. VNS and NCP have led to a new working hypothesis of brain self-regulation where research and medical treatment are intertwined, and a possible new treatment for cancer and infection. Despite the recognition that VNS and NCP may be an appropriate treatment for the foregoing conditions, and perhaps others, prediction of efficacy for a particular disorder is difficult because of limited bioelectromagnetic information. If development of VNS and NCP treatments continues, this limitation will be overcome, and a new medical breakthrough may occur. It has taken several hundred years of intensive effort for pharmaceutical therapy to achieve its dominance while bioelectromagnetic therapy is still in its infancy.

HISTORICAL ORIGINS

Galvani discovered "animal electricity" in nerves and muscles, but Volta took the position that the electricity was external to nerves and muscles and, on this basis, invented the voltaic pile battery that initiated, following Newton's Principia and Optics, a great development of physics resulting in most of our contemporary research and technological breakthroughs. VNS and NCP have attempted to bring together again these two diverging efforts into a seamless structure where both can be investigated simultaneously.

In an effort to demonstrate that lightning was a similar electric spark as Franklin had proposed, Galvani suspended frog legs with brass hooks from an iron railing during a thunderstorm and observed that the muscles contracted coincident with a lightning strike. Franklin utilized static electrical accumulation (Leyden jar, etc.) to stimulate nerve and muscle through the skin. This was developing beyond the semi-mystical concept of animal electricity, which led to many false claims of "electrical" cures. Franklin classified electricity into two categories (plus and minus) with attraction between opposite signs and repulsion between like signs. Even quantum electrodynamics has not developed a basis for electromagnetism beyond this.

Galvani suggested correctly that the frog's muscles were generating electricity similar to a small Leyden jar stored with electricity and proposed correctly that an external charge caused a flow between inside and outside due to the attraction of unlike charges, causing the muscle to contract (or the nerve to discharge). It is amazing that Galvani with virtually no technology developed a scientific principle that is still valid. Volta confirmed that applying two different metals to nerves caused contraction of their muscles. However, Volta rejected that there were electrical phenomena in muscles and nerves, and he built an electrical storage pile consisting of combinations of two different metal discs separated by cardboard soaked with acid or salt. This is still the basis of the wet-cell battery and was the first technology to generate a sustained electrical current leading to our present electromagnetic systems.

Humboldt demonstrated that electrical flow mediated by moist tissue contact with dissimilar metals and that generated by animal tissue were two genuine but different phenomena. However, with the invention of the cathode ray tube, it was observed that both had the same basis in electricity, and physics and biology merged.

The present technological era can be said to have emerged in 1786 when Galvani did his fateful experiment. Can a biological experiment today result in an observation with such profound effects for physics, biology, and technology? Although much is known (membrane and action potentials and their ionic basis, etc.), there are presently intensive studies to determine the exact mechanism of the brain's regulatory systems where new observations might spark such remarkable developments.

The observations of Galvani and Volta, and later Helmholz, initiated electrical currents (stimulation) as a general method of research, which has now given rise to VNS and NCP. Whether, in addition to research and treatment, VNS and NCP have fundamental consequences for physics and technology and medicine remains to be seen. For instance, the source of energy to pump ions is still not clear. The first step taken towards brain regulation was by Sherrington when he stated, "the whole quantitative grading of the spinal cord and brain appears to rest upon mutual interaction between the two central processes, 'excitation' and 'inhibition', the one no less important than the other." These received an electrical basis in depolarization and hyperpolarization of the membrane potential. At the synapse (Sherrington), the action potential gives rise to an interactive phase of excitation or inhibition of adjacent neurons.[14] For VNS, the initial synapses are in the solitary tract nucleus where vagal neurons terminate. This, and other nuclei, may resemble computer chips in that they are components of an integrated regulatory system that coordinates organs, tissues, and functions.

Thomas Willis presented the first coherent and scientific description of depression, which he called melancholia and suggested that the "animal spirits" ran up a sensory nerve and down a motor nerve. Newton wrote "all sensation is excited, and the members of animal bodies move at the command of the will, namely, by the vibrations of the spirit, mutually propagated along the solid filaments of the nerves, from the outward organs of sense to the brain, and from the brain into the muscles." By combining "will" and "spirit" and merging them into a bioelectromagnetic basis, we may arrive at a mechanism for brain self-regulation. This is where the matter rests.

Magnetic nuclear resonance was apparently discovered and developed to determine crystal atomic structure but was later ingeniously developed as MRI by Dr. Raymond Damadian as an important diagnostic tool in pathological processes. The EEG was invented by Hans Berger in Austria and used extensively as a diagnosis of epilepsy. The ECG, PET scan, etc., are other diagnostic tools, but bioelectromagnetic treatments have lagged far behind these diagnostic instruments, perhaps because of the dominance of pharmaceutical treatments.

The cardiac pacemaker is probably the most prevalent of present bioelectromagnetic treatments, but the electrical design is very simple compared to the sophistication of the MRI. For example, the electrodes, or wires, are placed directly into, or on the surface of, the heart muscle, which bypasses brain regulation of the heart (this has been partially corrected by development of the rate pacer). It would seem to be an improvement to aid the heart with the NCP (or enhanced VNS) that allows brain regulation to continue to act. The idea here would be the same as in epilepsy where repetitive nerve modulation allows brain regulation to return after a period of instability.

Apparently, 45% of cancer patients are "cured" by surgery and 5% by chemo radiation (inonizing radiation), where this therapy is aimed at destruction of the cancer cells. The biocybernetic prosthesis would act to return the cancer cell to normal regulation. Josiah Willard Gibbs and Norbert Wiener have the distinction of developing scientific fields in the USA, statistical mechanics, and Cybernetics, both dealing with regulation. The cyber suffix has been applied to numerous emerging electromagnetic technologies since about 1950 whether or not the companies so-named, or their technologies involved regulation. The technologies appeared to be purposeful in their action and could perform without direct human control (emergence of artificial intelligence). Norbert Wiener attempted to analyze this electromagnetic technology and its effects long before it had arrived.[15] It remains to channel this amazing repertoire of electromagnetic technology (and its descendants) into Wiener's, perhaps utopian, vision. Wiener might approve of VNS and the neurocybernetic prosthesis and, if so, this chapter is dedicated to him.

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24 Clinical Application of Biophysical Stimulation on Bone in Europe

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CONTENTS

The employment of physical energy to modulate osteogenetic response and, ultimately, to enhance fracture healing is a topic widely researched in Europe. Interest in the relationship between biological systems and electrical energy can be dated back as far as the studies by Galvani[1] and Matteucci (1811–1868) who, already in the nineteenth century, had identified the lesion currents and had perceived their role in repair processes.

In the last century, the studies performed by Fukada and Yasuda[2] and by Bassett and Becker[3] identified the relationship between mechanical loading and electrical activity in the bone, wherein lie the scientific origins of the electrical, magnetic, and mechanical stimulation of osteogenesis.

These methods have been approved for clinical use by the U.S. Food and Drug Administration (FDA) and are employed in many countries to promote and reactivate the formation of bone tissue. The electrical, magnetic, and mechanical stimulation of osteogenesis belongs to bioengineering and biophysics.

The above studies have clearly identified the relationship between bone tissue mechanical deformation and electric potentials. Since then it has become clear that bone generates two types of electric signal: (i) in response to mechanical deformation; and (ii) in the absence of deformation.

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ELECTRICAL SIGNAL IN THE PRESENCE OF MECHANICAL DEFORMATION

Structural deformation following the application of a load to the bone, not necessarily vital, generates an electrical signal that can be ascribed to a dual origin:

1. *Direct piezoelectric effect*: The signal measured on the bone surface deformed by a load can be attributed to the piezoelectric properties of the collagen matrix only when the bone is dehydrated. The signal is generated by the asymmetric redistribution of the molecular charges resulting from mechanical deformation.[4,5]
2. *Electrokinetic phenomenon of the flow potential*: In physiological conditions, the electrical signal induced by mechanical deformation can be imputed to the electrokinetic phenomenon occurring when ion flow occurs within haversian and endocanalicular spaces.[5–8]

Independently of the mechanism, piezoelectric or electrokinetic, by which it is generated, the electrical signal induced by the mechanical deformation, containing the information

on site, direction, and amplitude necessary to modulate the bone remodeling, has been considered to be the transducer of a physical force in a cell response. It is, indeed, intelligible from the cells, as is proved by the cellular effects that can be activated by exogenous electrical signals similar to the endogenous ones.[9] The aforesaid electrical signal has thus been taken to be the mechanism that determines the continuous adaptation of the mechanical competence of bone, according to Wolff's law.[10]

ELECTRICAL SIGNAL IN THE ABSENCE OF MECHANICAL DEFORMATION

In the absence of mechanical stress, vital bone generates an electrical signal detectable *in vivo* as surface stationary bioelectric potential and *ex vivo*as stationary electric (ionic) current that can be measured.

1. *Stationary bioelectric potential,* measured *in vivo*, in intact bone, displays a characteristic distribution with an electrically negative area in the metaphyseal site[11–14] and epiphyseal growth cartilage.[12] When the bone is fractured, the fracture immediately alters the typical distribution of the bioelectric potentials, inducing an electrically negative area at the site of the lesion.[11,15] It is thought that the lesion generates an electrical signal because it alters the different ion distribution between endocanalicular fluid and systemic extracellular fluid. The electrical signal at the site of the lesion has been ascribed to the endosteal cell layer.[16] Nevertheless, the electrical contribution from the concomitant muscular lesions[16] and cutaneous lesions[15] cannot be disregarded.
2. *Stationary electric (ionic) current* is detectable *ex vivo* on bones immersed in a physiological solution. The ionic current induced by a transcortical lesion enters in the site of the lesion.[17,18] The fracture exposes the endocanalicular ionic fluid to the external plasma environment, and thus, the cellular system deputed to maintaining the bone-plasma ion gradients is activated.[17,19]

Despite the different experimental conditions of detection, both the electrical signals induced by mechanical deformation and those generated by vital bone have been interpreted as local control factors of bone remodeling/modeling and reparative osteogenesis. Ever since the first detection of these signals it has been held that inducing them in bone by means of external generators could be of clinical importance, particularly in situations where repair processes have remained incomplete.[9,11,17,20–23]

In the research sector involved in the histophysiology of bone tissue, the above observations regarding the relation between bone tissue and electric potentials have aroused great interest in the possibility of active intervention, with physical stimuli (exogenous electrical, magnetic and mechanical stimulation), on bone cell metabolic activity, in particular that of pre-osteoblasts and osteoblasts. A number of experimental studies have shown how and to what extent, in various animal models, it is possible to enhance endogenous bone repair by applying physical stimuli. The effectiveness of biophysical stimulation is already well documented and it rests on solid scientific bases, as is proved by the results of *in vitro*[24–29] and *in vivo*[23,30–34] studies. It has, indeed, been possible to quantify the effect of electrical stimulation on the mineral apposition rate, which increases by 80%.[35,36]

Today, electrical, magnetic, or mechanical stimulation must be framed within a more extensive sector of orthopedic therapy: clinical biophysics, which deals with the study of the nonthermal effects of nonionizing radiation—effects mediated by a specific interaction of the physical agent with the structures of the cell membrane. Even though the final effects are the increase of osteogenetic activity, the pathways of the cell membrane through which this effect is achieved differ according to the energy employed: voltage gated calcium channels for capacitive coupling, intracellular calcium stores for inductive coupling and, lastly, inositol phosphate for mechanical stimulation.[26]

In humans, electrical, magnetic, and mechanical stimulation is used to speed fracture healing and to finalize bone repair in failed unions, such as delayed unions and nonunions. Research performed up to now has enabled evaluation of: (i) the different effectiveness of methods of applying electrical, magnetic, and mechanical stimulation to bone tissue; and (ii) modalities, times, and doses needed to obtain a positive influence on osteogenesis.

In Europe, research on the possible application of physical energy to bone repair processes has been ongoing throughout the past century: study has been made of the effects of electrical current directly applied (faradic) to the fracture site, of the employment of magnetic fields (inductive) and electrical fields (capacitive), and of the use of ultrasound to produce mechanical stimulation (ultrasound).

Analysis of the Methods

There are various mechanisms of action by which osteogenesis is enhanced through application of biophysical stimuli with the four methods described above.

DIRECTLY APPLIED ELECTRIC CURRENT: FARADIC SYSTEMS

The direct action of continuous electric current manifests both with purely electrical phenomena, which affect the dynamic of the ions at the site of the fracture, and with chemical-type phenomena, which lead to a reduction in the local tension of oxygen and a small increase in pH. Furthermore, the positioning of the electrode, by means of a small surgical intervention, determines a mechanical stimulus that may interfere with the osteogenetic processes. With the faradic systems the electrical tensions applied to the bone tissue are of various entities,[37] but in any case greater than those applied with inductive or capacitive systems.

The therapeutic effectiveness of the continuous electric current depends on its intensity. Values of electric current ranging from 2 to 20 μA/cm^2 are considered optimal for stimulation of osteogenesis. As regards application, the current is utilized 24 h per day; the negative pole must be positioned very precisely in the site of the fracture where stimulation of the osteogenetic response is desired, and the positive pole is placed in contact with the soft tissues, far from the site.

Values of applied current below 2 μA/cm^2 are ineffective, while currents of over 50 μA/cm^2 may cause necrosis of the tissue. For this reason, the apparatus employed in clinical practice is limited in tension (typically below 2.3 V).[37]

As regards the European experience, Traina and Gulino[38] proposed using as a cathode an endomedullary nail covered with insulating material, excluding the part near the fracture site, with the anode placed on the skin. The method was first tested on animals and was then employed on some patients, but further developments were limited, if not hindered, by technical problems connected with the difficulty of soldering the electric cable to the endomedullary nail.

Again, in the context of faradic stimulation, Jorgensen[39] suggested using the pins of the external fixators as electrodes, the proximal and distal ones respectively nearer to the fracture site. Statistical analysis reveals 30% acceleration in healing in the electrically treated group. Healing required 3.6 months in the control group and 2.4 months in the stimulated one ($p < 0.001$). Nevertheless, the method leaves unsolved problems of a theoretical kind in relation to its working, for the administration of the electric current to the pins (which are electrically insulated with respect to the frame of the external fixator) should be mainly distributed to the soft tissues, in consideration of the greater electrical resistance offered by the bone tissue.

Zichner[40] developed an implanted stimulator (FKS), with implant of the cathode in the fracture site and the anode in soft tissue or medullar cavity. The battery is housed in a capsule also implanted. Fifty-three patients out of 57 suffering from nonunion healed in 5.3 months on average.

In Europe, unlike in the USA, faradic techniques have never had much following, nor have they been applied beyond small series generally performed for purposes of research.

ALTERNATING ELECTRIC CURRENT INDUCED BY ELECTROMAGNETIC FIELDS: INDUCTIVE SYSTEMS

As regards pulsed electromagnetic fields (PEMFs), inductive methods: the biological activity may occur by means both of the magnetic component varying in time and of the electrical component, that is, the induced electric field. These are signals with a complex waveform, whose predominant spectral content ranges between a few tenths to a few ten thousandths of Hertz. To explain the biological effects of electromagnetic fields, mathematical models have been proposed: cyclotronic resonance, ligand-receptor interaction, and stochastic resonance. The first two have received most attention and they appear to be compatible with experimental results.[24,41] The cell membrane is the main site of interaction of PEMFs and the most favored candidates are the membrane receptors and Ca^{++} channels.[25,26] Experiments *in vitro* have shown that PEMF exposure increases the proliferation of lymphocytes, osteoblasts, and chondrocytes.[28,42,43] Furthermore, it has been described that electromagnetic stimulation of human bone cells recovered from a nonunion site increases the expression and release of TGF-β1.[27] *In vivo*, authors have observed an increase in the formation of bone tissue[29] and a shorter healing time of experimental fractures and/or bone lesions.[33–35,44]

All authors agree that there is a direct link between the specificity of the electromagnetic signals and the effects observed in bone tissue.

For both clinical and experimental applications, use has been made of signals with frequency of repetition rate ranging from 2 to 100 Hz, with spectral content up to 100 kHz, with intensity between 0.1 and 30 gauss of magnetic induction (10 G = 1 mT) and with induced electric field from 0.01 to 10 mV/cm. More limited findings have been reported with magnetic fields of greater intensity, up to 200 Gauss.

An inductive technique was initially applied to human pathology in 1972 in Garmisch by Kraus and Lechner,[45] who were the first to report the effect of an electromagnetic field on the healing of failed unions. The technique involved the implant in the fracture site of an electrical circuit. The method entailed three variables: surgical operation to implant the receiving circuit, an internal synthesis device to stabilize the fracture site, and the external time varying electromagnetic field used to induce an electrical current in the implanted circuits. In the outcome, it never became clear which of these factors was responsible for the healing.

The 1980s witnessed widespread development throughout Europe of the noninvasive methods of stimulation. Interest in the inductive systems had also been aroused by the results of studies performed by Bassett in the USA, contributing to the collection of a vast clinical experience of undoubted scientific value.[46]

On the one hand, some clinicians have enlarged the American experience by developing a series of investigations by utilizing the EBI method. On the other, new and effective signals have been studied and clinically validated in Italy, UK, and the Netherlands.

ALTERNATING ELECTRIC CURRENT INDUCED BY ELECTRICAL FIELDS: CAPACITIVE SYSTEM

With this noninvasive method, the biological effects are linked with the sole presence of the time-varying electric field. The literature on these systems[47] is certainly not as abundant as for the inductive systems. The site of interaction of the electric field lies at the level of the cell membrane; an increase in Ca^{++} transport across voltage-gated channels is observed followed by an increase in cell proliferation. Furthermore, the exposure to electric field of osteoblast-like primary cells increases the synthesis of bone matrix and favors their proliferation and differentiation.[26,48] In experimental fractures

in vivo, produced on rabbit fibula, a significant shortening of healing time has been observed.[31]

The method entails the use of electrodes placed in contact with the skin by means of conductive gel. The voltage applied ranges between 1 and 10 V at frequencies from 20 to 200 kHz. Optimal values lie, however, between 50 and 100 kHz. The electric field within the tissue ranges from 1 to 100 mV/cm. The density of the electric current produced in the tissue varies between 0.5 and 50 $\mu A/cm^2$.[31]

More recently, though in much more limited form, clinical experiments using the capacitive systems have also been performed in Europe along the lines of those of Brighton in the USA. Of late, the technique has been further developed in Italy and applied with good results to patients with failed union.

MECHANICAL VIBRATION INDUCED BY ULTRASOUND: ULTRASOUND SYSTEM

Ultrasound is a mechanical vibration with a frequency higher than 20 kHz. It propagates through a medium by the movement of mutual interaction of the particles. The method is based on the assumption that the mineral component of the bones, in response to a mechanical vibration, converts it into an electrical signal that enhances the osteogenesis.

Ultrasound irradiation at optimal dosage of 30 $mWatt/cm^2$ has been used to enhance fracture healing.[49–51] Ultrasounds are used at a frequency of 1.5 MHz and are delivered in pulse burst of 200 μs at 1 kHz. Exposure length does not exceed 30 min/day. Mechanical vibration interacts with the cell membrane affecting Ca^{++} transport and on the inositol-phosphate cascade, thus promoting cell proliferation. *In vivo,* ultrasound stimulation has been able to shorten the healing time of osteotomies in rabbits and rats, and to promote experimental nonunion healing in rats.[52]

The employment of ultrasound was originally put forward as far back as the 1950s by Corradi[53] who reported the positive effect of applying ultrasound in the fracture site in order to enhance healing—findings that remained long neglected.

The ultrasound method has lately been reappraised in various European countries, both to accelerate the healing of recent fractures and to treat failed union.

With all the above technologies, original research has been carried out in several European countries, extending knowledge and clinical experience in the employment of electrical stimulation. The latter has undoubtedly been favored by the absence of legislation prescribing prior approval by EU authorities of these methods before they are used on patients. Unlike the USA, where entry of apparatus on the market is regulated by the FDA, there is no norm in Europe regarding the use of nonionizing radiation on humans. While this has favored the development of new technologies, it has also meant the proliferation of systems of treating patients with no scientific basis or study demonstrating their effectiveness. Patients may actually undergo treatments potentially able to hinder the repair process. This deficiency will certainly need to be remedied by the authorities responsible in the matter.

TABLE 24.1
Most Relevant Clinical Studies Performed with Different Bone Growth Stimulation Techniques

Author	Method	Pathology
Hinsenkamp et al.[75]	IC	Recent fracture with external fixators
Fontanesi et al.[44]	IC	Recent tibia fractures
Borsalino et al.[79]	IC	Femur osteotomies
Traina et al.[104]	IC	Pseudoarthrosis
Sharrard[64]	IC	Tibia delayed union
Mammi et al.[80]	IC	Tibia osteotomies
Capanna et al.[81]	IC	Osteotomies + bone grafts
Massari et al.[95]	IC	Femoral head avascular necrosis
Dallari et al.[102]	IC	Total hip arthroplasty revision surgery
Cebriàn et al.[68]	IC	Pseudoarthrosis
Faldini et al.[77]	IC	Recent femoral neck fractures
Scott et al.[70]	CCEF	Tibia pseudoarthrosis
Goodwin et al.[86]	CCEF	Spine fusion
Impagliazzo et al.[71]	CCEF	Pseudoarthrosis
Rossini et al.[87]	CCEF	Vertebral fragility fractures
Emami et al.[78]	LIPUS	Tibial fractures

IC: inductively coupled; CCEF: capacitively coupled electric field; LIPUS: low intensity pulsed ultrasound.

Clinical Experiences with Biophysical Stimulation in Europe

In the following section, we summarize the results of clinical studies in the different bone pathologies; within each of these, we look at the results obtained with the stimulation methods described above.

Table 24.1 reports the clinical experience with biophysical stimulation of several authors from both Europe and United States.

STIMULATION OF REPARATIVE OSTEOGENESIS IN CONGENITAL PSEUDOARTHROSIS

Congenital pseudoarthrosis is a rare abnormality; almost all authors agree that the most common sequence of events leading to pseudoarthrosis occurs in a tibia of an infant in whom there are either stigmata of neurofibromatosis, particularly café-au-lait spots, or a family history of neurofibromatosis. Either the tibia alone or the tibia and fibula may be affected; more rarely the forearm may be affected. An extensive review of the treatment of congenital pseudoathrosis with PEMFs was prepared by Sharrard.[54] The European experience is limited to the use of the inductive systems and the only clinical series have been reported in the UK[55,56] and Italy.[57]

All clinical studies underline the importance of a correct orthopedic procedure to be associated with the electrical stimulation.[58–60] The treatment should aim not only at bone union

but also at preventing refracture and at protecting the failure of the osteosynthesis devices utilized to maintain alignment. The success rate with inductive systems reaches 80% when associated with endomedullary nailing. A control study on a group of congenital pseudoarthrosis of tibia has shown that employment of stimulation in support of surgical intervention with endomedullar synthesis is able to limit dysmetry of limbs and protect the patient from the risk of refracture.[61]

STIMULATION OF REPARATIVE OSTEOGENESIS IN FAILED UNION

The expression "failed union" comprises both delayed union and pseudoarthroses. Various studies refer to delayed union for fractures failing to consolidate in 6–9 months following trauma, whereas the pseudoarthroses are those fractures failing to consolidate at least 9 months from trauma. It should, however, be emphasized that the distinction based on time alone is nowadays felt to be insufficient, such that the FDA has recently suggested that any fracture failing to heal at more than 6 months after trauma be considered pseudoarthrosis.

The European clinical studies have mainly addressed the employment of the inductive techniques and, to a much lesser extent, the other methods. Regarding the faradic techniques, as was said above, there have been no significant European clinical series.

For the inductive method, in 1982 Hinsenkamp[46] reported the results of a European multicenter study, with success percentages above 70%. The same positive outcome was obtained in France by Sedel.[62] In Italy, Marcer,[63] reported the results of a series of 147 patients treated with external fixation and PEMFs, with a 73% overall healing rate, the humerus being the least successful site. Sharrard in 1990 demonstrated the efficacy of PEMF stimulation in a double-blind study involving patients suffering from delayed-union.[64] In the UK, Dehaas[65] in 1980, and Watson[66] in 1983, reported positive results (80% success) in the treatment of pseudoarthrosis with an inductive system at frequencies in the range 1–11 Hz and magnetic fields of intensity ranging between 20 and 500 Gauss, originally developed by them. Figure 24.1 shows the waveform of the induced electric field employed in these clinical studies.

Vast experience has been collected in Europe with the inductive technique developed in Italy; Figure 24.2 shows the waveform of signal employed. The success rate in the various series has always exceeded 75%. Dal Monte[57] reported a success rate of 84% in a clinical series of 248 patients, with average time to healing 4.3 months. The presence of infection did not influence the outcome of the treatments. Figure 24.3 shows examples of successful treatment in this clinical series. In Spain, a multicenter study, including 1710 patients suffering from nonunion, reported positive results with an average treatment time of 4.8 months. Hernandez Vaquero,[67] in a retrospective study on the effect of PEMF on nonunions, reported a success rate of 74%; among the factors influencing the results were the age of the patient ($p = 0.048$), the fracture site ($p < 0.001$), the type of nonunion ($p = 0.02$), and the presence of infection ($p = 0.01$).

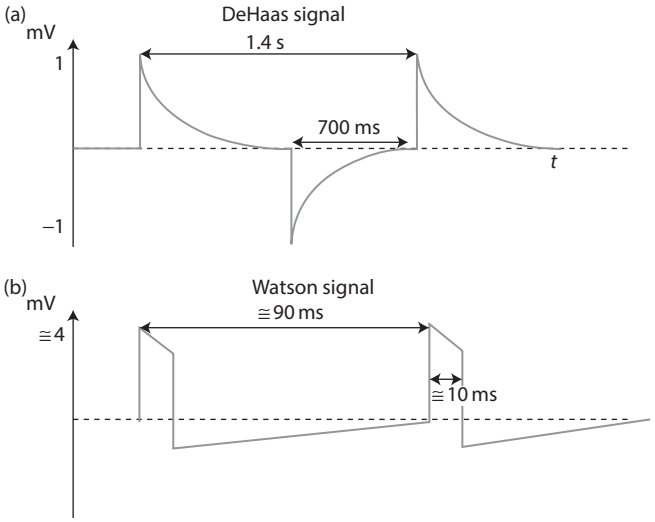

FIGURE 24.1 Waveform of the induced electric field used in the UK experience to treat patients suffering from nonunions. (a) DeHaas WG, Watson J, Morrison DM. *J Bone Joint Surg Br* 1980;62-B(4):465–70; (b) Watson J. *Bioelectrical Repair and Growth Society, BRAGS*, San Francisco; 1983.

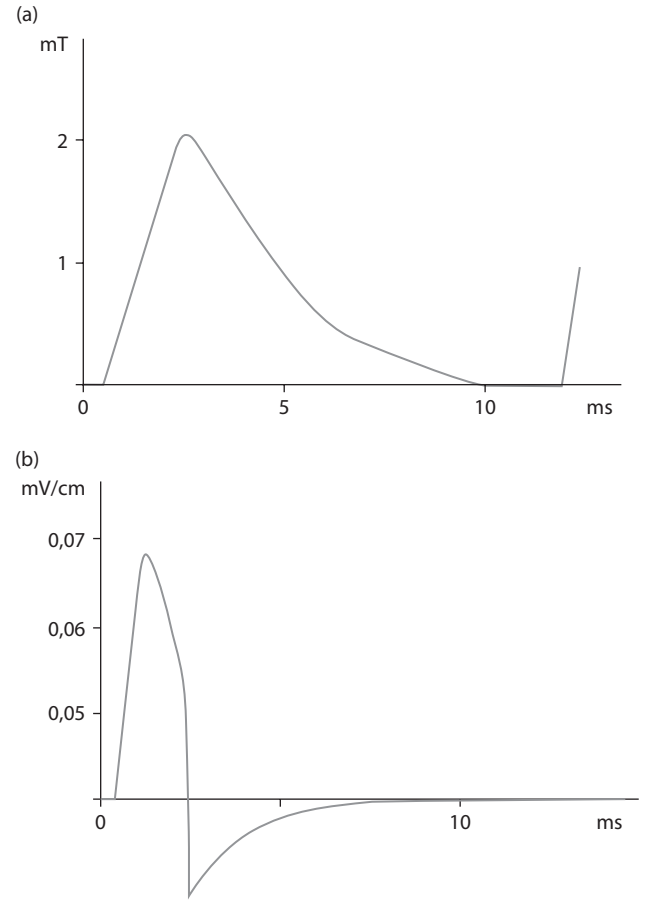

FIGURE 24.2 Waveform of the signal used by IGEA inductive method: (a) magnetic field, (b) waveform of the electric field induced in a standard coil probe[44].

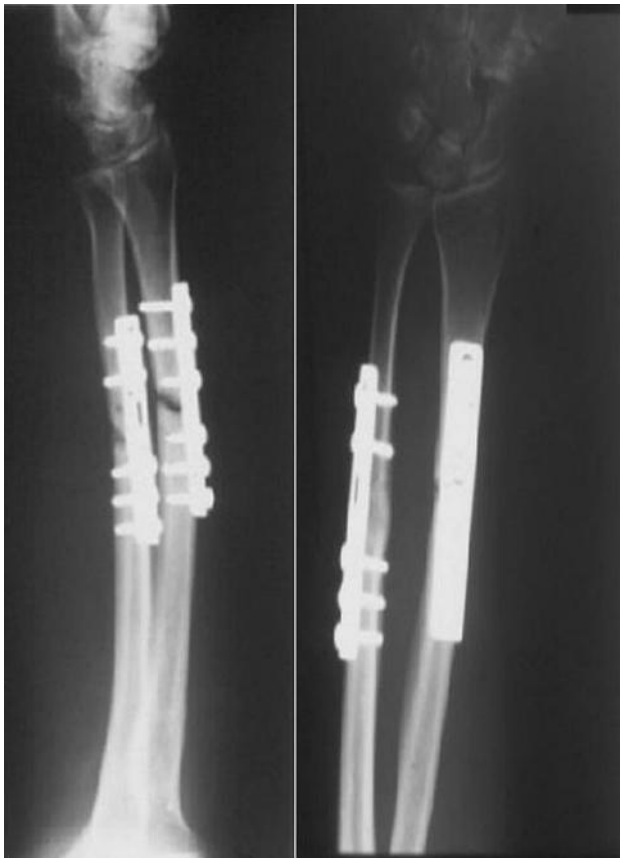

FIGURE 24.3 Female, aged 38. Left: pseudoarthrosis of radius and ulna 10 months from trauma. Right: complete healing after 4 months of inductive stimulation.

Cebriàn[68] made a comparative cohort study in patients suffering from tibial pseudoarthrosis, all of whom were treated by intramedullary nailing. Patients were divided into two groups: one treated by intramedullary nailing only (control group) and the other by intramedullary nailing combined with PEMF. The union rate was 91% for patients who underwent PEMF stimulation compared to only 83% of the control group. The average time until radiological evidence of union of the fractures appeared was 3.3 months (range 2–7 months) with PEMF and 4.9 months (range 3–9 months) without.

In the Netherlands, using high frequency electromagnetic fields, Fontijne[69] reported a positive experience with 85% success. Figure 24.4 shows the waveform used in his system as reported by Pienkowsky.

Although limited, the European experience with the capacitive system for the treatment of nonunions has achieved excellent results. Scott and King[70] conducted a prospective double-blind study in a group of 21 patients suffering from established nonunion, using the Orthopak. Sixty percent healing was achieved in an active group while none of the patients healed in the placebo group ($p = 0.004$). Impagliazzo[71] reported a success rate of 84% using the capacitive system in patients suffering from nonunion. In presence of mechanical stability, fracture alignment and bone loss less than half of the diameter of the treated bone, capacitively coupled electric fields were able to achieve healing of the nonunion. Figure 24.5 shows the characteristics of the signal used.

All authors report that electrical and magnetic stimulation with inductive and capacitive systems is particularly indicated in cases of infected lesions. The infection of the bone tissue or the surrounding soft tissues does not affect the outcome of the treatment. Employment of electrical and magnetic stimulation is able to promote healing in short times of large lesions of the soft tissues associated with very serious traumas. Figure 24.6 shows an example of a successful stimulation of an infected nonunion of the tibia with an inductive system.

Mechanical stimulation by means of ultrasound has recorded a fairly sizeable experience in Europe, in particular in Germany and Italy. The authors have reported a success rate of over 75% in the treatment of nonunions.[72,73]

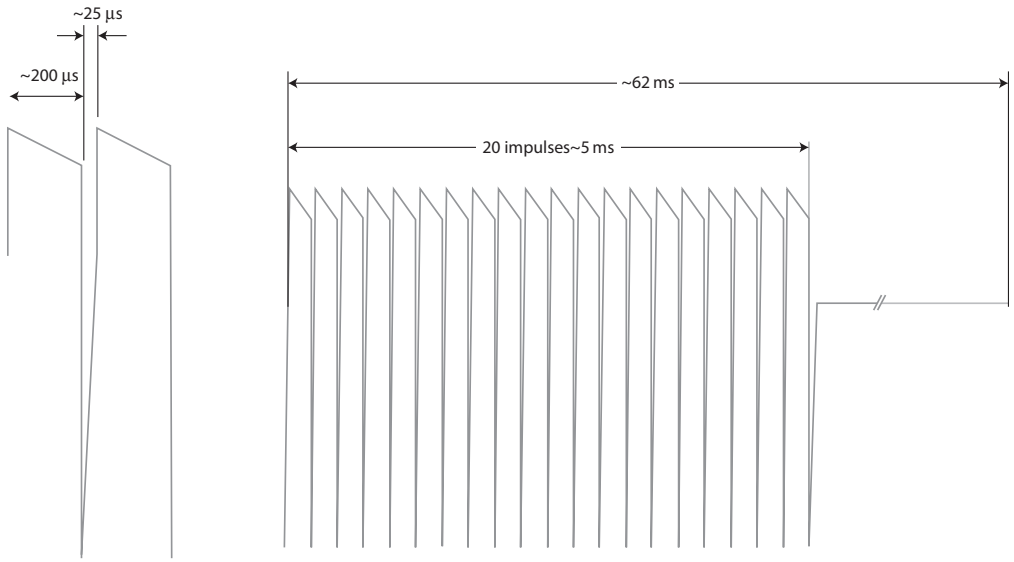

FIGURE 24.4 Schematic illustration of asymmetrical PEMF[32] used in a clinical series in the Netherlands.[68]

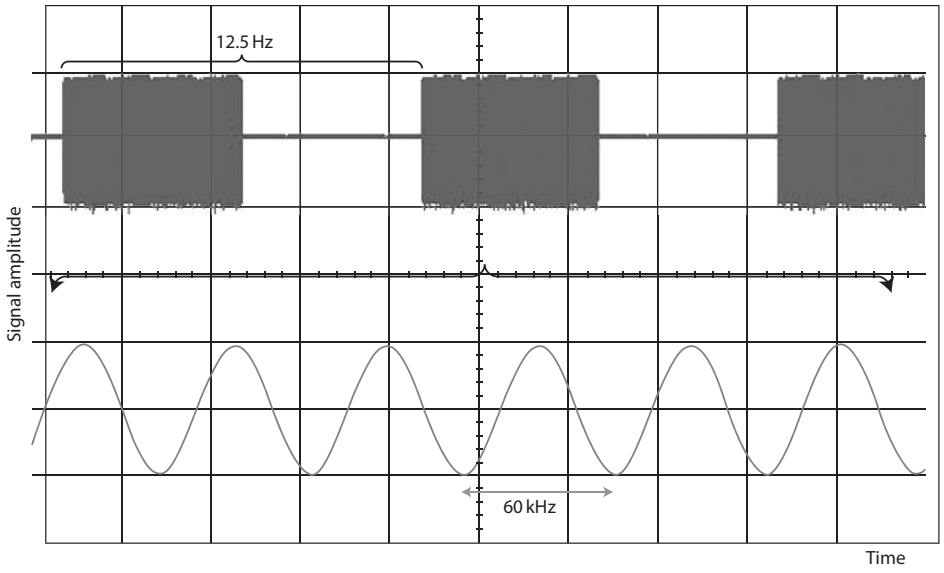

FIGURE 24.5 Waveform of the signal of IGEA capacitive method: sine wave at 60 kHz (16.6 μs period). Burst length 40 ms at 12.5 Hz.

All authors concur on the need to employ electrical, magnetic, and mechanical stimulation in combination with correct orthopedic treatment, and in particular, it has been observed that the possible diastasis of the fracture stumps must not exceed half the diameter of the skeletal segment site of the failed union to guarantee a successful outcome of the treatment.

STIMULATION OF REPARATIVE OSTEOGENESIS IN RECENT FRACTURES

Post-Traumatic

Biophysical stimulation has been shown to be capable of accelerating healing of recent fractures: either complex fractures with serious soft tissue damage and ample bone exposure or fractures that involve the vascularization of a specific bone fragment, thus increasing the risk of nonunion or osteonecrosis (i.e., femoral neck fractures). In all these cases, stimulation succeeded in shortening the average time of healing. Biophysical stimulation is particularly indicated in those cases where the site, type of exposure, morphology of the fracture, or conditions of the patient foreshadow difficulties in the repair process.[44,74–76]

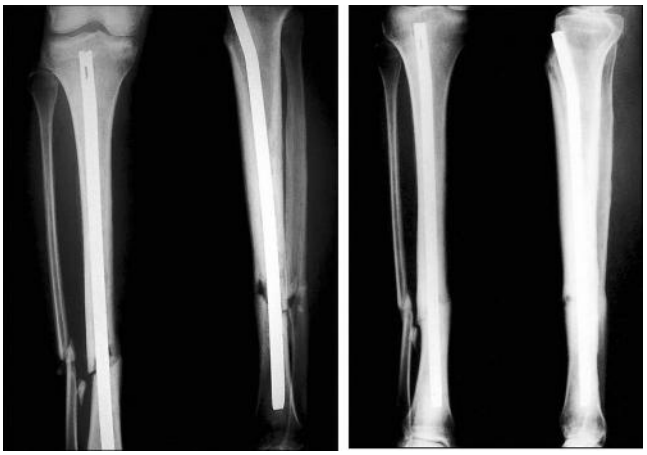

FIGURE 24.6 Male, aged 42. Left: infected pseudoarthrosis of the tibia 12 months after trauma. Healing was obtained after 3 months of stimulation. Right: x-ray image at 36 months follow-up.

Faldini et al. reported the effects of electromagnetic bone growth stimulation in patients with femoral neck fractures (Garden 1–3) treated with screw fixation in a randomized double-blind study.[77] Seventy-seven patients were randomized either to receive an active stimulator or a placebo one. PEMF stimulation started within 7 days after surgery. Patients were instructed to use it for at least 8 h per day for 90 days. Fracture healing was achieved in 94% of active patients compared with 69% of the placebo group. The percentage of osteonecrosis was higher in the placebo group (49% versus 37%). Biophysical stimulation with PEMF increased fracture healing rate and reduced healing time leading to a better quality of life in patients suffering femoral neck fractures.

Fontanesi,[44] in a controlled study of 40 recent tibia fractures treated with plaster cast, remarked how the effect of stimulation is evidenced through a reduction in average healing times. Stimulated fractures healed in 85 days compared to 109 for the control group ($p < 0.005$); however, no fractures were seen to heal before 70 days. This observation demonstrates how in optimal conditions, that is, of rapid healing, the repair process cannot be further accelerated. Hinsenkamp,[75] too, noted a shortening in the time to union of stimulated recent tibia fractures treated with external fixation. The author reports a significant but relatively important shortening in healing time for delayed healing, similar to that described by Fontanesi.

Benazzo,[74] however, using a capacitive coupling stimulation, observed earlier recovery in athletes with stress fractures.

The authors seem to rule out as inappropriate the use of stimulation on all recent fractures as against fractures that might present problems of union.

Ultrasound stimulation has been used to enhance the healing of forearm and tibia fractures with good results[51] in the United States. However, Emami, in Sweden, used ultrasound in a double-blind study[78] in patients with tibia fractures treated with endomedullary nailing, but did not observe any positive effect of the ultrasound. The effects of this internal synthesis device on ultrasound stimulation still have to be clarified.

Osteotomies

The study of electromagnetic stimulation on osteotomies represents an original approach in an attempt to quantify the effects of PEMF. Three double-blind studies have been performed: human femoral intertrochanteric osteotomies,[79] tibial osteotomies,[80] and osteotomies in patients undergoing massive bone graft.[81]

The osteotomies of tibia and femur showed how the application of electromagnetic stimulation favors rapid healing of the osteotomic line and, in the case of femur osteotomy, an early mineralization of the bone callus demonstrated by computer analysis of the x-ray films. As regards the effects on massive bone grafts, a significant shortening of the healing time from 9 to 6 months was observed for patients not undergoing chemotherapy after the operation.

Electromagnetic stimulation was also tested in two European studies, in which after the osteotomies the patients underwent limb lengthening. The first one, performed in the UK, with the EBI technique, noted and quantified with DEXA a positive effect on osteoporosis occurring distally in the lengthened limb.[82] The other one conducted in Spain, with the IGEA method, in patients undergoing bilateral limb lengthening showed that in the limb subjected to stimulation the external fixator was removed 30 days earlier than the controlateral nonstimulated limb.[76]

STIMULATION OF REPARATIVE OSTEOGENESIS IN VERTEBRAL ARTHRODESIS OR IN PRESENCE OF BONE GRAFTS

Various clinical experiences have also shown the validity of associating bone grafts (used to bridge an excessive bone gap) with stimulation for treating pseudoarthrosis. The ability of electrical stimulation to enhance healing of bone grafts in vertebral arthrodesis was demonstrated first on animal models then in clinical studies.[83] In Europe, two clinical studies have shown how the use of stimulation with electromagnetic fields immediately following operation for vertebral arthrodesis, with no internal synthesis devices, can favor the maturation of the bone callus according to the classification of Dawson.[84,85]

Capacitive systems have been successfully employed in the United States as an adjunct to lumbar spinal fusion. Goodwin performed a randomized double-blind study including 179 patients who underwent postero-lateral spinal fusion.[86] Patients were randomized within 3 weeks after surgery and were instructed to use the stimulator (active or placebo) 24 h per day until healing occurred or till 9 months if healing was delayed. Success rate was 84.7% for the active patient and 64.9% for the placebo patient. In Europe, in a Level I trial, Rossini reported excellent results when using capacitively coupled electric field for pain relief in patients with vertebral fractures and chronic pain.[87]

STIMULATION OF REPARATIVE OSTEOGENESIS IN AVASCULAR NECROSIS OF THE FEMUR HEAD

Avascular necrosis of the femoral head is an infrequent disease mostly affecting young males. Bone necrosis is observed in the femoral head as a consequence of sudden deficit in the vascular supply. In most instances, the origin of the deficit is unknown but it has also been associated with the use of steroids, dialysis, and metabolic diseases. In consequence of the osteonecrosis, an early appearance of osteoarthrosis is observed leading to the need for hip replacement. The diagnosis and the progression of the disease can be determined by x-rays, nuclear magnetic resonance, and computer tomography. The severity of the disease can be quantified according to the Ficat classification.[88]

The use of electromagnetic stimulation was initially proposed by Bassett.[89] In stages I, II and, with reservation, III of the Ficat classification, stimulation with inductive systems has proved effective in arresting the progress of the lesion, thus, limiting recourse to surgical intervention or replacement with hip prosthesis. The inductive systems have been demonstrated to be useful in treating avascular necrosis in association with core decompression.[90] The European experience[90–93] has confirmed the observations conducted in the USA.[94] In a Italian retrospective study,[95] Massari reported the results of 76 hips, Ficat stages I–III, treated with pulsed electromagnetic field stimulation for 8 h per day for an average of 5 months. Biophysical stimulation preserved 94% of the hips from total hip arthroplasty in patients with Ficat stage I or II disease. Pain, present in all patients at the start of the treatment, disappeared after 60 days of stimulation in 53% of the patients, and was mild in 26% of the patients. The indication for employing bone stimulation with electromagnetic fields is especially important when one considers that, thanks to the introduction of nuclear magnetic resonance, it is now possible to reach a very early diagnosis. In the initial stages of the disease, the use of PEMFs can justly be considered the treatment of choice for avascular necrosis of the head of the femur. Figure 24.7 shows an example of the treatment of avascular necrosis of Ficat I stage.

No experience has been reported in Europe concerning capacitive and faradic systems in the treatment of avascular necrosis; nevertheless, the information available for the U.S. experience has demonstrated that these methods are not indicated for the treatment of avascular necrosis.[96,97]

STIMULATION OF REPARATIVE OSTEOGENESIS IN THE PRESENCE OF A PROSTHESES

Biophysical stimulation has proven useful to favor experimental bone ingrowth.[98,99] For the orthopedic surgeon, the possibility to stimulate osteogenetic activity in order to enhance prosthetic secondary fixation is extremely attractive, especially in challenging situations such as revision arthroplasty.[100,101]

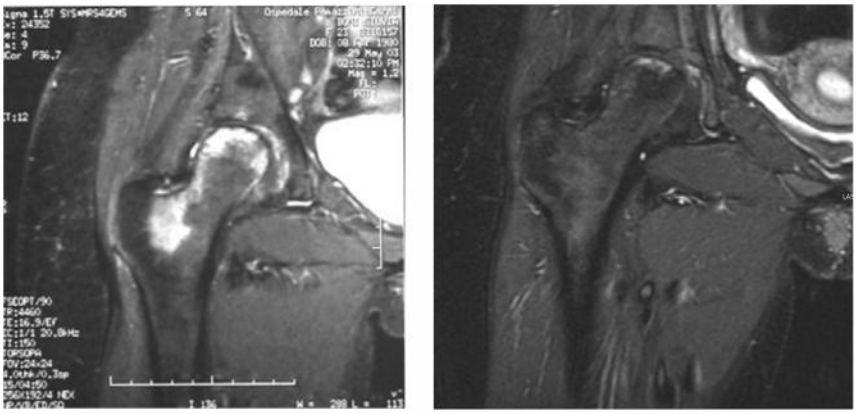

FIGURE 24.7 Male, aged 45. Left: computed tomography of the right femoral head showing an osteonecrosis area that does not alter the femoral head shape, Ficat I stage. Right: complete healing after 6 months stimulation and 1-year follow-up.

Dallari investigated the effects of PEMFs in a randomized, double-blind study on 30 subjects undergoing hip revision using the Wagner stem.[102] Patients were treated for 6 h per day up to 90 days after revision surgery. Ninety days after surgery, the clinical outcome, assessed with the Merle D'Aubigné scale, was significantly improved in stimulated patients[5,7] compared to control group[4,6] as well as bone mineral density. Authors conclude that PEMF treatment aids clinical recovery and bone stock restoration after total hip arthroplasty revision surgery.

Indication for use: in Table 24.2 we report the biophysical treatments that have proven to be effective in the various bone pathologies we discussed above.

Rationale for clinical use of biophysical stimulation of endogenous bone repair*:* the clinical use of biophysical stimulation as proposed by Bassett initially entailed immobilization in plaster of the bone to be treated and subsequent application of the stimulator to be maintained until healing; some patients underwent treatment even for 9–12 months and beyond.

TABLE 24.2
Clinical Applications for Biophysical Stimulation

	Modality of Application of Therapy			
Pathology	**DC**	**IC**	**CCEF**	**LIPUS**
Avascular necrosis	No	Yes	No	No
Bone grafts	Yes	Yes	Yes	No
Chronic pain in vertebral fractures	No	No	Yes	No
Congenital pseudoarthrosis	Yes	Yes	No	No
Delayed union	Yes	Yes	Yes	Yes
Fracture at risk	No	Yes	No	Yes
Limb lengthening	No	Yes	No	Yes
Prosthetic surgery	No	Yes	No	No
Pseudoarthosis	Yes	Yes	Yes	Yes
Recent fracture	No	Yes	Yes	Yes
Vertebral arthrodesis	Yes	Yes	Yes	No

DC: direct current; IC: inductively coupled; CCEF: capacitively coupled electric field; LIPUS: low intensity pulsed ultrasound.

This approach has never been considered adequate by European orthopedists, who have preferred to develop a rationale able to guide the surgeon in choosing or rejecting biophysical stimulation as a means of treatment. In particular, it has been observed how not all failed unions should be considered as potentially eligible for stimulation. In addition, the time needed for healing should not be considered as a secondary factor, as in modern orthopedics and traumatology, the healing time is not a negligible parameter.

In Europe, it has been felt necessary to pose the problem of the differential diagnosis, that is, to identify the causes underlying the failed union, in a prejudicial way.[103] Following the observations of Frost,[22] it can be recognized that in 50% of cases pseudoarthrosis is due to a mechanical failure, that is, the conditions of stability, alignment and contact of the stumps are not satisfied, 20% are due to a biological failure, namely inadequate activation and finalization of the reparative osteogenetic process, while in the remaining 30% of cases, the failed union is accounted for by combined problems of mechanical and biological order.

While mechanical failure has for many years been defined as inadequate alignment, contact and immobilization, it remains to be defined what is meant by biological failure. First, the failed union can be ascribed to a biological failure when, even in presence of adequate mechanical conditions, the fracture does not consolidate: owing to infection, serious local osteoporosis, patient's age, presence of systemic diseases that inhibit the repair processes, or an idiopathic energy of the bone tissue.

With these premises, differential diagnosis enables us to adopt the best solution/therapy. Identification of the causes underlying the failed union is an indication in the choice of surgical solution in the case of mechanical failure, of noninvasive solution by stimulation in the case of biological failure, and the adoption of both (surgery and stimulation) in the case where, as well as a biological deficiency, there is a mechanical condition of stability at the fracture site capable of hindering healing.

A clinical study based on these principles has enabled the observation on how the percentage of union obtainable with surgery (used to correct inadequate mechanical conditions)

or with stimulation (when the failed union can be attributed to a biological deficiency alone) is exactly the same, 87%, as noninfected pseudoarthroses. In the presence of infection, the percentage of success of surgery falls to 40%, whereas infection does not impair the good result of stimulation. It is clear that in the presence of infection, and unsatisfactory mechanical conditions, we face a case of combined (biological and mechanical) failure in which the association of surgery and stimulation can offer the best results.[104]

In view of all these observations, we are led to develop a further concept that has been gaining ground in Europe in recent years, namely fractures at risk. Sensitivity to the biological environment in which healing takes place is certainly a fairly new aspect in orthopedics. Once the surgical technique has achieved an optimal level, there remains the observation that some fractures show difficulties in healing, perhaps for reasons connected with the patient's state of health, type and site of fracture, and local complications. All these considerations have led orthopedists to employ biophysical stimulation at earlier times, that is, in the aim of preventing the onset of failed union. In particular, if after 45–60 days the x-ray picture shows no formation of bone callus, stimulation should be used to finalize osteogenetic activity and to obtain union.

Today, the orthopedic surgeon has available various physical and chemical (growth factors) methods, which are able locally to enhance endogenous repair. The orthopedist needs to develop an increasing sensitivity towards the biological environment in which the repair activity of a fracture takes place, bearing in mind that, while mechanical instability may impede union, in every case the healing of a fracture cannot but be the result of the local cellular activity.

The availability of chemical and physical methods capable of maximizing and finalizing endogenous osteogenetic response represents a further possibility for the orthopedist in order to reduce healing times and enable swifter functional and working recovery by the patient.

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Section V

Diagnosis and Treatment of Cancer

25 Electromagnetic Tissue Characterization in the Treatment of Breast Cancer

Dan Hashimshony, Gil Cohen, and Iddo Geltner*

CONTENTS

INTRODUCTION

Electromagnetic (EM) tissue characterization has been known to some extent for a few decades. Early attempts were focused on studying the sources of the differences in response of biological matter to external EM fields. The basic principles of EM characterization rely on the different electrical responses of tissue to an external oscillating field. These responses depend on tissue type and pathological status and they are measurable. In recent years, there has been increasing interest in using tissue-assessment capabilities for various surgical and diagnostic medical applications, such as early detection of abnormalities and malignancies or, during surgery, defining tumor margins in real time to improve the accuracy of surgical excisions.

In this chapter, we review the measurement and characterization of human breast tissue using EM fields. We will describe and discuss the theory of tissue dielectric properties and its recent practical realizations. We will cover the related engineering challenges involved in turning the basic principles and theory into an actual device that can reliably characterize tissue in clinical settings based on dielectric differences. We start with a description of the dielectric response of biological matter and tissue—both its underlying principles and empirical data. We then describe attempts to characterize breast tissue using devices operating in various ranges of the EM spectrum, namely from low radio frequencies (RF, in the MHz range) through GHz frequencies to the higher THz frequencies. We also review the use of tissue dielectric-property measurements and characterization by EM fields for medical applications, such as for detection and imaging, and as a surgical tool. We will focus on an application for surgical margin assessment during breast-tumor removal, which makes use of RF spectroscopy to characterize breast tissue *in situ* in order to guide surgeons in the removal of additional tissue, thereby reducing the need for repeat surgeries.

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DIELECTRIC THEORY (DEBYE TO COLE–COLE)

Any material can be characterized by its dielectric properties—conductivity and permittivity. Conductivity relates the electric-current density to an external electric field. It is a measure of the ease with which free charge carriers move through the material when a field is applied across it. Permittivity describes the polarization of bound charges under the action of an applied electric field. It is a measure of how the charge distributions are distorted or, in the case of polar molecules with a permanent electric dipole moment, aligned.

To illustrate these concepts, it is helpful to think about the following simplified microscopic interaction. An externally applied electric field generates force on charge carriers (free or bound) within a material. The direction of the force depends on the direction of the field and the charge of the carrier. When the field oscillates, the force changes its direction periodically. However, the reaction to the force depends on other variables as well, and does not necessarily follow the oscillation of the active force simultaneously. Bound opposite charges will move slightly apart creating dipoles, and polarized molecules (where the bound charges are already set apart) will align with the momentary field direction. This creates an additional internal electric field. Free charges will react by moving from their immediate neighborhood, typically colliding with other particles in their way, losing energy, and in turn absorbing the electric field energy in the material. (Note that bound charges can also collide and absorb energy.)

Overall, the different reactions occur on different time scales, which are characterized by the charged particles (their charge and size, whether free or bound) and their relation to their immediate vicinity. Therefore, external fields with different frequencies (oscillating at different time scales) will affect the material differently. This complex collection of simple responses, each with its own typical time scale, characterizes the material and dictates its overall response to the external field, manifested as the dielectric properties of that material, that is, permittivity and conductivity.

The electric field present inside the material (called the electric displacement field, D) is a result of the external field, E, and the reaction of the charged particles. This relation is described by Equation 25.1, where ε is the dielectric function (or response) of the material:

$$D(\omega) = \varepsilon(\omega) * E(\omega) \tag{25.1}$$

As the response depends on the different characteristic time scales, the equation is written in frequency space, ω, that is, a different equation for each frequency, where the value of ε changes as a function of the frequency. From Equation 25.1, it is clear that the function ε contains all of the information on the internal organization of the material, including charge migration and electric-dipole reorientation. Therefore, in its general form, it should include terms that impact the amplitude and phase of the incoming field, as well as terms that reflect the loss of energy in the material.

The simplest description of the response of a material to a time-dependent applied electric field, which assumes that there is a single type of dipole moment characterizing the object, is given by the Debye relation:*

$$\varepsilon(\omega) = \varepsilon_\infty + (\varepsilon_s - \varepsilon_\infty)/(1 + i\omega\tau) \tag{25.2}$$

where ε_∞ is the permittivity at frequencies that are too high for dipole induction, ε_s reflects the magnitude of the polarization when it is fully induced, τ is the characteristic time of the dipole excitation, and ω is the angular frequency of the external electric field. Note that ε(ω) is a complex number, and can be separated into its real part

$$\varepsilon'(\omega) = \varepsilon_\infty + (\varepsilon_s - \varepsilon_\infty)/(1 + \omega^2\tau^2) \tag{25.3}$$

which represents the dielectric permittivity, and its imaginary part

$$\varepsilon''(\omega) = \omega\tau(\varepsilon_s - \varepsilon_\infty)/(1 + \omega^2\tau^2) \tag{25.4}$$

which reflects energy loss (or absorption), and represents the dielectric relaxation of the polarized matter. A significant change in dielectric response is observed around the frequencies which are ~$1/\tau$ (see Figure 25.1), that is, the frequency at which the dipole can react to the oscillating field, usually referred to as its excitation frequency.

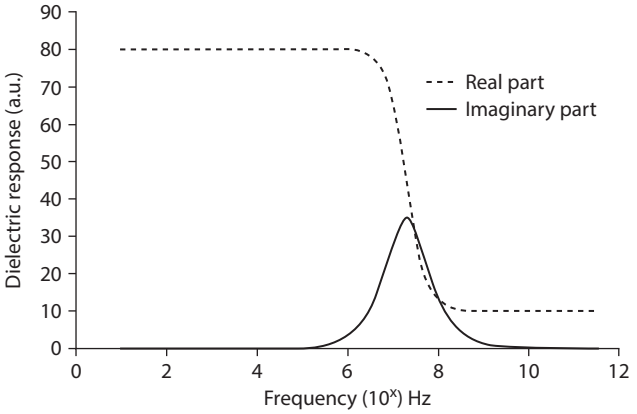

FIGURE 25.1 Dielectric response (real and imaginary parts) according to Debye theory.

The general term for the loss factor (the imaginary part) should also include the significant losses arising from collisions of free charges in the matter (also termed Ohmic losses):

$$\varepsilon''(\omega) = \frac{\omega\tau(\varepsilon_s - \varepsilon_\infty)}{1 + \omega^2\tau^2} + \sigma_0/\omega\varepsilon_0 \tag{25.5}$$

where σ_0 is the conductivity of the charges and ε_0 is the vacuum permittivity.

In practice, especially for biological matter, each polarizable entity (molecule) has multiple dipole-excitation modes. In addition, the interactions between molecules alter, locally, their polarizability. Moreover, in biological systems, higher order objects such as cell membranes, are also polarizable. Therefore, biological matter contains a multitude of induced dipoles, with varying and overlapping relaxation times and dielectric responses. The free charges are also comprised of various ions with different mobilities.

A phenomenological approach to tackling these complex systems was introduced by Cole and Cole.[2] They suggested a modification of the Debye equation in the form of

$$\varepsilon(\omega) = \varepsilon_\infty + (\varepsilon_s - \varepsilon_\infty)/[1 + (i\omega\tau)^{1-a}] \tag{25.6}$$

The Cole–Cole approach remains the most common method of describing measured data. While the actual distribution of relaxation times represented in the Cole–Cole formula is rather complex, it provides a compact presentation of experimental results.

DIELECTRIC PROPERTIES OF BIOLOGICAL MATTER AND DIELECTRIC SPECTROSCOPY[1]

The major building blocks of biological matter are proteins, composed of chains of amino acids. Their typical dipole excitation frequencies are in the range of 1–10 MHz, depending on the protein's size, arising from molecular-rotation responses. The real part of the response at high frequencies

* This section follows Pethig and Kell.[3]

is lower than that of water. Another important component of biological matter is DNA. Induced polarization of DNA arises from the electrical double layer around the macromolecule, at a frequency of approximately 1 kHz. DNA solutions also exhibit excitation frequencies in the range of 1–50 MHz.

Water is the most abundant molecule in biological matter. Its main relaxation frequency is at ~20 GHz, and $\varepsilon_s \approx 78$ and $\varepsilon_\infty \approx 5$ are typical values in the Cole–Cole representation. There have been reports of an additional relaxation peak in the THz range.[4] In addition, water interacts with proteins and other large biomolecules in biological matter, creating what is known as bound water. These interactions affect its relaxation time: the relaxation frequencies for bound water are significantly lower than those of "free" water, residing in the 100–1000 MHz range.

The cells themselves, and more specifically the cell membranes, also make a significant contribution to the frequency-dependent dielectric response. The main mechanism for dielectric polarization in the low RF range (and also below it), that is, 100 kHz–10 MHz, is the accumulation of charges at the membranes from extracellular and intracellular fluids. This has been shown in studies with cell suspensions. Cell size, membrane capacitance and conductance, and conductivities of the cell's internal and external media, all affect the strength of the induced dipoles and the relaxation frequencies.

Ions (electrolytes) contribute to the frequency-independent dielectric losses. Their contribution depends on their concentration and mobility (the ease with which they move in the surrounding medium).

TISSUE DIELECTRIC RESPONSE

Human tissue consists of collections of different cells surrounded by extracellular medium (mostly fluids). As such, in human tissue, the dielectric response is composed of contributions from all of the above-described processes. Changes in the composition and properties of the tissue will lead to different spectral signatures. The changes will be more pronounced in the frequency ranges where dielectric relaxation effects occur (Figure 25.2). Spectroscopic measurement of the dielectric response across the relevant frequencies is thus termed dielectric/bioelectrical spectroscopy or impedance spectroscopy.

The tissue dielectric response is typically divided into four regimes. The α-dispersion, at low frequencies (10 Hz–10 kHz), is affected mainly by the ionic environment surrounding the cells. The β-dispersion range (10 kHz–10 MHz) is affected mainly by the cell-membrane responses. At higher frequencies (above 100 MHz)—the γ-dispersion—the response is dominated by water molecules. The δ-dispersion region corresponds to the interaction of water with macromolecules within the tissue (i.e., "bound" water).

MEASUREMENTS OF DIELECTRIC PROPERTIES OF BREAST TISSUE

The dielectric properties of human tissue have been thoroughly investigated, with the first studies being performed at the beginning of the previous century. The values in the various frequency ranges are well established.[5–8]

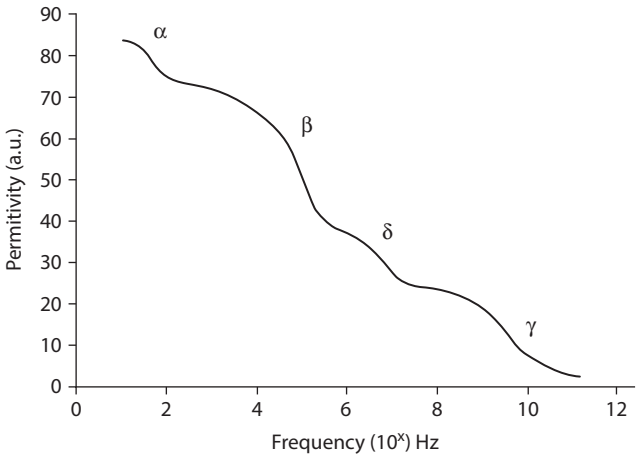

FIGURE 25.2 Schematic spectrum of the dielectric response (real part) of tissue. The step changes in the permittivity result from excitation of particular polarization processes with the increase in frequency. The α-dispersion is due to the ions in the extracellular environment, the β-dispersion results from the charge buildup at the cell membranes, termed Maxwell-Wagner effect, the δ-dispersion is related to "bound" water, and the γ-dispersion is due to water.

The properties of breast tissue were first investigated in the 1920s.[9] Since then, the properties of both normal and malignant breast tissue have been evaluated.[10–15] These properties have been investigated over a wide range of frequencies, from tens of kilohertz[8,9,14] through the megahertz range[7] to tens of gigahertz.[11,16–19]

Figure 25.3a (inset) and Figure 25.4 present setups for measuring tissue dielectric responses in the RF range. In the first setup, dielectric properties were measured in a coaxial waveguide cell: an in-line, coaxial waveguide configuration (Figure 25.3a inset) where the tissue replaces the material between the center conductor and the outer shield. The cell was connected to a two-port network analyzer through coaxial cables, and the impedance of the cell was measured. As the relation between the tissue dielectric response and the coaxial waveguide impedance is known,[20] the tissue response can be extracted from the measurement, following proper calibration of the measurement system.

Tissue composition of the whole sample enclosed within the coaxial cell was evaluated by histopathology analysis. Figure 25.3 presents the dielectric properties (permittivity and conductivity) of representative types of tissue present in the breast in the 50–500 MHz range. The values are similar to those reported in the above-cited publications.

In the second setup, breast tissue dielectric properties in the RF range were measured in an open-ended coaxial configuration (Figure 25.4) by reflection spectroscopy. In this configuration as well, a simple relation can be derived between the dielectric properties of the medium adjacent to the open-ended coaxial waveguide and its reflection coefficient.[21] The tissue properties can be extracted from the measurement. The results for representative tissue types in the

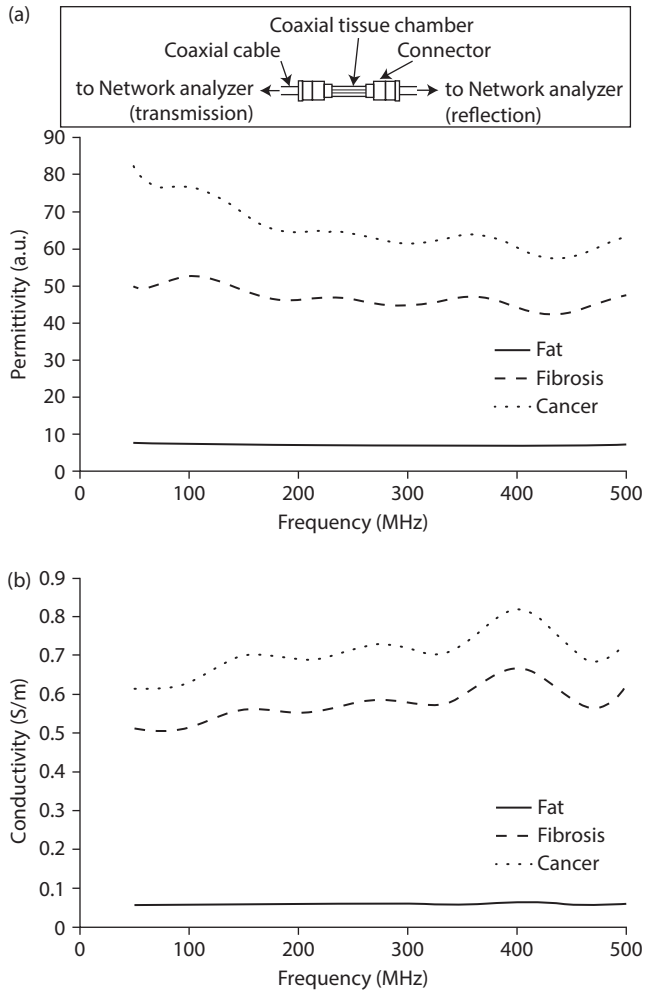

FIGURE 25.3 (a) Permittivity and (b) conductivity of various types of breast tissue in the 50 MHz–500 MHz frequency range. Measurements were performed with the coaxial cell configuration. Insert: coaxial waveguide cell. Tissue fills a cylindrical capsule, replacing the dielectric material usually separating the center conductor and outer shield. The cell is connected to a 2-port network analyzer via coaxial cables and measurements are performed in both reflection and transmission modes.

range of 5–100 MHz are presented in Figure 25.5, and they resemble the results in Figure 25.3. This method was used to measure the dielectric properties of numerous breast tissue types, some, to the best of our knowledge, for the first time.[22] Special care was taken not only of the measurement accuracy and setup calibration, but also of the measured tissue samples' histopathology characterization. The measurements were taken through a stencil suited to the probe tip's diameter (~2.5 mm). Each measurement site appears as a 2.5 mm diameter circle on the histology slide (see Figure 25.4 inset).

DIELECTRIC SPECTROSCOPY OF TISSUES: APPLICATIONS

Measurements of tissue dielectric properties can be beneficial in a variety of medical applications, such as early cancer

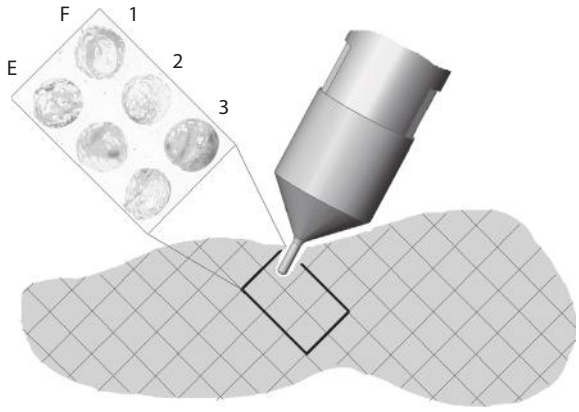

FIGURE 25.4 (**See color insert.**) Open-ended coaxial probe configuration. Measurements are performed in reflection mode. Inset illustrates pathology slide used to analyze measured tissue sites.

detection, improvement of biopsy and surgical procedures, and local treatment of cancer. However, the ability to measure and differentiate between tissue types is necessary but not sufficient for a medical application. Beyond the arduous engineering task of developing an actual working device, tissue characterization is more complex. Characterizing a

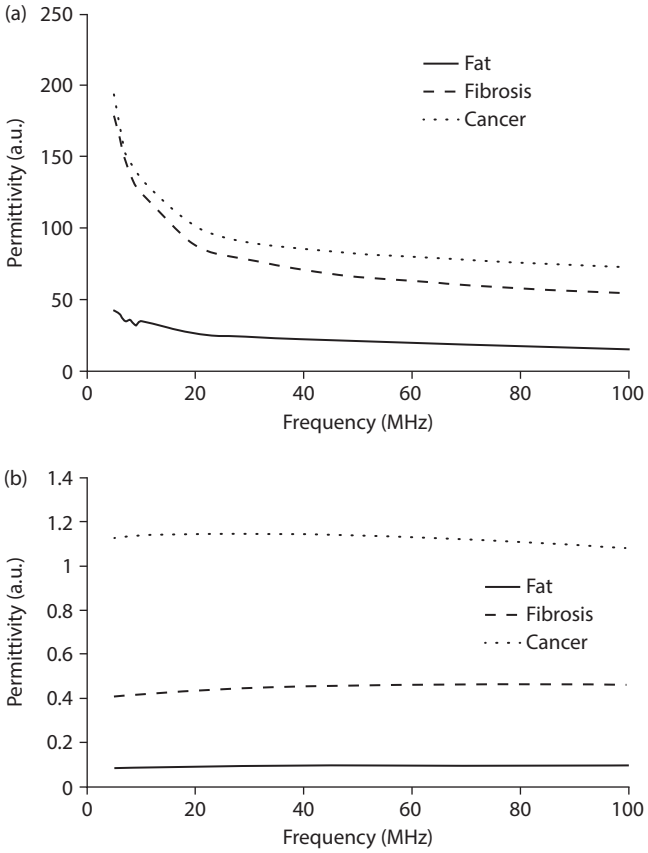

FIGURE 25.5 The dielectric properties of various types of breast tissue in the 5 MHz–100 MHz frequency range. The overlapping (frequency) values are similar to those evaluated by the coaxial waveguide cell configuration (Figure 25.4).

specific tissue type is challenging due to possible changes in its properties or between subjects, nonhomogeneity of the tissue encountered by the sensors, inherent instability of the measurement due to contact or movement, and similarity between specific tissue types present in a specific application. Real-time tissue characterization also requires the development of algorithms that provide the physician with instantaneous results. In imaging applications, there is also a need to process data from multiple sensors and reconstruct an image.

Imaging is an important tool in medicine; it provides the physician with a two- or three-dimensional representation that enables detecting and localizing a condition, and selecting a treatment method. In breast cancer, imaging enables early detection,[23] and therefore, better treatment success. Imaging also enables more accurate local treatment of breast cancer.[24] Much progress has been made in imaging by electrical impedance spectroscopy.[25] By using multiple nonionizing EM sources (transmitters) and receiving antennas located around the imaged organ, malignant or abnormal tissue can be detected.[26] These nonionizing imaging techniques hold further advantages for breast tissue. In the microwave and RF range, the malignant tissue is highly differentiated from normal breast tissue, with the surrounding healthy tissue being more translucent to the radiated frequencies. The breast is also easily accessible from the outside, enabling easy placement of the multiple antennas/sensors. Tomography, that is, cross-sectional image reconstruction from an array of sensors specifically arranged around the imaged organ,[27] has also been successfully used to show tissue abnormalities.[28]

Use of the dielectric differences between tissue types for the local detection of cancer has been shown to be successful in detecting prostate,[29,30] skin,[31] and breast cancer.[32] Local (nonimaging) devices measure the dielectric properties of the tissue in the vicinity of the sensor. While they are usually (minimally) invasive, they can improve cancer treatment by enhancing the accuracy of biopsies in the prostate[33,34] or breast,[22] for example. These local techniques can also improve skin cancer screening.[35] The nonionizing real-time techniques can also be utilized during surgical procedures to improve cancer localization and complete resection in breast[36] and brain tissue.[37]

The THz region, 0.1–10 THz, lies at frequencies higher than microwaves. The shorter wavelength provides higher spatial resolution. EM radiation at these frequencies excites molecular vibrational modes, and in tissue, THz radiation interacts with water molecules and can be modeled accurately using the double Debye theory.[4] The radiation is nonionizing and available systems operate at low power levels, as with all of the devices described in this chapter. THz radiation is less susceptible to scattering than infrared radiation when propagating in tissue, but it is strongly absorbed by water, therefore, has the potential for imaging and detection of cancer close to the surface.[38–40] Freshly excised or formalin-fixed tissue samples were analyzed using THz reflection[39,40] and transmission[38] images, and the results were compared to those obtained from histopathological analyses. The studies showed good correlation between the THz and optical images. This technology may therefore become useful in the future for the detection of skin cancer or margins in breast lumpectomy procedures.[41]

APPLICATION IN BREAST CANCER TREATMENT

Breast-conserving surgery (BCS) is the preferred surgical treatment for most women with Stage I and II breast cancer,[42] and 60%–75% of American women with early-stage breast cancer are treated by BCS.[43] Margin status of excised tissues is the most important quantitative variable for assessing the completeness of tumor excision. The presence of cancer cells at or near the surface of the removed tissue (a positive margin) may indicate incomplete removal of the primary tumor. The standard of care when assessing margin status is microscopic examination of the excised specimens. This process is known as permanent pathology, and results are not available until 2–4 days after the surgery.

Despite the clinical importance of obtaining clear margins during lumpectomy, it remains a challenge given currently available methods of intraoperative positive-margin detection (see below). Even in well-controlled series, the rate of patients with positive/close margins averages 30%. The general practice for positive margins following lumpectomy is re-excision surgery, at reported rates of between 20% and 40%.[43–45] Re-excision surgery holds a number of risks and can have deleterious effects on the patient.

The use of tissue measurements and identification of differences between tissue types in clinical applications in general, and in the treatment of breast cancer in particular, requires a further step, beyond a general understanding of dielectric responses. Most applications require assessing tissue dielectric properties or classifying them into two or more categories, usually in real time. While today's computational developments have made this feasible, the actual algorithms used to perform these tasks must be developed for each application.

In breast cancer, where there are indeed several types of tissue with varying degrees of (dielectric) differences and nonhomogeneity, real-time tissue-characterization technology using RF spectroscopy has been recently developed[32] to assist in real-time surgical margin detection. This technology is used in lumpectomy procedures to identify cancerous tissue at the specimen margins and to indicate further tissue for removal during the surgery, thereby preventing repeat surgeries.[46–48]

The device (MarginProbe, Dune Medical Devices, Paoli, PA, USA) includes a handheld probe, the distal tip of which is placed against the lumpectomy specimen surface where it locally measures the tissue properties. Using an algorithm, the device displays, in real-time, a binary result indicating whether the tissue in contact with the device is malignant or not. The measured tissue is a 7 mm diameter, several-millimeter thick disk. The device has been shown to differentiate well between malignant and nonmalignant tissue types in the breast.[32] However, the advantage of low RF radiation lies in its

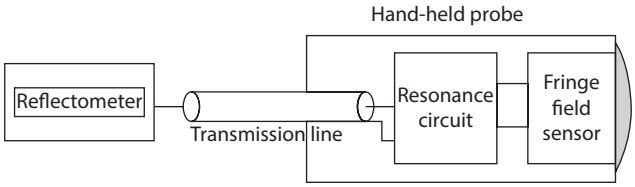

FIGURE 25.6 MarginProbe block diagram.

ability to differentiate not only between healthy and malignant breast tissue but also between benign and malignant lesions. The device was clinically tested and shown to be effective in intraoperative use during breast lumpectomies.[46–48]

The device is based on a fringe-field sensor with a resonant circuit (see Figure 25.6). The fringe field interacts with tissue in the vicinity of the sensor, effectively coupling this tissue to the resonance circuit. Therefore, any change in the tissue's dielectric properties immediately impacts the resonance. A RF reflectometer sends RF waves over a broad range to the sensor and measures their reflection. The resonating sensor structure, together with the adjacent tissue, creates a resonance signal. Figure 25.7 presents a schematic drawing of simple resonance signals, similar to those measured by the system. Note that the actual signals are not pure single resonances since the tissue dielectric properties vary over the measured range. The resonance frequency, amplitude and other characteristics of the signal are analyzed and the signal is classified as corresponding to malignant or nonmalignant tissue according to a pre-acquired database. This system provides the user with a binary (positive/negative) classification output on the malignancy of the measured tissue. The probe is used to sample the entire surface of the removed specimen, taking approximately 5–8 measurements per margin surface (the tissue specimen is typically divided into six faces/margins as in a cube). Each measurement cycle per tissue site takes approximately 3 s and generates a visual and audible output for the sampled tissue site. If any one of the device readings is positive, the margin is considered positive, and appropriate surgical action is taken. The detection of positive margins facilitates the intraoperative removal of additional tissue from the breast cavity, thereby reducing the presence of positive margins post-lumpectomy.

The RF approach has been demonstrated in various clinical studies and it has shown reliable real-time

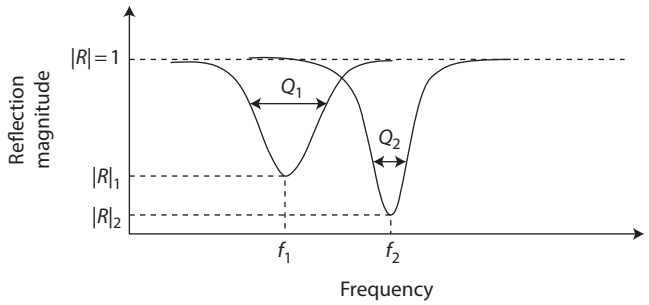

FIGURE 25.7 Schematic depiction of resonance signals.

tissue-classification capabilities. More than 1000 procedures have already been performed using this approach and re-excision rates have dropped significantly. It is estimated that by using this EM approach, relying on RF spectroscopy or other methods, percentages of re-excision surgeries will drop to the single digits range.

CONCLUSION

There is a substantial body of evidence supporting the use of EM radiation in the megahertz to terahertz range for the identification and classification of human tissue. This range of the EM spectrum corresponds well with the range in which the tissue's dielectric properties change when it turns malignant. The ability to react directly to the physiological changes is an important feature that is unique to this range. The RF range has been shown to be extremely useful for the identification and classification of breast cancer abnormalities and malignancies of various types. The ability to automatically classify tissue into normal versus abnormal based on this range's readings is extremely powerful and has far more potential than similar attempts using x-ray, magnetic resonance imaging, or optics. Therefore, this technology is expected to optimally contribute to clinical solutions if it is further developed as an automatic classification tool rather than for imaging solutions.

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26 Electrochemical Therapy of Tumors

Jing-hong Li and Yu-ling Xin*

CONTENTS

INTRODUCTION

The efficacy of electrochemical therapy (EChT) in mice with implanted Jensen sarcoma tumors was reported in 1953 by Reis and Henniger.[1] However, the clinical application of this modality was initiated by the Swedish radiologist, Bjorn Nordenström. In 1983, he published a book in which he described his theory of biologically closed electrical circuits (BCEC) and the results of two decades of research on EChT treatment of malignancies in animals based on this theory.[2] He also reported the results of EChT in 20 lung cancer patients with 26 tumors in which he used the "skinny needle" he had developed for biopsy purposes as an electrode. Follow-up after 2 to 5 years revealed that 12 tumors had either disappeared or were markedly reduced in size. This study stimulated interest in utilizing EChT for treating lung malignancies and Japanese researchers subsequently confirmed Nordenström's results in animals and in several patients.[3–7]

The wider application of this technique began in China after it was introduced to the country in 1987, with the China–Japan Friendship Hospital in Beijing, China, at the center of this application.

Platinum electrodes are inserted into the tumor through a trocar with plastic insulating cannula percutaneously, and the anodes and cathodes are connected separately to the apparatus. The current arouses strong chemical reactions around the electrodes, leading to the degeneration and necrosis of the tumor cells. This is a new type of method in treating tumors without surgical resection. The final result is caused by the direct current inducing chemical reactions; therefore, we call it electrochemical therapy.

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The advantages of EChT are that it has fewer traumas and complications, a quicker recovery, it is easier to administer, and it is less costly than surgical procedures, as well as being just as effective in certain instances. In addition, it provides an opportunity to treat malignant tumors in those patients in whom surgery, radiation, and/or chemotherapy has not been successful or may be contraindicated. For large-scale venous malformations, EChT avoids hemorrhoea and a rather high incidence rate of functional disturbance when treated with surgical resection. It has been proven that EChT can improve patients' symptoms significantly and control the development of the disease.

EXPERIMENTAL STUDIES ON THE MECHANISM OF ACTION OF EChT

It has been well established that tumor cells are more sensitive to certain changes in the environment than adjacent normal cells. Various treatment approaches, including radiation, chemotherapy, hyperthermia, microwave, laser, and antiangiogenesis strategies, are based on these differences. Multiple pathological changes occur in the tumor tissue during EChT, such as pyknosis of nuclei, disruption of cell membranes and mitochondria, as well as coagulation and necrosis of nuclear proteins.[2]

In animal experiments, histopathological studies have demonstrated that the lethal effect of EChT on tumor tissue in the anode area differs from that around the cathode site. Tumor tissue at the anode shows coagulation necrosis with destroyed cell structures, pyknosis of cells, and denaturation. Tumor tissue around the cathode has a different pattern characterized by necrosis due to liquefaction, complete disruption

of cell structures, and the accumulation of water molecules due to the presence of positively changed sodium ions and large protein molecules. Although the features of damage are different in anode and cathode areas, the extent of tissue destruction is about the same.[8]

Based on a large number of animal experiments and clinical pathological examination, the mechanism of the killing action of EChT is electrolysis by direct electric current, which induces pH changes in the environment.

The killing action of DC *per se* is limited only around the surface of the electrode. To expand the killing effect are the substances resulting from electrolysis of water and electrolytes, NaOH and HC1, which disseminate a certain distance from the electrode. Na^+ formed after electrolysis will move towards the cathode and combine with OH ions to form NaOH, which yields a strong alkaline environment (pH 12–14). Chloride ions accumulate around the anode and combine with H^+ to form HC1, which is strongly acidic (pH 1–2). The strong alkalinity and acidity are the main destructive mechanisms of EChT. During the application of electrochemical therapy, a large amount of foam oozes out from the surface of the electrode releasing Cl_2 and H_2O_2.[9] There are, however, additional mechanisms of action that are operative during EChT of tumors. These can be summarized as follows:

1. Electrolysis by direct current induces pH changes in the environment that, in turn, results in biological effects.
2. The application of the electric current increases the permeability of the cell membrane of tumor cells that allows ions to migrate inside cells and exert antitumor effects.
3. Activity of enzymes in plasma can be released; proteins will be denatured and coagulated and precipitated, whereby necrosis may be induced.
4. Electrolysis changes the distribution of ions, which results in necrosis around the anode and edema around the cathode.
5. Coagulation and extensive embolism may occur in blood vessels in the anode area, whereas significant edema in the cathode area results in blockage of the microcirculation, and the blood supply to tumor cells is interrupted.
6. White blood cells and T lymphocytes accumulate in the anode area that may also have antineoplastic effects. At the same time, the negatively charged tumor cells are attracted to the anode so that metastasis of tumor cells may be hindered or prevented.
7. Fragments of damaged tumor cells resulting from direct electric current application could serve as antigens and stimulate the body's immune system defences.[4–7,10] See Figures 26.1, 26.2, and 26.3.

The fundamental principles of EChT for treating venous malformations are

1. Strong chemical reactions in the tumor are produced by introducing a direct current into it with an electrochemotherapy instrument and special electrodes; the pH of the anode area is decreased to 1–2 to show strong acidity; the pH of the cathode area is increased to 12–13 to show strong alkalinity. The chemical reactions destroy erythrocytes and platelets inside the tissues, releasing hemagglutinin, and producing blood clots to harden the vessel cavity.
2. The direct current induces permeability of the cell membrane and the removal and diffusion of ions inside of the electrical field, inducing oxygen and chlorine gas, directly killing diseased vessel cells.
3. The direct current changes the external and internal environment, which induces degeneration and necrosis of protein.
4. The electroosmosis effect: the experimental pathology showed tissue dehydration, constriction of large

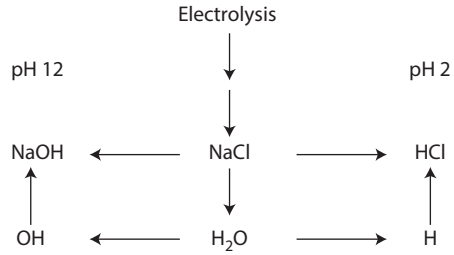

FIGURE 26.1 Strong alkalinity and acidity are the main killing factors of electrochemical therapy.

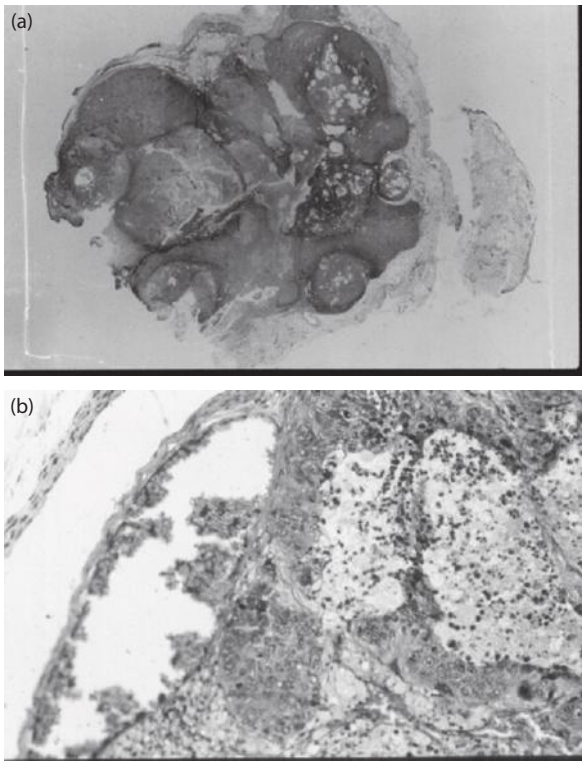

FIGURE 26.2 **(See color insert.)** Tumor tissue dehydration and carbonized, protein coagulated, and necrosis by the anode. (a) Low power lens, (b) high power lens.

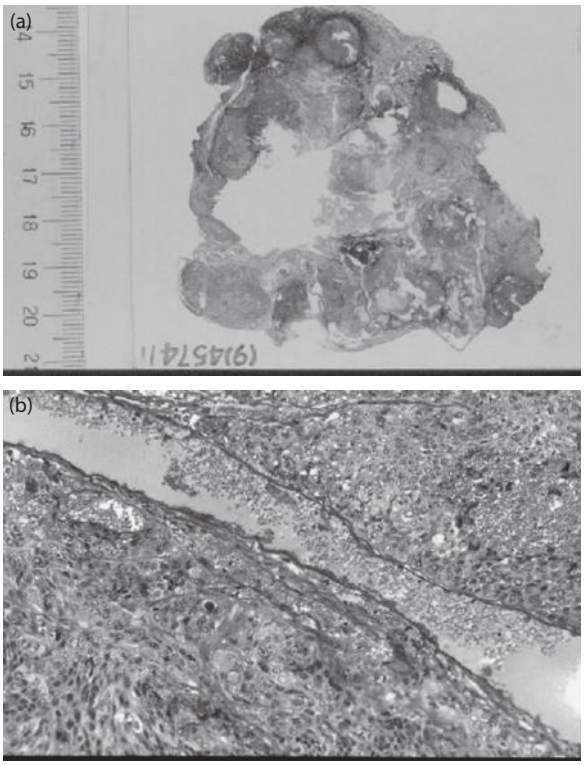

FIGURE 26.3 **(See color insert.)** Cancer cells were dissolved and underwent "breakdown," congestion and edema of tissue were represented in the area of the cathode. (a) Low power lens, (b) high power lens.

vessels and capillaries, and microthrombus formed extensively in anodes areas; interstitial edema capillaries are depressed by large fluid accumulation induced obstruction and tissue blood supply destroyed in cathodes.

5. Dissimilated tissues formed after EChT can be absorbed after 6 months or longer.
6. The effective style of the electrodes presented a cylinder killing, the diameter of which is about 10 mm.[11–13]

TREATMENT FACILITY AND METHODS

Treatment Facility

The apparatus used is a computer controlled ZAY-B multifunctional instrument. It has two outputs with data storage and a print function. Electric current, voltage, and electric quantity needed can be pre-set. Furthermore, an alarm system can be started when a short circuit or disconnection occurs.

The electrodes are made of platinum, which are 0.7 mm in diameter and 160 mm in length with high electrical conductivity and good anti-erosive properties. Needles are coated with a plastic catheter for insulation to protect normal tissue against electrical injury and strict sterilization is necessary (Figure 26.4).

FIGURE 26.4 The electrochemical therapeutic instrument type ZAY-B and platinum needles made in China.

Treatment Methods

Insulated plastic tubes are used to protect normal tissue from injury due to electrolysis; an 18G trocar was used for insertion into a diseased region 2 cm beyond the margin of tumor depending on the size and shape, usually along the Y direction of the tumor. The needle core of the trocar was pulled out and the electrode was inserted into the diseased region through the trocar. During treatment on venous malformations, it was shown that blood flow could be seen in the end of the trocar when the trocar was in the correct position. The plastic insulating cannula was draw out of the tumor to protect the normal tissue. Then the electrodes were connected to anodes and cathodes of the electrochemical therapeutic instrument and the electricity was set up to begin the therapy. The electric current, voltage, and electric quantity should be determined according to histological type, size, and location of the tumor. If the tumor is large or hard, a higher electric quantity should be employed. Usually the treating current was 100–180 mA and the voltage of 6–12 V. The total electricity used was in general 80–100 coulombs per 1 cm diseased tissue.

Based on the data obtained from our experiments, the destruction radius of each electrode is about 1 cm. There will be a rupture drop area of electric field between two electrodes when the distance of electrodes is over 2 cm. Therefore, 1.0~1.5 cm will be the best choice of the distance between electrodes during EChT and the number of electrodes can be calculated according to tumor size. The electrodes must be inserted into the full diameter of the tumor to avoid incomplete treatment.[14,15] For large tumors, the electrodes could be managed monolayer or multilayer according to the size of diseased region. In such cases, there will be two groups of electrodes in the same tumor and a multioutput instrument provides this advantage.

The therapeutic voltage should be elevated from small to large gradually. The mass of venous malformations might be changed from soft to hard by touching during treatment. The

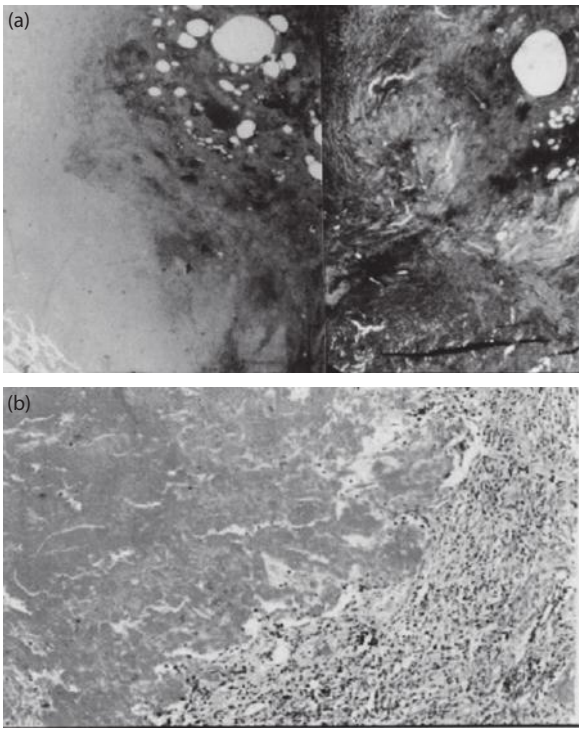

FIGURE 26.5 (See color insert.) (a, b) No cancer cells remained when the distance of the electrodes was shorter than 2 cm.

voltage is turned down to zero and the device is turned off when the therapy is completed. The treating time can range from several dozen minutes to over 2 h depending on the size of the tumor. Electrodes and trocars are pulled out and gauze is used for the needle hole in the skin to stop any bleeding. The operator might press the diseased region by hand during the operation, which could extrude the blood from the tumor, decrease the blood clot forming, and increase the therapeutic effect by making a closer contact of electrodes and tumors, all of which can help in the quicker absorption of blood clots and necrotic tissues after the operation (Figures 26.5 and 26.6).

The concept of increasing the electric current to a high level in order to shorten treating time is incorrect. That is

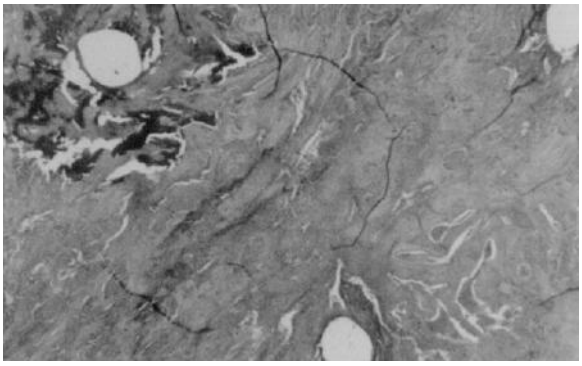

FIGURE 26.6 (See color insert.) The distance of the electrodes is over 3 cm, cancer cells can be found in the remaining area.

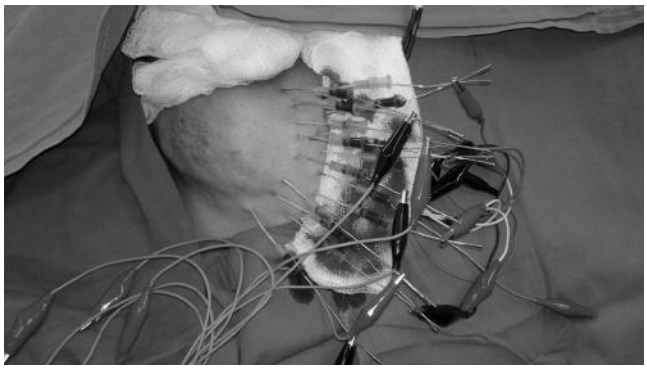

FIGURE 26.7 (See color insert.) Electrochemotherapy on a patient suffering from venous malformations in his right hip.

because the action of EChT is electrolysis and it needs time to perform the procedure correctly. According to an animal experiment, 4 V voltage and 20 mA is enough to have a killing effect.[14]

When treating tumors in the lower part of the body, epidural anesthesia is recommended. When treating tumors in the other part of the body, general anesthesia is preferable.

The large scale venous malformations that need to be treated again are usually operated on after 6 months[13] (Figures 26.7 and 26.8).

CLINICAL APPLICATION OF EChT TO TREAT MALIGNANT TUMORS

The clinical applications of EChT to treat cancer began in 1983. In that time, Nordenström reported 20 cases of lung cancer (26 tumors in number) that he treated with EChT. There were only ten cases (12 tumors in number) that disappeared or obviously reduced.

From 1987, the China–Japan Friendship Hospital in Beijing took the lead in using EChT, and since then, they have treated more than a thousand patients with various types of malignant tumors.

When a cancer patient is not suitable for surgical operation, or when radiotherapy and chemotherapy are not effective, EChT may show its effectiveness. Superficial tumors, such as cancer of the head and face, breast cancer, parotid cancer, cancer of oral cavity, cancer of tongue, cancer of superficial lymph node, and melanoma, are an indication for EChT.

Electrodes can be inserted accurately and arranged properly for those cases, as the electric field for treatment can cover the whole cancer. Position and number of electrodes should be adjusted as necessary.

EChT can be a complementary method for surgical operation. For the cases that cannot be operated during thoracotomy (central type of lung cancer, mediastinal tumor), electrodes can be inserted accurately to treat the tumor.

It is the same for abdominal surgery and gynecological operation for cancers that cannot be resected (liver cancer, kidney cancer, pancreas cancer, ovarian cancer, etc.).

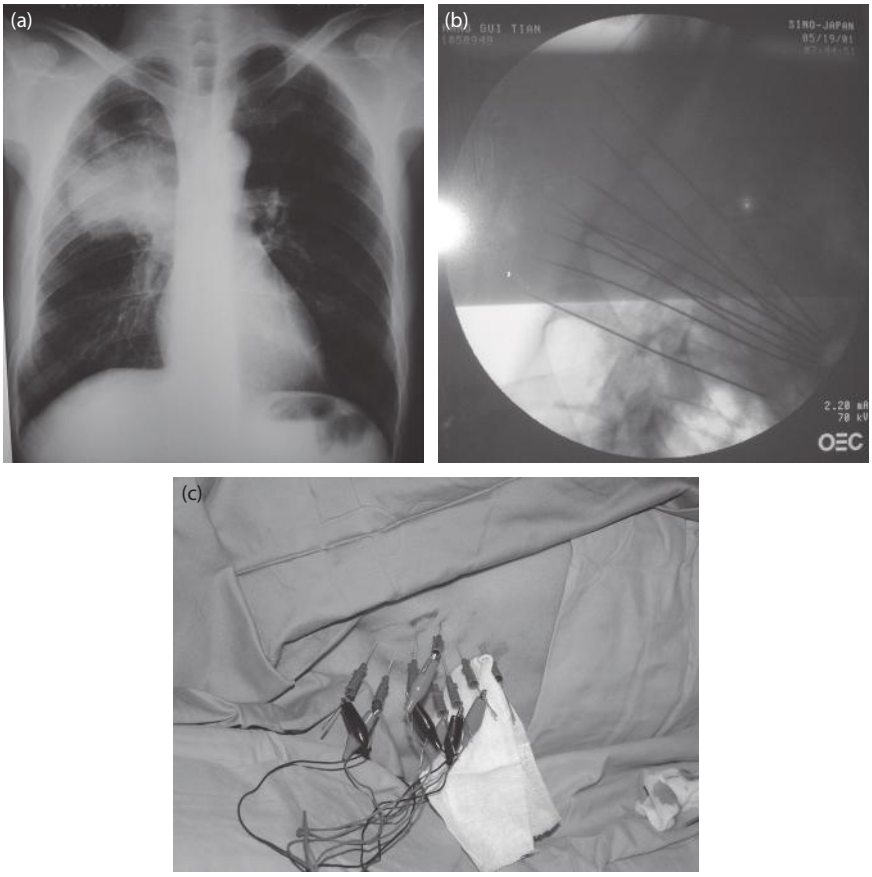

FIGURE 26.8 (See color insert.) Male, 67 years old. (a) Right: lung cancer. (b) Electrodes inserted into the tumor. (c) During electrochemical therapy.

Symptoms can be relieved and there is a certain amount of effectiveness.[12,16–19]

Several years ago, we summed up 7642 malignant tumors treated by EChT in China retrospectively (Table 26.1).

Among the 7642 malignant tumors, 4681 were in males and 2961 occurred in females. Among the patients observed, 1284 patients were 20–40 years old, 4084 were 41–60 years old, and 1985 were 61–80 years old, with 289 older than 81 years of age. With respect to the types of tumors, 3932 were superficial growths and 3710 were visceral tumors. In regard to tumor staging, there were 749 stage I cases, 2504 with stage II, 2862 with stage III, and 1527 with stage IV. Furthermore, 1723 tumors were 3.0–5.0 cm in diameter, 2758 were 5.1–7.0 cm, 2333 were 7.1–9.0 cm, 628 were 9.1–13.0 cm, and

TABLE 26.1
Malignant Tumors Treated by EChT According to Localization in 7642 Cases

Superficial Tumors	No. of Cases	Visceral Tumors	No. of Cases
Skin cancer	958	Esophageal cancer	1595
Breast cancer	644	Lung cancer	1113
Head and facial tumor	598	Liver cancer	961
Metastatic cancer of superficial	361	Throat cancer	21
lymph nodes	250	Prostate cancer	20
Thyroid adenocarcinoma	237		
Vulval tumor	227		
Melanoma	172		
Tumor of abdominal wall	138		
Cancer of oral cavity	133		
Rhabdomyosarcoma	84		
Parotid cancer	130		
Others			
Total	3932	Total	3710

TABLE 26.2
Malignant Tumors, Age and Sex in 7642 Cases

Age	No. of Cases	No. of Males	%	No. of Females	%
20~40	1284	765	59.6	519	40.4
41~60	4084	2710	66.4	1374	33.6
61~80	1985	1103	55.6	882	44.4
>81	289	181	62.6	108	37.4
Total	7642	4759	62.3	2883	37.7

there were 200 cases with a diameter of more than 13.0 cm. All tumor typing and staging were confirmed by histopathologic examination.

According to the international standard stipulated by the Union for International Cancer Control (UICC), the short-term effective rates of 3932 superficial cases were: complete response (CR) 29.1% (1144/3932), partial response (PR) 45.4% (1785/3932), no change (NC) 15.3% (602/3932), and progressive disease (PD) 10.2% (401/3932). Taking CR and PR as the effective rate, the total effective rate was 74.5%.

The short-term effective rates of 3710 visceral cases were: complete response (CR) 16.1% (597/3710), partial response (PR) 31.5% (1169/3710), no change (NC) 33.3% (1235/3710), and progressive disease (PD) 19.1% (708/3710). The total effective rate was 47.6%.

The clinical effectiveness varied with the stage, size, and location of the tumor. The effective rate of stage I and II tumors, the smaller sized tumors, and the superficial tumors were better than the stage III and IV tumors, the bigger sized tumors, and the visceral tumors. The study was statistically significant (Table 26.2).

One reason for the better effect observed for superficial tumors could be that needles can be more accurately inserted and better distributed. For this reason we often insert needles under direct vision when treating large visceral tumors.

The 5-year survival rate of superficial tumors was 49.5% (1946/3932) and that of visceral tumors was 21.7% (806/3710), where $p < 0.01$. The clinical effectiveness was related to stage. The 5-year survival rate of patients with stage I and II was 61.6% (2004/3253), while the survival rate in patients with stages III and IV was 17.0% (748/4389), where $p < 0.01$ (see Figure 26.9).

To improve the effectiveness of EChT for treating malignant tumors, the following measures are recommended:[20,21]

1. For patients with advanced tumors who cannot be treated with other therapies, EChT might relieve their sufferings and their life quality could be improved.
2. For a large tumor mass, more electrodes are needed. If a short circuit does not occur, the distance between electrodes could be reduced to 1.0 cm in order to increase the killing effect.
3. EChT should be combined with radio-chemotherapy as EChT could make tumor cells more sensitive to radio-chemotherapy. Positively charged antitumor agents, such as adriamycin and bleomycin, can be injected into the tumor, whereby the electric gradient will move the chemotherapeutic agent towards the cathodic area and destruct the tumor cells. Systemic chemotherapy, interventional therapy, and immunotherapy can also be considered in combination with EChT.
4. Chinese herbs could improve the immune system and inhibit growth of tumors, and may be a supplementary treatment in combination with EChT.

CLINICAL APPLICATION OF EChT TO TREAT VENOUS MALFORMATIONS

EChT was found to have a very good coagulation effect for bleeding tissue when patients suffered from lung cancer. After a number of animal experiments, EChT has been broadly applied on venous malformations since the 1990s in our hospital.[22,23]

Venous malformation (VM) results from an error in vascular morphogenesis. Lesions are composed of thin walled, dilated, sponge-like channels of variable size and mural thickness.[24] They are normal in histology, but with abnormal architecture and continue to grow throughout life by slow expansion.[25–27] VMs range from small, localized cutaneous lesions to diffuse malformations, involving multiple tissue planes, vital structures, and internal organs. VMs represent a group of benign yet locally aggressive tumors.[28]

Despite their benign nature, they can cause significant morbidity and even mortality if not properly diagnosed and treated.[29,30]

The influence for the human body by venous malformations includes soreness in the diseased area as the tumor compress and infiltrates the adjacent tissue, the hindering of the correlated limb's function, internal and external hemorrhage of the diseased area, damage of the patient's features, and some tumors might provoke coagulation disorders.[31,32] These venous lesions may become more pronounced with increased physical activity and during a Valsalva maneuver. VMs can usually be diagnosed by careful history and physical examination techniques aided by imaging such as magnetic resonance imaging (MRI).

MRI can confirm the location and extent of the tumor. Needling biopsy can be used when a high-grade malignant tumor is suspected.[33,34]

Treatment of VMs poses a major clinical challenge for contemporary medicine. The traditional surgical resection is difficult and can be unsuccessful due to complications, a high recurrence rate, potential scars of the operation, and limb disturbance. Treating methods by radiological intervention with embolization has an ill-defined role, and conventional sclerotherapy has little to offer for a large scale disease.[29]

The definitive treatment of venous malformations is one of the most controversial topics in medical practice, and it has

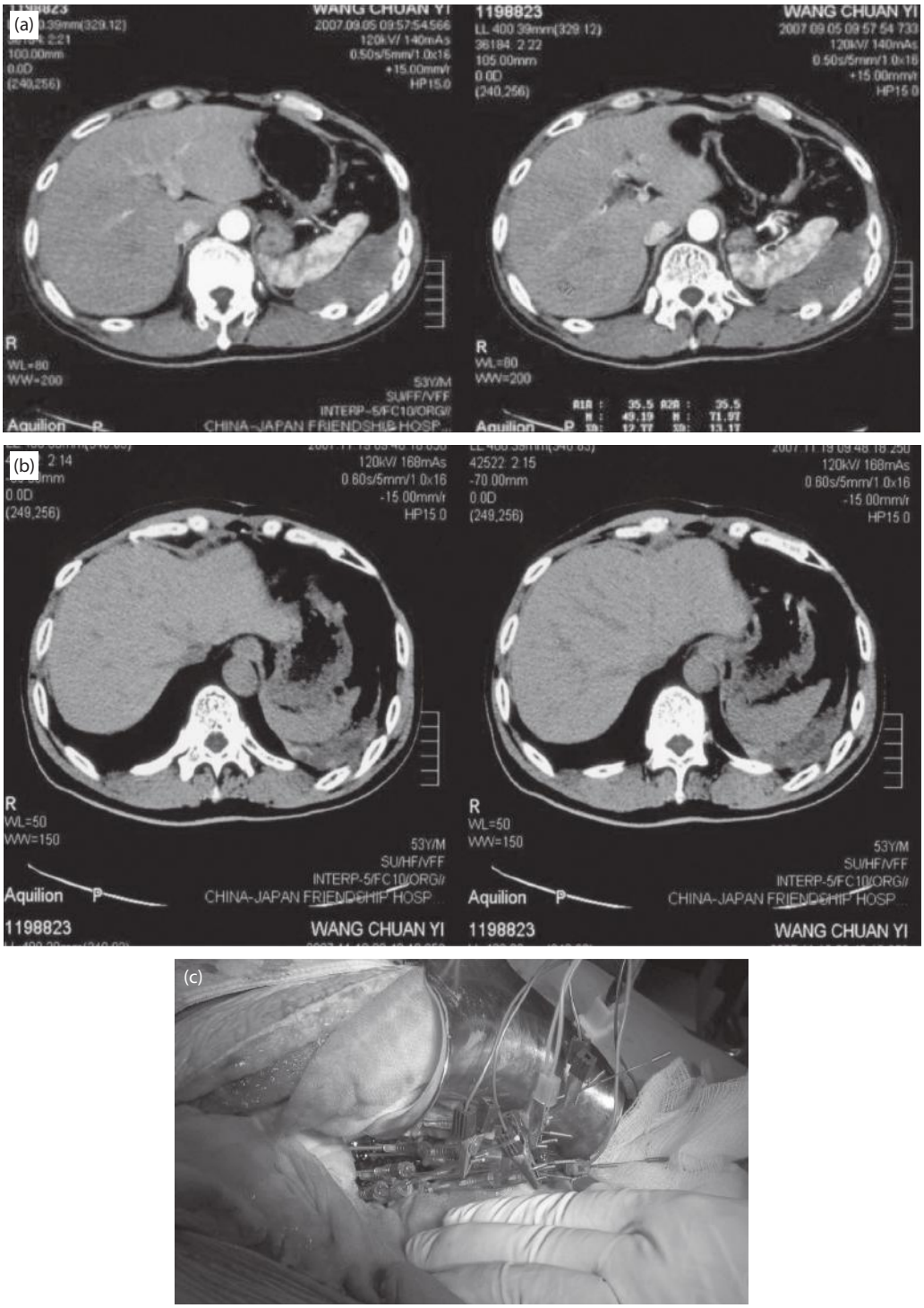

FIGURE 26.9 **(See color insert.)** Male, 53 years old. He suffered from a left thoracic and abdominal tumor, $14 \times 8 \times 4$ cm^3. The thoracic cavity and abdominal cavity was opened but the tumor could not be resected. Pathologic diagnosis: neurofibroma. Electrochemical therapy (EChT) was performed. The patient was followed up for 5 years and recovered well. (a) Before EChT; (b) 13 ms after EChT; (c) during EChT.

been a particular obstinate disease for modern medicine.[35] The best treatment for venous malformations is unclear in part because the outcome is variable. The common therapeutic modalities include elastic compression garments, sclerosing agents, and surgical resection.[36,37]

Elastic compression garments are only useful for symptomatic improvement in some cases.[38]

Intralesional sclerosants remains a mainstay in the contemporary management of venous malformations. However, sclerotherapy can require repeated treatments to maintain

control of the lesion and it is usually not considered curative as the lesion may eventually re-expand.[39]

Another mainstay of therapy for venous malformations remains complete surgical extirpation but it is often not possible except for small, well-localized disease or the muscles that are involved are expendable.[40] However, the surgical treatment of more extensive lesions can often lead to massive bleeding, nerve damage, loss of motor function, cutaneous scarring, and disfigurement.[35] There are only a few reports on the surgical treatment of these lesions, this is because the lesions may be difficult to remove due to their high vascularity, location of proximity to neurovascular structures, a tendency to infiltrate into the muscle and other tissues, and a quite high recurrence rate.[41]

The reported local recurrence rates range from 18% to 61%.[29] Intraoperatively, the surgeon usually relies on tissue signs such as pulsatility, color changes, bleeding, and refill to determine the margins of resection, but all of which fail to give an exact border of the margin. Some reports show that 40% of cases recur with incomplete excision and 17% of those recur even with microscopically complete excision.[37,38] Nevertheless, incomplete attempts only make future surgery both necessary and more difficult, as subtotal resection leads to recurrences, which are often larger than the primary lesion. Therefore, if the lesion is more diffuse, the morbidity created by extensive resection has to be weighed against the morbidity of the original disease. The focus of treatment should be improvement of pain, function, and appearance.[11,41,42]

The effectiveness of treating venous malformations by EChT is admirable. It can improve the patients' symptoms significantly and control the development of the disease. In fact, it has been shown to be a unique therapeutic method and superior to surgery for treating venous malformations, as there is no bleeding and no scar formation. In addition to a good cosmetic result, function is maintained. It offers a completely new effective method for treating venous malformations.

The poor clinical effect of EChT is usually caused by: (i) the electrode distribution is unreasonable and does not cover the tumor completely; (ii) the electric quantity is not enough; and (iii) the tumor size is too big or is close to a motor nerve trunk.

The 1325 patients diagnosed with VMs (1046 cases were followed up) and treated with electrochemotherapy (EChT) in our hospital from January 2000 to July 2012 were studied retrospectively. The diagnosis of VMs was made by clinical manifestations and MRI.

TABLE 26.3
The Tumor Distribution and Size in 1046 Cases

Item	Case (%)
Disease region	
Maxillofacial	262 (25.0)
Limbs	488 (46.7)
Trunk	296 (28.3)
Diameter (cm)	
<10	127 (12.1)
11–20	118 (11.3)
21–30	498 (47.6)
>31	303 (29.0)

In this study, 1046 cases were followed up for 6 months to 8 years, including 487 male and 559 female, aged 2–65 years and 14.3 years old on average. There were 5.8% (61/1046) of cases in our group that had remained or recurred in clinical manifestations after 1 to 2 years treated by EChT, the clinical manifestations were controlled by repeat EChT management. There were 55.1% (576/1046) recurrent patients in our group that had surgical resection in another hospital before they were treated by EChT.

Table 26.3 shows the distribution and size of tumors in these cases. The evaluation of the therapeutic effect of EChT was made 6 months after treatment as it could take 6 months to absorb the local necrotic tissues and coagulated clot after EChT. The therapeutic effect was evaluated as 4 grades according to WHO guidelines for solid tumors and based on our clinical follow-up and MRI test for the change of improvement of patients' symptoms and reduction in size of tumor. Grade 1: clinical obliteration, functional impairment of the diseased area recovers to normal and the tumor decreases by over 75%. Grade 2: most clinical symptoms disappear and/or functional impairment of the diseased area improves significantly and the tumor decreases by 50%–75%. Grade 3: clinical symptoms and functional impairment of the diseased area improves and the tumor decreases by 25%–50%. Grade 4: poor, little, or no improvement of symptoms and functional impairment of the diseased area, the tumor decreases less than 25%. Grade 1, 2, and 3 were regarded as effective.

The final result of this group was that 19.8% cases (207/1046) were classified as grade 1, 41.2% cases (431/1046) as grade 2, 29.6% cases (310/1046) as grade 3, and 9.4% cases (98/1046) as grade 4. The final effective rate was 90.6% (Tables 26.4 and 26.5).

TABLE 26.4
Therapeutic Effect in Different Diseased Region (Case [%])

Region	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Effective Rate (%)	
Maxillofacial	46 (17.6)	100 (38.2)	86 (32.8)	30 (11.4)	248/262 (88.5)	262 (25.0)
Limbs	95 (19.5)	184 (37.7)	148 (30.3)	61 (12.5)	427/488 (87.5)	488 (46.7)
Trunk	66 (22.3)	147 (49.7)	76 (25.7)	7 (2.4)	289/296 (97.6)	296 (28.3)
Total	207 (19.8)	431 (41.2)	310 (29.6)	98 (9.4)	948/1046 (90.6)	

TABLE 26.5
Therapeutic Effect of Different Tumor Size (Case[%])

Diameter (cm)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Effective Rate (%)
<10	105 (82.7)	15 (11.8)	7 (5.5)	0	127/127 (100)
11–20	68 (57.6)	28 (23.7)	13 (11.0)	9 (7.6)	109/118 (92.4)
21–30	25 (5.0)	222 (44.6)	202 (40.6)	49 (9.8)	449/498 (90.2)
>31	9 (3.0)	166 (54.8)	88 (29.0)	40 (13.2)	263/303 (86.8)
Total	207 (19.8)	431 (41.2)	310 (29.6)	98 (9.4)	948/1046 (90.6)

The therapeutic effect is closely related to the diseased region and extent. Those needing second therapy were those with extensive disease, which were usually managed by interval procedures to avoid complications.[13]

INDICATIONS FOR ELECTROCHEMICAL TREATMENT

EChT for Malignant Tumors

The choice of treatment for cancer patients needs to be individualized. The first choice is usually a surgical procedure with radiation and/or chemotherapy generally being second options. However, EChT has specific features, which makes this method useful in some cases where surgery, radiotherapy, or chemotherapy is not indicated.

EChT for Venous Malformations

Most of our patients suffering from venous malformations could be treated with EChT. The only problem for applying EChT is for tumors that are close to the important vascular nerve trunk and/or joint cavity. The main indications for VMs in our study included symptomatic relief from persistent or progressive pain, swelling, discomfort, acceleration of tumor growth, functional impairment, and cosmetic deformity. EChT was applied on breast hypotrophy and endometriosis in the abdominal wall and satisfactory results were achieved.[43]

The technical aspects are important. If possible, the needles should be inserted under direct vision. The distribution of, and the distance between, electrodes should be rational and adjusted when necessary. The electric quantity should be adjusted to the type and the size of the tumor.

COMPLICATIONS OF EChT AND ITS MANAGEMENT

EChT is relatively nontraumatic so that even fragile patients are able to tolerate the procedure without difficulty. A moderate rise in body temperature and in white blood cell (WBC) count may occur but a return to normal generally takes place after 3–5 days. DC is not harmful under 30 V, therefore, EChT can be considered to be quite safe. During EChT, a voltage much lower than 30 V is used but, if the insulation around the cannula is not properly arranged, surrounding normal tissue and skin may be damaged. Such damage is usually limited and typically restricted to an area of about 0.5–1.0 cm in diameter around the electrode; the injury can be self-healed in most cases. Injury to the adjacent motor nerve is also possible, which is usually caused by arranging electrodes too close to the motor nerve. Incomplete injury can naturally recover slowly while complete injury could cause permanent limb incapacity.

SUMMARY

In 1987, Professor Bjorn Nordenström was invited to come to Beijing to give lectures on BCEC theory and demonstrated the use of EChT on malignant tumors. Following 3 years of animal and clinical practice in China, good therapeutic effectiveness has been achieved. It was approved as a new therapeutic method to be used and spread clinically by the Ministry of Public Health of China.

Over 10,000 cases of various kinds of tumors have been treated with EChT in China within 20 years. It could be used not only for malignant tumors, but also for some benign diseases, such as venous malformations. In fact, EChT has been shown to be a unique therapeutic method for large scale venous malformations. Its effectiveness is due to there being no bleeding, no scarring, and no harm to the appearance and function. EChT was also applied on breast hypotrophy and endometriosis in the abdominal wall and a satisfactory result was achieved.

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27 Systemic Treatment of Cancer with Low and Safe Levels of Radiofrequency Electromagnetic Fields Amplitude-Modulated at Tumor-Specific Frequencies

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CONTENTS

INTRODUCTION

Over the past century, there have been many attempts to diagnose and treat cancer with electromagnetic fields. While the use of high energy ionizing radiation has become a mainstay in the diagnosis (x-ray and computed tomography) and treatment (radiation therapy) of cancer, the use of low intensity, nonionizing electromagnetic fields is much less common.[1] More than two decades ago, we pioneered the use of low and safe levels of radiofrequency electromagnetic fields (RF EMF) in the treatment of insomnia.[2] Our original hypothesis was that administration of low and safe levels of electromagnetic fields by means of an antenna placed inside the mouth cavity would allow for safe delivery to the brain.[2] Experiments conducted in healthy subjects in the United States[3] and Switzerland[4] demonstrated that a single modulation frequency (42.7 Hz) had a sleep inducing effect in healthy individuals. We tested the hypothesis that amplitude modulation of a carrier frequency such as 27.12 MHz, which is approved worldwide for medical use, could be used therapeutically for the treatment of sleep disorders and demonstrated that such an approach was both feasible and effective for the treatment of chronic insomnia.[5]

In 2001, Pasche and Barbault hypothesized that the growth of tumor cells might be inhibited by a combination of specific modulation frequencies. They developed novel, noninvasive methods to determine whether patients with a diagnosis of cancer exhibited biofeedback responses that differed from those observed in healthy individuals. These confirmed that cancer patients responded to a series of very specific modulation frequencies.[6] A feasibility study was designed in which patients with advanced malignancies who had no curative therapeutic options were offered treatment with 27.12 MHz radiofrequency electromagnetic fields. These were amplitude modulated at specific frequencies that had been previously

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been identified in patients with the same type of tumor. The primary purpose of this chapter is to review the literature pertaining to the interactions between RF EMF and humans, and to update previous reports on the use of amplitude modulated electromagnetic fields to treat cancer.

RECENT CHANGES IN ENVIRONMENTAL EXPOSURE TO ELECTROMAGNETIC FIELDS

Until relatively recently, little attention has been paid to the possible adverse health effects of the low frequency fields of the electromagnetic spectrum, that is, wavelengths greater than that of the visible range. Concerns about the lower energy range were originally limited to cancer risk associated with increased exposure to electromagnetic fields (EMFs) from high voltage power lines.[7] Over the past few years, there has been increasing interest in the effects of occupational and other environmental exposure to RF EMF.

Unlike higher frequency energy waves, RF EMFs do not cause predictable DNA damage, as they are well below the energy threshold required for ionization. DNA strand breakage and free radical formation that results from exposure to high energy gamma radiation is the basis for radiation therapy used to treat several types of malignancies, as well as to destroy proliferating bone marrow cells in preparation for bone marrow transplant. The effects of exposure to fields in the lower energy radiofrequency range are far less predictable, and in some cases, hotly debated.[8]

However, rapidly changing technology and a steady increase in RF EMF exposure has led to environmental exposure levels far surpassing those of previous generations. For example, since the turn of the millennium, the use of cellular phones has increased dramatically, with a recent estimate of more than 4.6 billion subscriptions globally.[9] It has become increasingly important not only to gain an understanding of possible risks associated with long-term exposure, but also to exploit possible benefits in a manner similar to that for the use of gamma fields in radiation oncology.

THE CONTROVERSY SURROUNDING THE POTENTIAL TOXICITY OF EXPOSURE TO RF EMF

The body of literature discussing the health risks of exposure to RF EMF is inconclusive. Epidemiologic and laboratory data demonstrate a cause-effect relationship between uncontrolled exposure to high-energy radiation and the incidence of radiation sickness and cancer. However, in contrast to the outcomes of populations exposed to high levels of ionizing radiation in Chernobyl, Nagasaki, and Hiroshima, there is no convincing epidemiologic evidence of increased disease risk associated with exposure to lower energy RF EMF.[10–12] Studies evaluating exposure to lower energy RF EMF have been unable to identify a direct cause-effect relationship between RF EMF exposure and malignancy or dementia. Several specific exposures and consequential health risks have been assessed in the literature, with limited consistency among studies.

Leukemia

One research emphasis has been investigating the risk for childhood leukemia as a consequence of living close to power lines, that is, exposure to 50–60 Hz EMF. This focus is potentially due to children's lower threshold of tolerance to exposure. A study in lymphocytes demonstrated no significant increase in chromosomal damage following exposure to extremely low frequency electromagnetic fields.[13] Similarly, no alteration in apoptosis was identified in multipotent hematopoietic progenitor cells exposed to low frequency magnetic fields.[14] Further, an Australian case-control study evaluating leukemia risk in the offspring of mothers with occupational exposure, found no increased risk for acute lymphoblastic leukemia.[15] While two case-control studies did associate increased risk of acute lymphoblastic leukemia with living in close proximity to power lines, the significance of the relationship was inconsistent.[16,17] Finally, a 2003 report from the Children's Health Workshop suggested there was no increased risk for acute lymphoblastic leukemia as a function of living in close proximity to power lines, but the group did admit that more thorough studies are necessary.[18]

While most of the literature has focused on the risk for childhood leukemia because of environmental exposure to power line EMF, increased risk for leukemia has also been evaluated in adults who live or work in close proximity to power lines. A Norwegian case-control study showed a nonsignificant increase in leukemia risk in the population with the greatest time-weighted average exposure to power line EMF, with no significant increase in incidence for those with occupational exposure.[19] A case-control study from Brazil evaluated mortality from leukemia and determined that there was a higher mortality rate in the population close to transmission lines.[20] Similarly, a Spanish study found a higher rate of acute myeloid leukemia in the population living in close proximity to thermoelectric power plants and maximum density high-power lines.[21] Ultimately, there is no conclusive study demonstrating leukemia risk as a function of long-term proximity to power line EMF exposure, as many studies are relying on patient memory and suffer from small numbers. A comprehensive evaluation of a dose-response relationship between exposure to EMF emitted from power lines and leukemia incidence will be difficult due to the significant number of confounding variables.

Neurodegenerative Disease

In addition to common occupational exposures, such as pesticides and heavy metal, occupational exposure to RF EMF has also been evaluated as a risk factor for Alzheimer's disease. A study in Swedish twins found no significant increased risk for dementia as a consequence of RF EMF exposure, but did suggest that occupational exposure may be linked to earlier onset in those patients who did develop dementia.[22] However, the exposure levels of the participants in this study varied greatly depending on their occupation, with magnetic field exposures ranging from 0.24 to 4.03 μT.[22,23] In both a review

and a meta-analysis of occupational exposure to EMF and subsequent dementia, the findings were inconsistent and did not clearly identify a cause-effect relationship between EMF exposure and Alzheimer's disease.[24,25] Furthermore, the authors of a review discussing the quality of these epidemiologic studies observed that there were few studies evaluating occupational EMF exposure and Alzheimer's, and that the infrequency of this occupational exposure would necessitate large studies.[25] They further concluded that the only occupational exposure that appears to be linked to Alzheimer's risk is exposure to pesticides.[25]

In contrast to the epidemiologic studies, recent *in vivo* studies suggest that EMF may have a protective effect on cognition in mice. Arendash et al. have completed two studies demonstrating that RF EMF at frequencies similar to cellular phone exposure (918 MHz) may suppress β-amyloid aggregation in Alzheimer's transgenic mice while also having a cognitive benefit in normal mice.[26,27] Similar findings were reported when 50 Hz RF EMF was used as repeated electromagnetic field shocks (REMFS) to prevent cellular senescence through a mechanism of increased expression of heat shock factor-1 (HSF1).[28] Further, animal models demonstrated increased lifespan and decreased amyloid toxicity following exposure to REMFS.[28] These studies suggest that EMF might be used as a noninvasive therapeutic option for Alzheimer's patients.

Similar outcomes were seen in an evaluation of the effects of 60 Hz RF EMF on an inducible rat model of Huntington's disease.[29] Rats exposed to EMF had improved neurological scores, reduced oxidative damage, and decreased neuronal loss.[29]

Evaluating this phenomenon epidemiologically, specifically by investigating a link between neurodegenerative disease and cellular phone usage, would be an interesting but difficult study to complete due to risk for recall bias. Current data from epidemiologic and animal studies are not sufficient for drawing a conclusion about any relationship between RF EMF exposure and neurodegenerative disease.

Glioblastoma Multiforme

In the age of mobile technology where many mobile phones are actually de facto handheld computers, a heated debate has emerged regarding RF EMF exposure from these devices and the possibility for increased brain malignancy, specifically glioblastoma multiforme. Glioblastoma multiforme is the most aggressive brain malignancy with the highest mortality rate.[30] Though there will undoubtedly be additional studies in the future, current prospective studies are limited and retrospective studies have been inconclusive. The largest retrospective study to date, the INTERPHONE Study, was a 13-country interview-based case-control study.[31] This study demonstrated a decreased risk for glioblastoma and meningioma in cellular phone users in all usage groups except for the highest exposure group.[31] The study also reported that glioblastomas most frequently occurred in the temporal lobe of the same hemisphere as where the phone was held, but these data were not significant, nor are they definitively reliable, as this study was plagued by recall bias and methodology limitations.[31] In a follow-up report of this cohort, the INTERPHONE Group reported no elevated rate in acoustic neuromas in cellular phone users.[32] These studies relied on significant self-reporting ranging from the daily usage to the side of the head exposed. Standardization proves difficult but it will be necessary in order to gain a better epidemiologic evaluation of any increased risk that may exist.[33] Studies that have shown an association between cellular phone use and glioblastoma have shown a very weak association, and consistency in reporting is, and will continue to be, a challenge.

In vitro and *in vivo* studies have also been unable to definitively link cellular phone RF EMF to glioblastoma risk. Big Blue mice, used as an *in vivo* model of mutagenesis, received cellular phone EMF locally to the head and did not demonstrate increased incidence of mutations.[34] Further, a study in young rats exposed to 1800 MHz Global System Mobile signal modulation (GSM) RF EMF revealed no changes in heat shock proteins or glial cells, suggesting that RF EMF does not adversely affect the developing central nervous system.[35] *In vitro,* the exposure of glioblastoma (U87MG) cells to 1.9 GHz pulsed RF EMF did not affect gene expression.[36] Moreover, there is no evidence that exposure to cellular phone RF EMF results in cytogenetic effects or changes in TP53 activation.[37,38] A 2010 review concludes that there is very little evidence supporting the hypothesis that RF EMF exposure results in genotoxicity.[39] The current body of literature suggests that cellular phone exposure is unlikely to be directly linked to brain tumor formation.

Without a driving mechanism functioning to increase cancer risk, it will be difficult to conclusively draw an association between cellular phone usage and risk for glioblastoma. The explosion of cellular phone use is still a relatively recent phenomenon; therefore, true long-term risk has yet to be assessed. Still, a recent publication posits that minimal evidence suggesting an association between cellular phone use and cancer makes a direct association less likely, especially when evaluating less than 10–15 years of use.[9] Although glioblastoma incidence is increasing in the United States, this increase began many years before the explosion of cellular phone use, further suggesting that cellular phone use does not substantially contribute to glioblastoma risk.[40–43]

BIOLOGICAL EFFECTS OF RADIOFREQUENCY ELECTROMAGNETIC FIELDS AMPLITUDE-MODULATED AT SPECIFIC FREQUENCIES: THE WINDOW PHENOMENON

In 1973, Bawin, Gavalas-Medici, and Adey reported altered brain rhythms in cats that were exposed to very high frequency (VHF) electric fields, amplitude-modulated at biological frequencies (1–25 Hz).[44] The "windows phenomenon" was first identified in 1975 when the efflux of radioactive calcium ($^{45}Ca^{2+}$) from chick forebrains was found to occur upon exposure to specific modulation frequencies of a 147 MHz carrier wave at low exposure levels (1 mW/cm^2).[45] Forebrains

from neonatal chicks were incubated in physiologic medium, containing a solution of $^{45}Ca^{2+}$. Samples were then washed and placed back into physiologic medium for 20 min and were exposed to one of the following experimental conditions: irradiation with sinusoidal modulation of the carrier wave at 0.5, 3, 6, 9, 11, 16, 20, 25, and 35 Hz; no modulation of the carrier wave and absence of irradiation (modulation depths were kept between 80% and 90%).[45] $^{45}Ca^{2+}$ effluxes from chick forebrain samples were then compared at the various frequencies of amplitude modulation of the carrier wave.

These experiments were the first to identify significantly higher calcium efflux in samples exposed to an amplitude-modulated carrier wave when compared to an unmodulated carrier wave and nonirradiated samples. Moreover, these experiments also identified that within amplitude-modulation frequencies there is a range (window) of specific frequencies which result in greater release of calcium (6, 9, 11, 16, and 20 Hz) from chick forebrains as compared to other frequencies in the same panel of exposure (no exposure; 0.5, 3, 25, and 35 Hz). Lastly, within the set of frequencies that triggered calcium efflux (6, 9, 11, 16, and 20 Hz) two frequencies (11 and 16 Hz) resulted in the highest amount of calcium efflux.[45] The "windows phenomenon," has been confirmed by other investigators in different settings. Specifically, Blackman et al. identified calcium efflux from chick brains using a 50 MHz carrier wave, which was amplitude-modulated at 16 and 50 Hz.[46,47] Additionally, Schwartz et al. were able to show that isolated frog hearts exposed to a 240 MHz carrier wave amplitude-modulated at 16 Hz also exhibited movement of calcium ions akin to the forebrains of neonatal chicks.[48] Taken together, these results point to a common response (calcium efflux) that comes from a narrow band of specific amplitude-modulation frequencies of a nonspecific carrier wave (50 MHz, 147 MHz, and 240 MHz) in both mammalian (avian, feline, and human/hamster-mouse neuroblastoma cells) and amphibian tissues.[44,46–50]

USE OF RADIOFREQUENCY ELECTROMAGNETIC FIELDS AMPLITUDE-MODULATED AT TUMOR-SPECIFIC FREQUENCIES

Discovery of Tumor-Specific Frequencies

More than a decade ago, we hypothesized that the growth of tumors might be sensitive to specific modulation frequencies. To test this hypothesis we began examining the biofeedback responses of patients with a diagnosis of cancer exposed to low and safe levels of radiofrequency electromagnetic fields using various carrier frequencies such as 27.12 and 433 MHz. RF EMFs were administered either with an antenna placed intrabuccally or with an external applicator placed in proximity to the tumor site (Figure 27.1). Exposure to these RF EMF results in minimal absorption by the human body, significantly below international electromagnetic fields safety limits.[51,52] Changes in the amplitude of the radial pulse were recorded while the 27.12 MHz or 433 MHz carrier frequencies were modulated with frequencies ranging from 0.1 Hz up to 114 kHz. Changes in pulse amplitude were the primary

FIGURE 27.1 Administration of radiofrequency (RF) electromagnetic fields (EMF). The antenna is placed intrabuccally, coming into contact with the mucosa to administer radiofrequency electromagnetic fields to the patient.

biofeedback methods used for disease-specific frequency identification.[6] According to the Federal Communications Commission (FCC), US340, the 27.12 MHz carrier frequency is not in use by federal and nonfederal, maritime, and aeronautical for actual communication. Additionally, this carrier wave does not fall in the band range designated for industrial, scientific, and medical (ISM) applications.[53] Therefore, usage of this carrier wave will not interfere or be interfered with by any electronic devices that would be in close proximity.

These experiments led to the discovery that patients with a diagnosis of cancer exhibit biofeedback responses at very specific frequencies, which are reproducible among patients with the same type of malignancy. However, only a small proportion of frequencies identified in patients with a diagnosis of cancer are common to several types of malignancies. We also found that patients with early-stage disease have biofeedback responses to some but not the majority of tumor-specific frequencies. Conversely, patients with advanced, metastatic disease exhibit biofeedback responses to the majority of the corresponding tumor-specific frequencies.[6] Examination of healthy individuals did not reveal biofeedback responses to tumor-specific frequencies.[1]

Treatment of Patients with a Diagnosis of Cancer

Identification of consistent and reproducible biofeedback responses to specific frequencies among patients with the

same tumor type led us to hypothesize that these frequencies might be implicated in their pathogenesis. We further hypothesized that administration of these frequencies might have a beneficial therapeutic effect. We therefore designed a feasibility study in which patients with a diagnosis of cancer and no curative treatment options were offered experimental treatment with the specific frequencies discovered in patients with the same tumor type. A total of 28 patients suffering from breast cancer, ovarian cancer, pancreatic cancer, colon cancer, prostate cancer, glioblastoma multiforme, hepatocellular carcinoma, mesothelioma, neuroendocrine tumor, nonsmall cell lung cancer, oligodendroglioma, small cell lung cancer, sarcoma, and thyroid cancer were offered experimental treatment until progression of disease or death.[6] Treatment was self-administered for 3 h every day by means of a portable device emitting a carrier frequency of 27 MHz, which was amplitude-modulated at tumor-specific frequencies. Each tumor-specific frequency was admitted for 3 s, starting from the lowest frequency and ending with the highest frequency. The sequence was repeated for 1 h, three times a day.

Two of the seven patients with stage IV breast cancer had major responses following intrabuccal treatment to breast cancer-specific frequencies. One patient with metastases to the bone and the adrenal gland had a complete response lasting 11 months. Another patient with metastases to the bone and liver had a partial response lasting 13.5 months. Both patients had estrogen receptor/progesterone receptor (ER/PR) hormone refractory breast cancer. A patient with recurrent thyroid cancer metastatic to the lungs had stable disease for 7 years.[1] Disease stabilization was observed in one patient with mesothelioma for 6 months, one patient with nonsmall cell lung cancer for 5 months, and one patient with pancreatic cancer for 4 months. All other patients had disease progression despite administration of tumor-specific frequencies.

These exciting and unexpected results led to the design of a phase I/II study in advanced hepatocellular carcinoma.[54] A total of 41 patients were offered treatment with hepatocellular carcinoma-specific frequencies until progression or death. Objective response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was observed in four (9.8%) patients. One patient with disease progression at the time of enrollment had a near complete response lasting more than 5 years.[1,54]

Treatment was well tolerated in both studies with only grade 1 toxicity reported, that is, fatigue and mucositis.[6] No patient experienced grade 2, grade 3, or grade 4 for toxicity even after 5–7 years of treatment. Complete blood counts and chemistry profiles obtained in these patients did not suggest any treatment related toxicity.

Laboratory Studies

In vitro experiments were conducted using exposure systems designed to replicate the exposure levels achieved in humans.[55] These experiments have shown that tumor-specific frequencies have the capability to block the growth of corresponding tumor cells, for example, breast cancer-specific frequencies were able to block the growth of breast cancer cells and hepatocellular carcinoma-specific frequencies were able to block the growth of hepatocellular carcinoma cells. However, breast cancer-specific frequencies did not block the growth of hepatocellular carcinoma cells and hepatocellular carcinoma-specific frequencies did not affect the growth of breast cancer cells. Similarly, tumor-specific frequencies did not affect the growth of noncancerous cells.[55] These findings demonstrate that tumor-specific frequencies identified in patients with cancer have the capability to have a direct impact on the growth of cancer cells. These exciting findings also suggest that the existence of a novel receptor mechanism, which may be modulated exclusively with radiofrequency electromagnetic fields.[56]

CONCLUSIONS AND FUTURE DIRECTIONS

There is growing environmental exposure to RF EMF worldwide, which is causing potential concern with respect to potential long-term toxic effects. As of today, there are no consistent findings pointing towards increased risk for cancer or dementia. However, additional well-designed long-term studies are needed to further characterize the safety profiles of these novel man-made environmental changes.

Both *in vitro* and animal studies conducted over the past two decades have shown that RF EMFs have an impact on calcium metabolism but only when amplitude modulated at specific frequencies. This nonlinear effect, which occurs at well-defined frequencies and exposure levels, is independent of the carrier frequency.

Our clinical investigations as well as our laboratory investigations suggest that the growth of cancer cells may be effectively blocked when exposed to low and safe levels of radiofrequency electromagnetic fields, which are amplitude modulated at specific frequencies identified in patients with a diagnosis of cancer. This novel therapeutic approach is potentially paradigm changing as it appears to only affect tumor cells without collateral damage to noncancerous cells. Additional studies in patients with advanced cancer and limited therapeutic options are warranted.

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28 Electroporation and Electrochemotherapy

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CONTENTS

INTRODUCTION

The term electroporation (EP) (also known as electropermeabilization) was originally coined to describe a method and process to temporarily permeabilize lipid membranes, including cellular membranes, by exposing such membranes to electric fields of sufficient magnitude and duration.[1] On the one hand, the development of EP was based on earlier observations that the permeability of artificial and biological membranes temporarily increases for ions and molecules when these membranes are subjected to short pulses of strong electric fields.[2,3] On the other hand, the development was prompted by the need of the then emerging field of genetic engineering for a more efficient, less cumbersome technique to transfect cells, that is, to introduce "foreign" DNA into cells. After the first publication describing highly effective transfection and stable transformation of mammalian cells by *in vitro* EP,[1] this new method quickly replaced earlier, less effective or more cumbersome ones. EP has since proven invaluable for the advancement of biological science, has given rise to new medical research and treatments, and has spawned applications in other fields. For example, DNA delivery by EP has become the preferred procedure for gene therapy and DNA vaccines, respectively, due to advantages over early chemical and viral DNA transfer methods.[4] Another early and successful medical application involves the *in vivo* delivery of anti-cancer drugs into cancer cells.[5] EP has proven highly effective in increasing trans-membrane flux by two to four orders of magnitude without causing significant side effects.[6] This application has created the new field of electrochemotherapy (ECT). Particularly in Europe, ECT is now increasingly accepted for routine clinical use, mostly in the palliative treatment of cancerous tumors, including cases where traditional therapies are not feasible or advisable.[7] More recently, EP methods employing electric pulses of higher field strength than those used for DNA or anti-cancer drug delivery have demonstrated, in initial clinical studies, their potential for nonthermal tissue ablation without a drug.[8] Higher field strengths induce necrotic and/or programmed (apoptotic) cell death selectively in the targeted tissue while sparing tissue scaffolds, in contrast to treatments based on thermal effects. Ablative techniques based on EP may be applied to a variety of therapies, including cancer and vascular therapies.[8] Other medical areas that either already benefit from EP, or may benefit from ongoing research in the future, include intra- or trans-dermal delivery of therapeutic substances, insertion of agents into membranes, electro-encapsulation, and others.[9]

Considering the intrinsic capabilities of EP, its potential impact on the future of medicine will probably be substantial: depending on the electric pulse parameters selected, EP can either (i) provide efficient access to the cell interior for essentially any ion, molecule, or small particle while maintaining cell viability, or (ii) essentially destroy any targeted cell or cellular tissue in a nonthermal, nonmechanical fashion

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with little or no effect on adjacent cells and tissues.[10,11] With the continuing development of suitable instruments and procedures, EP is bound to contribute to the introduction of new and improved therapies in the future. New and advanced applications of EP are now published in the medical and scientific literature at high frequency.

In this chapter, we will describe the different versions of EP, that is, reversible, irreversible, and nanosecond EP. The emphasis will be on reversible EP and its application in electrochemotherapy (ECT) because of its advanced stage. Irreversible and nanosecond EP have been developed over the last decade and offer intriguing possibilities for new therapies, but have not yet been the subject of extensive clinical studies.

ELECTROPORATION

Electroporation, also referred to as electropermeabilization (EP), occurs as the response of biological or artificial lipid membranes to pulses of strong electric fields. This response involves a rapid rise in the transmembrane voltage and a major increase in membrane conductance, accompanied by mass transport through the affected membranes.[1,10] The latter two effects are thought to be the result of hydrophilic pore formation across the membrane(s).

Manifestations of EP have likely been reported at least 250 years ago but the underlying principles and mechanisms were obscure.[11] It was not until the 1950s and 1960s that the interactions between electric pulses and cell membranes were dissected and quantitatively evaluated, primarily thanks to studies related to neural function and other studies on the nonthermal bactericidal effect of electricity.[12,13] Also, a 1965 paper described the effect of plasma membrane "breakdown" (the author called this effect "membrane punch-through") when the plasma membranes of giant algal cells were subjected to hyperpolarizing potentials.[14] Additional investigations found that short electric pulses above certain field strengths made biomembranes transiently permeable without permanently damaging the membrane structure[2,3] and that the induced permeability increase leads to a transient exchange of matter across the affected membrane structure.[15] Thus, the stage was set for the first application of these findings.

In a 1982 paper, Neumann et al. reported the first plasmid DNA transfer into mammalian cells by *in vitro* EP. The transfer resulted in the stable transformation of mouse L cells deficient in thymidine kinase (TK) by the plasmid carrying the TK gene of herpes simplex virus.[1] In the same paper, the authors introduced the term "electroporation" and proposed a mechanistic model of pore formation that, in its basic concept, is still in favor today and has been confirmed and refined by accumulating experimental evidence and mathematical modeling.[10,16] Reversible EP quickly became a mainstream technology in biological and medical research and its use expanded beyond DNA transfer to the delivery of other large and small molecules and particles into cells and vesicles, including enzymes, antibodies, viruses, particles and dyes. Moreover, essentially the same pulse parameters as used in reversible EP were found to cause membrane fusion when membranes are in close contact with each other, and thus, can induce cell fusion.[17,18] Both EP and electrofusion of cells have become standard methods employed in the construction of hybrid cell lines and in the cloning of organisms applicable to essentially all life forms, from microorganisms to plants, animals and humans.

Biological membranes are cooperatively stabilized organizations of lipids and proteins. The lipid portion of a membrane consists of a double layer of phospholipid molecules, which feature a polar, hydrophilic head group linked to two relatively long hydrophobic tails. In aqueous environments, these molecules spontaneously aggregate into a phospholipid bilayer, that is, they form a planar membrane with the polar head groups of the two monolayers oriented "outward" into the aqueous environment and the hydrophobic tails facing "inward" toward the center of the bilayer. The hydrophobic effect (Van der Waals interactions between adjacent lipid molecules) is the primary force holding lipid bilayers together.[19]

The originally proposed hypothesis of membrane pore formation in response to an external electrical field was based on thermodynamic and electrodynamic principles and is still favored as an explanation of the observed molecular and physiological effects of EP.[1] Over time, this hypothesis has been supported and refined by experimental measurements, as well as by increasingly sophisticated molecular dynamic simulations.[10,16] In the context of this chapter, we will only present a brief qualitative summary of the present model of pore formation, transmembrane transport and pore resealing. Some excellent review articles covering the mechanism, applications, and other aspects of EP are available.[20]

At physiological temperatures, biological membranes function as stable barriers separating two aqueous compartments, for example, the aqueous phases inside and outside the plasma membrane. Thermal motion at physiological temperatures causes random fluctuations in the relative positions of phospholipid molecules and the spaces between those molecules. This can result in "membrane defects" or "hydrophobic pores," but the extent of these disturbances is usually insufficient to cause membrane permeability. At higher temperatures, or under the influence of external electric fields, these spontaneous defects are likely to be the preferred sites for the intrusion of water molecules between phospholipid molecules and thus the formation of hydrophilic pores, that is, aqueous "channels" across the hydrophobic part of the membrane.[21] In an external electric field of sufficient strength the polar head groups re-orient themselves parallel to the external field direction, according to the electric field force exerted on their electric charges. The resulting field-stabilized structure is thought to be a transmembrane pore whose walls consist of the hydrophilic head groups of the re-oriented phospholipid molecules.[1,22] Once established, these structures allow trans-membrane transport of small ions and large and small molecules into the cell, as well as the transport of intracellular components out of the cell. If not interfered with, these pores will reseal spontaneously at a time scale of minutes, aided by

thermal motion of the lipid molecules. Direct observation of such pores has not been achieved, but extensive experimental data and results of molecular dynamic simulations are largely consistent with the described structures and processes.[10,16,21,23]

At least two types of stable "electropores" are thought to exist: (i) fluctuative, short-lived hydrophilic pores (P1) with an average diameter of 1.2 ± 0.2 nm and an after-field life-time of 1–5 ms;[24] and (ii) larger, fluctuative, longer-lived pores (P2) with an average diameter of ≥2 nm with after-field life times of minutes.[25] The characteristics of the P2 pores are consistent with the fact that mass transport across the membrane continues *after* an electric field pulse. In the case of "reversible EP" (see below) the pulse time is kept short in order to prevent cell damage to the point where pores can no longer spontaneously reseal and the cell dies. Thus, mass transport during the pulse is small compared with after-field transport. Pore longevity is also consistent with empirical results concerning optimal pulse parameters (field strength and duration) and time intervals between pulses (pulse frequency and number).[26] For example, significantly different pulse conditions have been found optimal for trans-membrane delivery of relatively small molecules (drugs) and large ones (plasmid DNA). Nominal field strengths of about 1000 V/cm and pulse durations of approximately 100 μs are optimal for delivering the drug bleomycin to mammalian cancer cells,[27,28] whereas 200 V/cm or less and tens of milliseconds are optimal for DNA.[29] Especially for the delivery of large molecules pulse trains of different design have been useful for maximizing trans-membrane transfer. In addition to choosing the best pulse parameters, many other factors influence the EP process, including the type of cell and tissue, size and shape of the cell, the electrical conductivity outside and inside the cell, composition and conductivity of the cell membrane, and mechanical stress exerted on the membrane. Poration of the plasma membrane does not occur uniformly over the surface of the cell. Maximal poration occurs at the pole caps (apexes) of cells in the direction of the external field vector.[1,22]

Mass transport across biological membranes triggered by EP is an interactive process involving transient electrostatic complexes between the ions, molecules, or particles crossing the membrane and sides of the pore wall. Larger molecules such as proteins or polyelectrolytes (e.g., DNA, RNA) form multiple contacts with membrane lipids.[23] While small ions may pass through hydrophilic pores in a relatively uncomplicated way (largely by diffusion), the transport of macromolecules is much more complex and is still not well understood. It is thought to involve initial adsorption to the cell membrane followed by interactions with lipid molecules of a porous patch of the membrane. It can essentially be excluded that a DNA molecule simply threads its way through a hydrophilic pore into the cell interior like a thread through the loop of a needle. It is more likely that a length-wise adsorbed DNA molecule becomes transiently part of the membrane structure. Such a structure can be imagined as DNA occluding a long macro-pore. Once within a porous patch of membrane, the DNA is an interactive part of this local membrane patch.[22] This model is to a certain extent supported by experimental data.[23] Analogously, proteins, drugs, and dyes also appear to transiently occlude large pores, or a porous membrane patch. Membrane-bound DNA can either dissociate from the membrane into the cell interior or return to the outside of the cell. The lipids of the previously occluded large pore can now re-organize to restore the standard membrane configuration. The lipids of the former "pore walls" will go through many mismatched lipid-water associations before the standard membrane structure is re-established. The observed slow return to the standard membrane structure is consistent with the random thermal nature of the pore resealing process.

So far, we have almost exclusively focused on "reversible EP," the method of exposing cells to electric field pulses within a certain range of strength and duration that transiently render the plasma membrane permeable, but allow the pores to spontaneously reseal and thus maintain cell viability. However, it has long been known that electric pulses of higher field strength and longer duration than those used for reversible EP lead to extensive rearrangements of membrane molecules, which can no longer be reversed by the spontaneous pore resealing mechanism: the membrane damage has become irreversible.[1] Such "irreversible EP," now also known by its acronym IRE, has been used in the past to kill microorganisms in drinking water and food, as well as to non-thermally destroy cell membranes to extract cell contents of value, for example, sugar from sugar beets, in a more energy-efficient way than by thermal methods.[30] More recently, IRE has been explored for medical applications, namely the non-thermal, nonmechanical ablation of undesirable tissue, such as cancerous tissue or tissue formed during restenosis.[8]

Another major innovation in the field of EP over the last decade has been the development of ultra-short pulses of very high field strength. Schoenbach et al. and Zimmermann's group pioneered this field, which is now variously known as Supra EP, Ultra EP or nanosecond EP. This technique uses pulses of sub-microsecond duration and field strengths of tens to hundreds of kV/cm (nanosecond pulsed electric fields, nsPEFs).[31,32] Interestingly, such pulses affect cell-internal membranes like the endoplasmic reticulum and the nuclear and mitochondrial membranes, while also causing poration of the plasma membrane. The implications of this type of EP are far-reaching, although medical applications are still in the early phase of development.[8]

Table 28.1 presents an overview of the different areas of EP in relation to the applied field strengths and pulse durations, as well as some of the resulting physiological effects and their applications. Weaver's group has put the various areas of EP into the context of a continuous field strength-pulse duration space, which stretches from field strengths of 0.1–100 kV/cm and pulse durations of 1 ns to 1 s. This approach facilitates the recognition of the differences and similarities of the different areas of EP and highlights relatively unexplored areas within the field strength-pulse duration continuum.[10]

TABLE 28.1
Electroporation by Electric Field Pulses of Various Strengths and Durations and Resulting Effects and Uses

	Applied Field Strength	Pulse Duration	Use/Effect
		Conventional EP	
Reversible EP			
Nucleic acid delivery	0.2 kV/cm	100 μs–1 s	*In vitro* or *in vivo* nucleic acid delivery for DNA and RNA therapies and vaccinations.
Electrochemotherapy	1.0 kV/cm	100 μs–1 ms	Intracellular delivery of anti-cancer drugs in malignant tumors.
Irreversible EP			
Tissue ablation	2.0 kV/cm	100 μs–200 ms	Nonthermal ablation of cancerous and other unwanted tissues. Tissue necrosis due to destruction of plasma membrane.
Electrical accidents	>4.0 kV/cm	>1 ms–>1 s	Tissue necrosis due to destruction of plasma membranes and thermal effects.
		Supra EP	
	0.1–20 kV/cm	1 ns–1 μs	Poration of intracellular and plasma membranes.
	20–100 kV/cm	1 ns–1 μs	Apoptosis triggered by secondary effects of intra-cellular membrane damage.

Source: Adapted from Weaver JC, Smith KC, Esser AT. *Bioelectrochemistry* 2012;87:236–43.

Note: The effects of various combinations of pulse strength and duration are listed in the order of increasing pulse strength. Pulses of 0.2–1.0 kV/cm and durations as indicated result in reversible electroporation (EP), that is, the pores generated in the plasma membrane reseal spontaneously within minutes after the pulse and allow the cells to survive. Note that effective pulse conditions within the range of reversible EP differ significantly for nucleic acid delivery and drug delivery for electrochemotherapy (ECT), respectively. Pulses of about 2 kV/cm and durations as indicated trigger irreversible EP (IRE), that is, the generated plasma membrane pores do not reseal spontaneously, leading to cell death and tissue necrosis. While IRE does not cause significant thermal or neural effects, higher field strengths, and longer pulse durations as encountered in electrical accidents inflict thermal and neural damage in addition to plasma membrane destruction. Conventional EP, which includes reversible and irreversible EP, affects almost exclusively the plasma membrane. However, Supra EP induced by pulses of up to 100 kV/cm and sub-microsecond duration affects both the plasma membrane and cell-internal membranes. Pulses of the highest field strengths (over 20 kV/cm) induce apoptosis as a consequence of internal membrane disruption and cascading intracellular responses. The ranges of pulse strength and duration values given are to some extent arbitrary as the EP effect depends on many factors, of which pulse strength and duration are usually the most prominent (see text). The values given do not delineate abrupt changes in pulse effects but it should rather be understood as markers in a continuous strength-duration space.

The field strength of "conventional" EP pulses ranges from 0.1 to 4 kV/cm, with pulse durations between 1 μs and 1 s. Despite this wide range of pulse characteristics conventional EP pulses have several features in common: (i) conventional pulses almost exclusively affect the plasma membrane and exert no significant effect on cell-internal membranes; (ii) pulse durations equal or exceed the passive charging time of the plasma membrane of approximately 1 μs, depending on the size and other properties of the cell and its environment; (iii) conventional pulses induce greater than physiological trans-membrane voltages at certain locations of the plasma membrane, cause membrane pore formation and, consequently, an increase in membrane conductance and permeability; and (iv) most of the electric field passes around and not through the cell. Presently, the two major applications of reversible EP are the intracellular delivery of anticancer drugs and biological macromolecules (DNA, RNA, antibodies, and other proteins), respectively. Pulse conditions for these applications have been optimized within ranges shown in Table 28.1. For example, pulses of relatively low field strength and long duration are preferred for nucleic acid delivery while the opposite relation of field strength to duration is applied for drug delivery in electrochemotherapy.

Table 28.1 also points out clear differences in cellular response within the spectrum of conventional pulse parameters. Whereas cells exposed to pulses of up to 1 kV/cm and 1 ms duration generally experience spontaneous resealing of hydrophilic pores within minutes after pulse cessation and remain viable, exposure to pulses of higher field strength and longer duration result in irreversible membrane damage characterized by cell lysis and/or necrosis. IRE is usually a component of electrical injury, but has for a long time not been recognized as such because it was not as apparent as other symptoms of electrical injury.[33] Normally, injuries sustained by lightening, electrocution, and electrical accidents involve several components, including thermal effects (burns and local tissue heating), neural paralysis and EP. Irreversible EP uses pulses of about 2 kV/cm and up to 1 s duration (Table 28.1). As mentioned, these pulses cause irreparable changes in the plasma membrane, leading to cell death and necrosis *without* a thermal injury component.

THERAPIES BASED ON REVERSIBLE ELECTROPORATION

The term electroporation therapy (EPT) has been introduced to describe the delivery of therapeutic agents across plasma membrane barriers facilitated by EP.[27,34] The first report foreshadowing the potentially broad use of EP for therapeutic purposes was published by Okino and Mohri.[5] The authors

treated tumor-bearing mice with intramuscular injection of bleomycin and observed retardation of tumor growth only when the tumor was electroporated after drug administration. Four years later, the first results of the treatment of cancerous skin lesions in humans, also with bleomycin and EP, were published by Mir et al.[35] The authors named the combined treatment involving an anti-cancer drug and EP electrochemotherapy (ECT). Subsequently, several clinical research groups in Europe and North America treated a variety of cancers in animal models and humans using various drugs and EP conditions. About a decade later, the treatment of over 600 patients with different types of cancer had been published. Besides progress in ECT, EP was starting to be used in imaginative new approaches in gene therapy, DNA vaccines, intra- and trans-dermal drug and gene delivery, vascular therapy, and other medical fields. An encompassing review of ECT and other applications of EP up to about 2002 has been published earlier.[36] This section will cover the fundamentals and new developments during the last decade of therapies based on reversible electroporation.

Electroporation is distinct from a method called "electrochemical treatment," which has also been used for cancer treatment but employs significantly lower electric field strengths over longer time periods.[37–41] These electrical conditions are not thought to induce EP but may function by an as yet unknown mechanism.

Electrochemotherapy of Cancer

Rationale

The size of the dose of chemotherapeutic drugs is generally limited by the severity of the induced toxic side effects. Administration of limited doses results in corresponding limited systemic drug concentrations, which, in turn, frequently result in drug concentrations inside tumor cells that are insufficient to achieve the desired therapeutic effect. Electroporation of tumor tissue can enhance intracellular drug concentrations to levels that are up to several thousand-fold higher than can be obtained in conventional chemotherapy.[42,43] Therefore, high intracellular concentrations can be reached in the electroporated tumor cells with relatively low extracellular drug concentrations.[6,44]

As EP enhances cell membrane permeability only transiently, the drug molecules that have entered the cell get trapped when the membrane reseals, thus, greatly increasing intracellular drug residence time and efficacy. This results in relatively high local therapeutic efficacy in the absence of systemic toxic side effects. Considering these factors, it follows that drugs with high intrinsic intracellular cytotoxicity and poor cell membrane permeation, such as bleomycin, will show the greatest gain in efficacy when combined with EP.

Drugs for ECT

Soon after the first electrochemotherapy paper appeared in 1987,[5] the effect of EP on the potency of different drugs against many specific cancer types started to be tested *in vitro* and *in vivo*. The effect of EP *in vitro* can be expressed as the cytotoxicity enhancement ratio (CER). The CER represents the drug dose necessary to kill 50% of the cells in the absence of EP (LD_{50}) divided by the drug dose required to kill 50% of the cells in the presence of EP ($LD_{50,\,EP}$). For different drugs this ratio varies from 1.0 (no enhancement) to 2500 or more and depends on the cancer cell line tested.[27,45] A low CER can either result from a drug that readily passes through the cell membrane without EP (e.g., 5-fluorouracil (5-FU) or from a drug whose permeation is not enhanced by EP. Suramin may be an example for the latter.[27]

In vivo, the effectiveness of EP can be determined by tumor response (growth, shrinkage, or disappearance) or by survival rate. Usually, such tests are performed with human tumors grown subcutaneously in immune-compromised mice. Tumor responses are scored on a multi-step scale from complete response (CR: no detectable tumor) to progressive disease (PD: appearance of new lesions or increase in tumor volume of more than 25% since the beginning of treatment).[46]

The effect of EP on the anti-cancer activity of 22 drugs against specific cancer types has been tested *in vitro* and *in vivo* and has been summarized in Reference 36. Among the drugs tested, bleomycin is exceptional. Bleomycin efficacy is enhanced for every tumor type tested, varying from several hundred- to several thousand-fold, depending on tumor type. More importantly, the combination of bleomycin and EP yielded the highest anti-tumor efficacy in essentially all cases. Cisplatin produced CERs between two and ten, depending on tumor type, and was the second most effective drug with EP. Out of the 22 drugs tested eleven more also yielded enhanced efficacies in combination with EP. Three other drugs showed marginal enhancements.

In vitro results were found to be generally predictive of *in vivo* results. Exceptions include carboplatin for melanoma,[47] and cisplatin and 5-FU for colorectal cancer.[48,49] Also, in most, but not all cases, EP enhanced the efficacy of a particular drug across all cancer types tested. Aside from exceptional cases such as 5-FU, it has not been possible to predict from the physicochemical properties of a drug the degree to which its efficacy will be enhanced by EP.

As mentioned, bleomycin is the most effective drug for ECT found so far. The drug bleomycin marketed in the United States and other countries under different brand names consists of a mixture of 11 molecular species that differ in their terminal amine region. The most prevalent species is A2. All bleomycin components are water-soluble glycopeptide antibiotics of approximately 1500 Da.[6] The relatively high hydrophilicity and molecular weight probably account to a large extent for the drug's poor membrane permeation in the absence of EP. However, its high intrinsic cytotoxicity accounts for its exceptional efficacy when ready access to the cell interior is made possible by EP.[43] Bleomycins chelate a variety of divalent heavy metal ions and cleave single- and double-stranded DNA and RNA at preferred sequences with high efficiency.[6,50,51] The cytotoxicity of bleomycin is

considered to be mainly due to DNA double strand breaks induced by free radicals generated by the active bleomycin-Fe^{2+} complex.[52,53] In addition to cleaving nucleic acids in the target cells, other effects induced by bleomycin may also contribute to its exceptional efficacy (see section "Anti-Cancer Mechanisms Induced by ECT").

Drug Administration

Intravenous (i.v.), intratumoral (i.t.), intraperitoneal (i.p.), and other parenteral drug administration routes have been used in ECT. Tumors differ from healthy tissue by elevated interstitial pressure, typically in the range of 10–40 mm Hg. The pressure gradient from tumor to normal tissue diminishes the effectiveness of i.v. drug delivery into the tumor.[54] Another disadvantage of i.v. injection is the systemic rather than local administration of relatively high doses of drug, which is prone to cause side effects. Early animal and human studies successfully used i.v. injection, but later comparative studies resulted in a preference for i.v. delivery.[55–58] When injecting drug intratumorally, it is important to inject the tumor as homogeneously as possible. This can be achieved by employing a "fanning" technique,[59] by pushing drug into the tissue while slowly retracting the needle, and by using multiple injection sites for larger tumors.

However, there are situations where i.v. administration may be appropriate. For example, treatment of patients with several or many tumor nodules has become a frequent use of ECT, especially since the European Standard Operating Procedures concentrated on the treatment of metastatic cutaneous and subcutaneous superficial tumors.[60] If many nodules are to be treated in one session, a single i.v. administration of drug may be preferable to individual i.t. injections for every tumor to be treated.

The recommended dose of bleomycin in conventional chemotherapy (without EP) is 250–500 International Units (IU)/kg once or twice weekly by one of several parenteral routes.[61] (Note: 1000 IU equals one unit as defined in the U.S. Pharmacopeia [USP].) However, the approved routes of administration differ from country to country. The maximal recommended cumulative lifetime dose of bleomycin is 400,000 IU. In early animal and clinical ECT studies throughout the 1990s various doses and modes of drug administration have been studied in the context of ECT, summarized in References 46, 62, and 63.

Starting in about 2000 and continuing into 2007, the first large Phase II clinical study for the treatment of recurring squamous cell carcinomas of the head and neck (SCCHN) was conducted by Genetronics, Inc., later renamed Inovio, Inc. (Plymouth Meeting, PA, USA), at multiple clinical sites in North America and Europe. The standard therapy in this study involved i.t. injection of 0.25 mL of a 4000 IU/mL bleomycin solution per cm^3 tumor volume.[36,64] These conditions were based on prior animal and smaller clinical studies.[55,57,65,66] In the Genetronics-Inovio clinical studies bleomycin solution was routinely injected intratumorally several minutes before EP, although injections up to 30 min before or after EP were reported to be effective.[55,67,68]

In 2006, standard operating procedures (SOPs) of ECT for the treatment of cutaneous and subcutaneous malignant nodules were published by a group of European scientists and clinicians and these SOPs have been widely followed for electrochemotherapeutic treatments in Europe.[60] The recommended treatment modalities are flexible and let physicians choose, within certain limits, between two different drugs, two different routes of administration and two forms of anesthesia. One of the two drugs, bleomycin, in an aqueous solution of 1000 IU/mL is either injected intratumorally at 0.25–1.0 mL per cm^3 tumor tissue, or may be administered intravenously as bolus at 15,000 IU/m^2. The other drug, cisplatin, may only be administered intratumorally as an aqueous solution of 2 mg/mL, in volumes analogous to those described above for bleomycin. The European SOPs call for starting EP within 10 min after i.t. drug injection. When bleomycin is administered intravenously, EP may start 8 min after drug infusion is complete and treatment should then be completed within the next 20 min to ensure a sufficiently high concentration of the drug in the tumor tissue.[60]

Pharmacokinetics of Bleomycin

The pharmacokinetic behavior of bleomycin upon i.v. bolus injection is reasonably well known. The drug does not bind to serum proteins and the plasma elimination half-life is 2–4 h in patients with normal renal functions (4–6 h after continuous infusion). Bleomycin elimination is primarily by renal excretion. In patients with normal renal function, 50%–70% of the drug appears in the urine within 24 h after administration.[61] When bleomycin, cisplatin or sulfhydryl boron hydride (BSH) was administered intratumorally or intravenously, in animal studies the drug in question accumulated more rapidly and to a much greater extent in tumors that were electroporated after drug injection than in nonelectroporated tumors. The residence time of the drug within the electroporated tumors was also significantly longer than in nonelectroporated tumors or in the blood stream.[48,69–75] These findings are supported by measurements of drug concentrations in tumor cells exposed to bleomycin *in vitro*, with or without EP, respectively.[43,49,76] Taken together, the *in vivo* and *in vitro* results are consistent with the notion that EP causes increased uptake of the drug during membrane permeabilization and causes the drug to be retained inside the cells after the plasma membrane reseals, while drug present in the interstitial space is washed out relatively quickly.

While the above findings project a general picture of the pharmacokinetics of bleomycin, they may not provide sufficient information for specific applications in human patients. In one study involving 21 patients with squamous cell carcinomas of the oral mucosa, about 27% of the amount of ^{57}Co-bleomycin injected per tumor was found in the blood as early as 10 min after injection. One hour after injection, an average of about 95% of the injected drug had cleared the tumor tissue. This rapid drop in drug concentration, which was particularly pronounced in carcinomas of the tongue and the floor of the mouth, might be caused by rapid resorption due to the high degree of vascularization of the maxillofacial

region.[77] Additional pharmacokinetic studies for special applications of ECT may be useful to achieve optimal and consistent clinical results.

Devices for Electrochemotherapy

A basic electroporation system consists of a pulse generator and an applicator. The applicator contains the electrodes that are brought in contact with the target tissue and allows the operator to safely deliver the high-voltage, high-current pulses produced by the generator to the treatment site. In addition, accessory instrumentation may be used, such as oscilloscopes, electronic data storage devices, and printers to measure and record pulse parameters, treatment times, and other data.

Pulse Generators

Early ECT treatments were performed with relatively simple generators designed for research purposes rather than for clinical applications. Some of these instruments delivered exponentially decaying pulses generated by discharge capacitors. Such pulses are not very suitable for *in vivo* applications as the pulse duration and current flow will vary depending on the resistance of the tissue and the surface area and distance of the electrodes. Conversely, well-designed "square" pulse generators allow the programing of exact amplitudes and pulse durations independent of variations in tissue resistance and electrode configuration. An overview of the design process of high-quality pulse generators and commercially available research and clinical EP systems is given in Reference 78.

The first electroporation system cleared for clinical investigational use in the United States (in about 2000) and also approved for therapeutic purposes in Europe was the MedPulser® System by Genetronics, Inc. (now Inovio, Inc.). This instrument delivers square wave pulses of predetermined voltage, duration and polarity to a six-needle-array applicator; it automatically generates a pulse cycle of six pulses of 100 µs each, delivered at 4 Hz, at a nominal field strength of 1300 V/cm.[79] The nominal field strength (V/cm) is the applied voltage (V) divided by the distance of the corresponding electrodes in centimeters. Two opposing needle pairs are energized simultaneously during each pulse. The polarity and direction of the pulses are varied in such a pattern as to achieve more uniform and effective EP of the tissue within the six-needle array than would be possible to achieve with a single pulse, or multiple pulses of the same polarity and direction. Directed by a microchip in the applicator, the MedPulser® automatically selects the pulse parameters for each type of applicator plugged into this instrument. The same microchip also records data on how and when the applicator was used. Applicators are selected by the surgeon as needed for a particular treatment. The MedPulser® also contains hardware and software to assure the safety and accuracy of the treatment and guides the surgeon through the procedure with prompts on the display screen. This instrument system has been extensively used in clinical studies of ECT and is being used for DNA delivery in gene therapy and DNA vaccine studies (www.clinicaltrials.gov).

A pulse generator of similar capabilities and producing pulses of similar characteristics as the MedPulser® is the Cliniporator™ (IGEA S.r.l, Modena, Italy). This instrument is the standard EP device featured in the European SOPs (also known as ESOPE) of ECT for the treatment of cutaneous and subcutaneous nodules.[60] The Cliniporator™ is CE-certified for use on patients and is widely used in Europe; however, it may not be used for human therapy in the United States (www.IGEAmedical.com). The instrument can be operated at two different pulse frequencies: at 1 Hz or at 5 kHz. The higher frequency will reduce the number of muscle contractions, but will enhance the force of the fewer contractions that will still occur.[60]

Applicators

Applicators contain the electrodes that determine the geometry and strength of the electrical field in a particular tissue when a pulse is delivered. In early animal and clinical studies plate (caliper) electrodes were used which consist of two parallel metal plates of fixed or adjustable distance that can be placed on each side of the tumor. Measuring the distance between the plates allows for easy calculation of the nominal field strength. Plate electrodes have the theoretical advantage of generating a rather homogeneous field; however, the tumor does not always fill the space between plates homogeneously and the resulting inhomogeneous field may be insufficient to electroporate the entire tumor. Tumors close to a body surface can be treated with this design,[35,57,60,80] although, arcing and burns affecting the skin may occasionally occur, which can be diminished or prevented by using conductive gels. Efficacy of EP can be improved by rotating the position of the plate electrodes 90 degrees between pulses, thus, electroporating cells sequentially in perpendicular fields.[81]

The limitations of plate electrodes can be overcome by using needle electrodes that are inserted into the target tissue and allow deeper seated tumors to be effectively electroporated. This invasiveness of needle electrodes is a slight disadvantage, yet it is presently the only feasible approach for generating the critical field strength in larger, subsurface tissue volumes. Single pairs of needles have the disadvantage of generating a relatively inhomogeneous field and of electroporating a relatively small tissue volume.[56] To overcome this limitation, multineedle arrays have been designed that have proven very effective.[56,82,83] Most notably, a six-needle array, energized via a suitable switching pattern allows an approximately cylindrical tissue volume determined by the 1 cm diameter of the array and the length of the needles to be subjected to fields of acceptable homogeneity and field strength.[34,56,57,82,84] As shown by computer generated field plots,[27,56] the minimum efficacious field strength of approximately 600 V/cm can easily be achieved with a six-needle array of 1 cm diameter (needles are placed equidistantly around a circle of 1 cm diameter) when pulses of 1130 V are applied in an appropriate pattern. An increase in the array diameter is not advisable because the higher voltage necessary to achieve the desired field strength over longer distances between needles would cause unacceptable side effects.

As the Cliniporator™ system is primarily intended for the treatment of cancerous cutaneous and subcutaneous nodules, the system offers a choice of three types of electrodes suitable for that purpose: (i) plate electrodes for treating small nodules that are relatively easy to treat with this type of electrode; (ii) six-needle hexagonal electrode arrays for larger (over 1 cm) and deeper seated nodules. These electrodes must be operated at the 5 kHz setting to reduce the number of potentially painful muscle contractions (see above); and (iii) parallel needle electrode arrays for certain types of nodules that cannot be treated with plate electrodes but do not require the use of hexagonal electrode arrays.[60]

Clinical Results

After publication of the first treatment of cancerous lesions in humans with bleomycin and EP in 1991,[35] several groups in different countries started to contribute both preclinical and clinical studies to this emerging field of ECT. About a decade later, a review of the published ECT studies revealed that over 700 evaluable lesions in over 200 patients had been treated in about a dozen locations in North America and Europe.[28,36] The treated lesions included, in the order of decreasing numbers, (i) malignant melanoma (primarily cutaneous metastases); (ii) squamous cell carcinoma of the head and neck (SCCHN) (primary and recurrent/refractive tumors as well as cutaneous metastases); (iii) basal cell carcinoma (primary and recurrent/refractory tumors); (iv) adenocarcinoma (recurrent/refractory tumors and cutaneous metastases); and several other malignancies in small numbers, including breast cancer, hypernephroma, transitional cell carcinoma, and Kaposi's sarcoma. These studies established that ECT was effective in treating a broad variety of malignancies in various manifestations.[28,36] The equipment used for these treatments consisted of different types of pulse generators and plate electrodes until in the late 1990s when the MedPulser® system was developed (see section "Devices for Electrochemotherapy"). This system, featuring hexagonal needle electrode arrays with needles of various lengths and diameters, and the capability of the pulse generator to deliver defined field pulses regardless of tissue resistance and electrode dimensions made it possible to treat primary and recurrent/refractory SCCHN and other tumors that could not be treated with plate electrodes.[64,66,79,85–90] In addition to improvements in equipment, procedural variations were also introduced. For example, drug injection changed from initial intra-arterial injection to intravenous and intratumoral injections, respectively, and the use of cisplatin was preferred by some investigators over bleomycin.

During the next decade from about 2000 to 2010, several major developments took place in electroporation therapies. ECT became an acknowledged treatment modality for malignancies, although its application was, and for now still is, mostly confined to certain niches of cancer therapy. An important step forward was the formation of a European consortium for the advancement of ECT, which eventually resulted in two projects funded by the European Union: the development of European Standard Operating Procedures for Electrochemotherapy (ESOPE) and the development of the Cliniporator™ electroporation system[60,91,92] (see the section "Devices for Electrochemotherapy"). These two projects have resulted in the dissemination of knowledge and hardware for the treatment of cutaneous and subcutaneous malignancies within the European Union and have made many physicians and clinical investigators aware of the therapeutic potential of ECT.

The implementation of ECT as a new medical technology is an interesting example of the often decisive role regulatory policies play in determining the success or failure of a new medical technology: While the European authorities approved the Cliniporator™ system for therapeutic purposes in combination with any qualified drug, the U.S. authorities concluded that the new EP delivery concept for bleomycin may lead to unpredictable effects of the drug, therefore, the drug-device combination must essentially meet the qualifications required for the regulatory clearance of a new drug. Although the Phase II clinical studies with bleomycin and the MedPulser® device demonstrated efficacy and safety of the procedure, [64,66,79,85–90] the financial requirements to complete a full-fledged "New Drug" application became overwhelming. The sponsoring company, Inovio, Inc., discontinued the application in 2007 and ECT is no longer present in the United States. Because the same U.S. regulatory rationale also applies to the Cliniporator™ system, the Cliniporator™ may not be used for therapeutic purposes in the United States.

Other major developments in electroporation therapies between 2000 and 2010 that are likely to play a role in the future of cancer therapy include the use of reversible EP for nucleic acid delivery in gene therapy and for DNA vaccines, delivery of proteins and nucleic acids for immune therapy, delivery of dyes and particles for advanced photodynamic therapy, and intracellular delivery of metal nanoparticles for targeted drug delivery and other medical applications. Of course, irreversible EP (IRE) and nanosecond EP for tissue ablation also hold great potential for future cancer therapy. Some of these applications of EP will be discussed in more detail under "Conclusion and Future Directions of ECT").

After the introduction of ESOPE and the Cliniporator™ system, ECT has gained momentum in Europe. The use of ECT for the treatment of cutaneous and subcutaneous tumor nodules has spread to many cancer treatment facilities where clinical studies involving relatively large numbers of patients have been conducted. For example, a study at the University of Padova, Italy, enrolled 52 patients with superficial metastases of different histotypes unsuitable for conventional treatment, including 34 of malignant melanoma, 11 of breast cancer, five of soft tissue sarcoma, and two of squamous carcinoma.[93] Six hundred and eight tumor nodules were treated with bleomycin and EP according to ESOPE, with 27% of patients presenting with nodules >3 cm in size. An objective response was obtained in 50 patients (96%) 1 month after the first treatment. Twenty-two patients received a second treatment because of partial response and/or newly appearing lesions. For the same reasons, a few patients received up

to five treatments. After a mean follow-up period of 9 months (range 2–21), only two patients relapsed in the treatment field. Through a questionnaire, most patients stated an improvement in local disease-related complaints and in activities of daily life. The investigators concluded that, in a palliative setting, ECT proved to be safe and effective in all tumors treated, and useful in preserving patients' quality of life.

Studies similar to the one just mentioned, also mainly concerning melanoma metastases, have been published.[94–100] One extreme example that demonstrates the efficacy, tolerability, and benefits of ECT for the control of metastatic nodules is the treatment of a patient with numerous unresectable skin metastases; ECT with bleomycin achieved good local control of the disease with a complete response of all 224 treated melanoma nodules. This remarkable number of nodules was treated in four sessions using 5 kHz pulse repetition frequency.[101]

Metastases of other cancers have been treated as well in fairly large numbers, for example, breast cancer in about 80 patients,[93,102–105] Kaposi's sarcoma in about 43 patients,[106,107] SCC in about 40 patients,[108,109] and a mixture of different histotypes in about 104 patients.[110,111] For most patients, multiple lesions were treated. In addition, patients were treated for recurrent or metastatic cancers where earlier treatments had failed or where conventional treatment was not feasible (for example, see References 112–120).

As pointed out by the authors, the studies cited above have demonstrated the strength and potential advantages of ECT compared to other treatment options. ECT achieved good local tumor control with tumors that were either chemoresistant, located in irradiated areas, located in areas difficult to treat, or for various reasons were classified as nonresectable.

Likewise, investigators have emphasized the observed and potential benefits of palliative ECT treatments, including tissue preservation, brief hospitalization (most procedures are performed on an outpatient basis), repeatability of the treatment for improved outcome, and favorable cost to benefit ratio. Depending on the situation of a specific patient, each of these benefits may contribute to an enhancement of the quality of life for that patient.

To summarize the present ECT status in Europe: ESOPE has helped to increase the awareness of ECT and the resulting studies have increased the understanding as to how ECT may fit into the overall concepts and policies of the treatment of cancer. At present, ECT is accepted by oncologists mainly in palliative settings and not as a first line treatment. Another area in which ECT has been practiced successfully involves special cases where more established procedures either are not applicable or have been tried but have failed repeatedly.[112–120] ECT is now seen by an increasing number of members of the medical community in Europe to have the potential for greater impact on the treatment of cancer. How this potential can be realized is presently being discussed by medical practitioners and scientists who are striving to better define ECT's role in treating malignancies of different types, stages and prognoses.[7]

Several future directions, which are not mutually exclusive, have been suggested. One direction being pursued is to implement well planned, large clinical studies to generate the necessary data to make ECT fully acceptable by the oncological community. Another direction emphasizes exploration of ECT applications outside the present ESOPE guidelines, which are very much focused on the treatment of cutaneous and subcutaneous tumor nodules.[60] There already exists a fair amount of published data on the treatment of cancer types, tumor sizes and earlier stages of cancer, which are well outside of the ESOPE guidelines and which can be helpful in planning new ECT applications.[64,66,79,85–90] A third direction, which is relevant to both directions mentioned above, is the development of new and improved equipment. For example, the present restrictions in treating large tumor-involved areas, tumors larger than those recommended in ESOPE, or tumors previously irradiated, can relatively easily be addressed by modifications of the present Cliniporator™-based equipment. MedPulser®-based equipment capable of treating primary and recurrent/refractory SCCHN tumors of sometimes large size has already been developed and successfully used in clinical trials earlier on.[64,66,79,85–90] More recently, impressive initial advancements both for treating deep seated tumors and the tools for essential treatment planning have been achieved.[121–123]

Anti-Cancer Mechanisms Induced by ECT

Bleomycin in combination with EP induces a strong and rapid anti-tumor activity. The typical macroscopic tumor response to ECT in mammals and humans involves slight erythema and swelling at the treatment site within the first and second day after treatment. The tumor mass of cutaneous and subcutaneous lesions becomes increasingly necrotic and 2 to 6 weeks after treatment forms a dry eschar that falls off, revealing healthy tissue underneath.[58,65,124–128] Tumors in a moist environment (e.g., upper aerodigestive tract) also necrotize, but necrotic tissue is washed away or separates from healthy tissue in pieces.[66,85,87] The void left by smaller tumors usually heals well, but necrosis of some large tumors (above 100 cm^3) has caused complications.[88]

Histological examination of the "edema" formed early after treatment of SCCs in mice resembles liquefactive necrosis but conspicuously contains apoptotic cells and cell fragments.[129] Gene expression analysis shortly after ECT reveals the activation of pro-apoptotic genes while certain anti-apoptotic genes are turned off.[74] Induction of apoptosis or pseudo-apoptosis, caused by rapid DNA cleavage by bleomycin, has also been observed *in vitro* after ECT.[53,130,131]

While destruction of tumor cell DNA by bleomycin may be the most important component of ECT's anti-tumor activity, other mechanisms apparently also contribute. (i) Both EP and ECT cause a "vascular lock" immediately after exposure to either procedure, which affects all tumor blood vessels as well as normal vessels surrounding the tumor. Vascular lock refers to a reduction or cessation of blood flow with a decrease in functional vascular density and an increase in the diameter and permeability of affected vessels. A clinical manifestation of this mechanism is the stoppage of bleeding of certain cancerous lesions, followed by crust formation. ECT actually has

proven very effective in the treatment of bleeding tumors.[125] The end result of ECT exposure is the destruction of essentially all tumor blood vessels, while normal vessels recover to a large degree and remain functional.[132–135] (ii) Bleomycin and EP each raise the level of intracellular reactive oxygen species, causing membrane lipid peroxidation and other cytotoxic effects.[136,137] (iii) Bleomycin releases cytokines such as IL-2, IL-6 and tumor necrosis factor,[138,139] and upregulates the tumor suppressor protein P53,[140] even in the absence of EP. These effects may contribute to tumor killing and may initiate a local and/or systemic immune-stimulatory effect, at least in some patients, as indicated by observations in animal experiments.[141–143] (iv) Recent reviews of immunotherapeutic approaches employing ECT or gene electrotransfer discuss the role EP and ECT can play in eliciting immune responses for cancer therapy. Results of such studies may also shed more light on the immune response mechanisms triggered by routine treatments of cancer with ECT.[144,145]

Advantages of ECT

Some of the advantages of ECT have already been mentioned in section "Clinical Results." Here we want to summarize strengths or advantages of ECT first from a safety and efficacy point, followed by advantages as experienced by patients.

One of the strengths of ECT is its excellent safety record. The ECT procedure is relatively short and the treatment is less invasive and toxic than most other cancer treatments. Side effects common for chemotherapy, radiation therapy, or surgery are not observed with ECT.[86,128,146] Adverse effects have not been reported with the exception of those discussed in the following section "Limitations of ECT."

Another significant strength of ECT is its broad spectrum of efficacy. Among the many types and stages of cancers treated so far, treatment efficacies varied relatively little and local tumor response rates compared favorably with other treatment options.[121] The broad-spectrum efficacy of ECT is probably related to multiple anti-cancer-mechanisms induced by ECT, including the actions of bleomycin on tumor cells and the effect of ECT on the vasculature and blood supply of the tumor (see section "Anti-Cancer Mechanisms Induced by ECT").

ECT generally results in good local tumor control. If complete tumor response is not achieved at first treatment, retreatment can usually be performed without complications, with a resultant increase in tumor response. As ECT is a tissue and organ-sparing procedure, the advantage translates into preserving function and appearance of the affected areas.[7,86]

While ECT is effective in destroying cancerous tissue, its effect on normal tissue is much milder. Healthy tissues treated with ECT are usually not severely affected and the mildly affected tissue readily heals. Because of the advantages mentioned, ECT has also been used, in many cases successfully, to treat cancerous lesions where no other treatment has been possible or justifiable.[74,86,147–149]

For patients, ECT may also offer advantages over other treatment options. Some of the advantages already mentioned in regards to safety and efficacy also represent a benefit to the patient. In addition, ECT treatment is almost always well tolerated, which allows older and sicker patients to be treated who may otherwise be at risk when subjected to conventional cancer treatment. Usually, the treatment needs to be performed only once and because of the relative ease and speed of the procedure, it is frequently performed on an outpatient basis, or it involves only brief hospitalization. These factors also contribute to the overall cost-effectiveness of ECT treatments.[7,28,86,91,128]

Limitations of ECT

Inherent limitations of ECT include muscle contractions and pain triggered by the electrical pulses, which can be attenuated during the procedure by sedation or various degrees of anesthesia depending on the condition of the patient and the location, size and number of lesions to be treated.[60] Other restrictions may be imposed by the accessibility of the tumor(s) to drug injection and electrode insertion, which can be overcome by suitable instrumentation or by providing access through surgery. Treatment of large SCCHN tumors, although effective in controlling the tumor, has in some cases led to wound healing complications and tissue deficiencies after the tumor necrotized and dissipated.[88] Therefore, especially when the tumor has invaded adjacent tissues, the treatment of large tumors should be carefully evaluated and, if performed, healing should be closely observed. High-dose irradiation of the tumor and adjacent tissue prior to ECT tends to enhance wound healing complications. These potential complications argue for an earlier use of ECT while the tumor is of smaller size and the tumor and its surrounding tissue have not been compromised by other treatment attempts. The difficulty of deviating from presently accepted treatment regimens in favor of a new relatively unproven treatment will be discussed in the following section.

Conclusion and Future Directions of ECT

ECT has gained credibility as a method for treating cutaneous and subcutaneous tumor nodules of essentially any histotype in a palliative setting.[150] Efforts are now underway to establish ECT as a mainstream treatment for cutaneous and subcutaneous metastases by designing and implementing major clinical trials that will determine ECT's position relative to other presently practiced treatment options. In addition, new instrumentation will be available to treat larger nodules.[7,151] ECT has also shown promise for treating other solid tumors, including primary and refractive/recurring tumors,[86,87,89,90] as well as deep-seated soft tissue tumors.[152] The development of new instrumentation and treatment planning procedures for the treatment of solid tumors has been progressing well.[122,153,154] One specific area where it appears ECT is ready to be introduced for more general use is the treatment of bleeding tumors. It seems that the experience in health care facilities where this treatment has been practiced for an extended time has been very positive concerning both safety and efficacy of the procedure.[103,125]

Essentially, any promising new treatment faces the challenge of designing clinical studies that will qualify the new

treatment for broader use without jeopardizing the chances of patients to benefit from established, generally accepted, and possibly more predictable, treatment regimens. In the case of ECT, one clinical study that addressed this dilemma successfully seems worthwhile mentioning. The problem was to justify treating SCCHN tumors at a relatively early stage without depriving the patients of the standard treatment indicated, in this instance, the surgical resection of the tumor including a margin of healthy tissue. The objective of the study was to evaluate the safety and effectiveness of ECT in treating primary head and neck cancers. The study design called for treating the tumor with ECT and 4 weeks later to excise any remaining tumor mass, including the usual margin. The excised tissue was to be examined histologically for any viable tumor cells. Such a treat-and-resect procedure was considered a prudent first step towards the treatment of early stage cancers by ECT, as it offers the opportunity to evaluate the degree of tumor eradication by ECT without withholding the benefit of conventional surgical treatment. The study involved 12 patients with T1 or T2 SCC of the oral cavity or oropharynx. After ECT treatment, the tumors necrotized as expected. Histological examination of resected specimens revealed tumor-free tissue in ten cases. In one case, cancer cells were found at the mucosal margin of the specimen, suggesting underestimation of the tumor extent during ECT treatment. In the second case, where the tumor extended to the base of the tongue, viable tumor cells were found in the center of the necrotic tumor, raising the possibility that the malignant cells may have been eliminated if the resection had been performed at a later time. After follow-up periods between 7 and 20 months (mean: 13.4 months), 11 patients were tumor-free without any sign of local or regional recurrence. One patient died 11 months after treatment due to rapidly growing neck metastases; however, the primary tumor site showed no evidence of recurrence. The results of this study indicate that ECT is an effective treatment for early-stage primary SCC of the upper aerodigestive tract and further studies should be conducted to confirm its safety and efficacy and to define inclusion and exclusion criteria for this application.[87]

This approach of treat-and-resect, or a modification of it, could be a valuable concept in the future expansion of ECT therapy to patients who do not want to accept the risk of foregoing standard-of-care treatment but could still benefit to a certain extent from being treated with ECT and, at the same time, contribute to the development of a new cancer therapy that potentially offers greater benefits to patients than present treatment modalities.

Another source to learn about the potential benefits and drawbacks of ECT in treating malignancies that have not, or only rarely, been treated with ECT in humans is the experience gathered by veterinarians. A large variety of tumors has been successfully treated with ECT in larger animals and the lessons learned could be helpful in identifying promising directions in which to expand the use of ECT for humans.[154]

One trend in the continuing development of ECT that has received increasing attention is the combination of ECT with other forms of treatment to achieve better regional and systemic tumor control. Most frequently, ECT has been combined with immunological or immune-stimulating treatments. Although efficacy has been shown in animals, success in humans has been modest.[155–158] However, the concept remains appealing.

In conclusion, it appears that the momentum and infrastructure that has been built in the last 20 years has put ECT on a trajectory for continuing improvement and growing therapeutic use. Most of the activity in the area of ECT has so far been in Europe but other regions in the world have taken notice. It will also be interesting to see how the different types of EP, reversible, irreversible, and supra-EP, will contribute to the improvement of cancer treatments.

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29 Bioelectromagnetic Paradigm of Cancer Treatment
Oncothermia

*Andras Szasz**

CONTENTS

INTRODUCTION

Modern hyperthermia treatments in oncology use electromagnetic effects by overheating the living object completely (whole body) or partly (regionally or locally). "Overheating" is understood to be a "higher temperature than normal." The deep, noninvasive heating is usually measured by the specific absorption rate (SAR) in the radiofrequency range from 100 kHz to 10 GHz,[1] while the elevation of the temperature in the whole body (whole body heating, WBH) uses an infrared radiation range heating up the blood in the subcutane volume. The heating up of the whole body or certain regions of it, or a definite local volume, started the rapid development in the area of modern oncotherapeutic practices from the late 1980s. Selective energy absorption has several favorable physiological and cellular effects promoting direct and indirect tumor destructions without notable toxicity. Its main success lies in its complementary applications. Oncological hyperthermia is intended to be an ideal combination therapy; it provides synergies with most of the conventional treatment modalities, boosts their efficacy, and helps to desensitize the previously noneffective treatments.

Hyperthermia has a constrained energy delivery, forcing the homeostatic equilibrium to change. From this point the control of the processes becomes complicated, with the adequate dose and protocol of the method and the reproducibility of the results being complex tasks. The thermal status of the heated volume is far from equilibrium.

There are multiple physiologic feedbacks trying to reestablish the lost homeostasis. The main correction factors in thermal control are the blood flow and the surface regulation processes, such as sweating, orientation control of the hair in the skin, etc. While WBH fixes the living body in thermal equilibrium, the same could never be realized in local treatments because the body certainly has a temperature gradient due to local heating. The local heating immediately activates the physiological controls, with first the blood flow, creating intensive heat-exchange conditions to re-establish the local out-of-equilibrium situation.

The locally or systemically increased blood flow tries to compensate for the growing temperature and cools down the target volume. The blood flow drastically modifies the pumped in SAR, irrespective of how accurately it was focused. As a consequence, the SAR and the temperature mapping of the targeted volume are significantly different.[2] Therefore, competition starts between the cell-killing potential of the heat and the cancer-supporting potential of the gained blood supply by the higher temperature of the targeted volume (Figure 29.1).

The focus on the radiofrequency (RF) energy is not an easy task, but not impossible. However, the focus of the energy does not mean the focus of the temperature. The temperature is naturally spread by the convective and conductive heat flow, derived from the temperature gradient and controlled by the physiologic constrains. Temperature spread is a natural process, and its termination is impossible. The time limits only the heated volume. This is how the ablation techniques work. In addition, the isotherms of the heating can be defined only with the help of the time factor.

Following the temperature distribution is a safety issue, as it is important to block the local burn of the healthy tissue,

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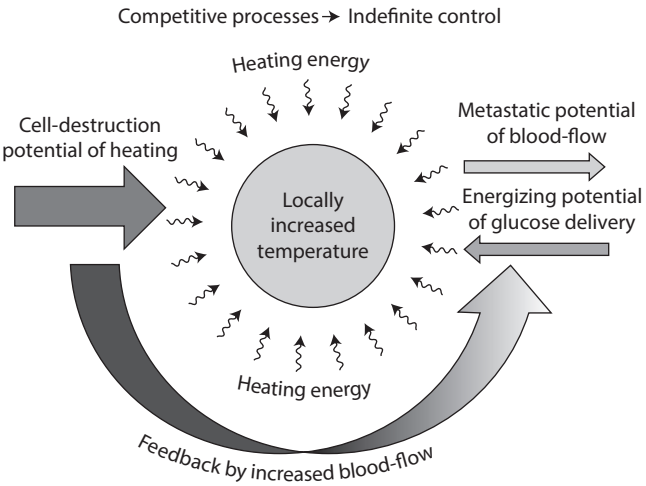

FIGURE 29.1 The growing temperature has physiological feedback. The homeostatic control increases the blood flow to cool the local disturbance and reestablish the homeostatic equilibrium. A competition starts: the cell destruction potential of the temperature is higher or the tumor energizing is stronger by glucose supply combined with higher risk of the metastatic potential.

while allowing the temperature for necrosis in the tumor. The temperature control shows the temperature spreading well, as well as the formation of the unwanted and uncontrolled hot-spots.[3–6]

The main challenge is to find a correct method to measure the temperature. Accurate, invasive point measurements are possible, but should not be applied as frequently as the hyperthermia treatment is provided, because there are multiple disadvantages, such as risk of dissemination or risk of inflammation and infection. The correct temperature mapping needs multiple probes in the nonuniform target, which is again a safety problem. However, the point measurement is inaccurate, depending greatly on the location of the chosen point in the tumor: the measured temperature is certainly less than the tumor average near to blood vessels, while in the necrotic part it is the opposite. As a consequence, invasive probes are rarely applied for guiding the actual treatment. Another possibility is noninvasive magnetic resonance imaging (MRI) or ultrasound measurements. The MRI parameters (time-shifts and other spectroscopic information) actually show the temperature change. However, these parameters certainly depend on the chemical, dynamical, and structural changes in the target, while the calibration of the temperature uses water or other phantoms, where the nontemperature dependent changes are excluded and, consequently, the calibration is incorrect. The most prevailing temperature control is the intraluminal measurement nearby, at a definite distance from the target. This method measures the "side-effect," meaning the temperature, which is not focused on the location.

The temperature is not only a safety parameter, but has an important role in the actual dose concept of hyperthermia. It is again a complex problem because the temperature is not extensive (not volume dependent), so its use as a dosage is impossible. A special dosage parameter was introduced, proportional with time: the cumulative equivalent minutes (CEM). This is proportional to the time of exposure, and refers to 43°C where the necrotic cell destruction is measured by an Arrhenius fit,[7] noted by CEM43°C. This parameterization, however, raises many doubts,[4] and does not fit into the observed tumor destruction.[8]

These challenges of characterization are accompanied by the nonuniform spatial distribution of the temperature, which, of course, results in the variation of the cell destruction in different volumes of the tumor. This is "counted" with the extra assumption of CEM43°CT_x, which means what large volume of the full target reached the given CEM43°C on average. Generally, the CEM43°CT_{90} is used (90% of the target reached the given CEM43°C on average).

The doubts about the temperature characterization are well supported by the fact that the uniform and high temperature in the tumor (at the physiological threshold of 42°C) caused by extreme whole body hyperthermia (WBH) has not resulted in better results by >15 CEM43°CT_{100}/treatment, than the local/regional heating with lower dose (<5 CEM43°CT_{90}/treatment) and with a very heterogeneous temperature distribution.

Application of lower temperatures (<40°C; mild-WBH) for treatments of longer periods (<2 CEM43°CT_{100}/treatment) showed surprisingly good efficacy.[9] This application of fever range activates the immune reactions and gives excellent addition to tumor therapies,[10–12] despite its low dose of CEM43°CT_{100}/treatment. This effect questions the necessity of the necrotic reference at 43°C in the time equivalence. Therefore, the CEM43°C dose underestimates the value of the nonnecrotic cell killing under 43°C.

The other side of the temperature range (high temperatures >47°C) does not fit again to the CEM43°C dose concept. This was measuring *in vivo* the time to the skin blistering on the given temperature.[13,14] The CEM43°C dose model overestimates the accumulation of thermal damage for high-temperature thermal therapy applications.

Another more general question is the value of the local treatment in malignant diseases. The malignancy is systemic, its local appearance is misleading, and the real threatening factor is its systemic behavior by micro and macro metastases. The real treatment must face the nonlocal approach, together with the local effect destroying the primary tumor, block the dissemination of the malignant cells, and stop the metastasis forming in distant localizations. For this task, the local treatment must have effects on the systemic formation of the malignancy.

Together with the above definite and serious physiological-medical problems, the technical solutions are also questionable, due to the fact that the deep heating needs complicated bioelectromagnetic considerations. The energy has to be delivered in depth without overheating the healthy layers between and has to be focused in depth on the heterogeneous and nonregular form of the tumor. The penetration depth of the biological material has strict frequency dispersion, quickly shortened by the growing frequency, and so contradicting with the demand of the high frequency for precise

beaming. The bolus-transmitters have to be constructed so as to be nonabsorbing but transfer the applied electromagnetic effects well; the temperature of the body surface has to be limited under the blistering threshold. The safety issues in actual cases usually modify the upper threshold of the action. Possible safe energy flow through the skin limits the Poynting vector (flow of energy in W/cm^2),[15] and as a consequence, a 60 min treatment has to have a power density of less than 0.5 W/cm^2 on the surface.

To provide enough energy in depth a power of >20 W/kg is needed,[16] which is far above the surface tolerance. Usually intensive cooling of the surface is applied to avoid blisters on the skin. This method has also various physiological feedbacks. When the cooling is too large, the feedback isolates the skin from the deeper cooling, reducing the blood flow in the subcutane layer under the cooled area. This could increase the permittivity of the skin and also decrease its conductance by intensified blood perfusion.[17] This increases the jump of the complex dielectric function at the incidence to the skin, which increases the jump of the electric field vector at the incidence point. The increased potential drop will increase the risk of burn. The surface cooling is again complex and needs a definite balance to be optimal. Another further complication is the loss of a control parameter by the cooling process. The incident (controlled) energy loses its indefinite part by cooling and so the energy is not suitable to characterize the process.

The history of hyperthermia in oncology has been hectic and controversial.[18] As a consequence, general professional skepticism blocked its application for a long time. The actually applied doses are unsatisfactory,[19,20] and due to the applied technologies could not be significantly improved.[21] The applied CEM43°C as a hyperthermic dose and, together with this, the complete control of the process has been debated, causing the rare acceptance of hyperthermia in oncology. Many prospective clinical trials of conventional hyperthermia are questioned.[22] A definite statement has been formulated by the well-known research group of hyperthermia: "Reference point is needed."[23] The future of oncological hyperthermia depends on the definition of dosing prescribed as usual in medicine.[24] A recognized specialist of hyperthermia formulated a long time ago[25]: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment."

The modulated electrohyperthermia (oncothermia) offers a new paradigm with nanoscopic heating having adequate answers on the present complex challenges.

SELECTION PARAMETERS IN THE NANOSCOPIC RANGE

Oncothermia changes the paradigm of local hyperthermia in oncology to solve the above problems.[26] During conventional hyperthermia applications, the macroscopic heating concentrates on the equal (homogeneous) temperature of the entire targeted volume or, at least, it constructs isothermal (isodose) patterns. The above described physiological feedbacks and the very inhomogeneous target make this aim impossible. Oncothermia is a new paradigm of hyperthermia technology. It produces nonequal heating, it does not try to reach any macroscopic "isotherm" curves. It differs from concept of the dose of ionizing radiation, which applies "isodose" as a usual goal. The isotherms are consequences of the "bad reflex" of the equilibrium effects. Heating in biosystems are far from equilibrium, when the physiological feedback, as well as the thermodynamical conditions, are contracting the macroscopic equilibrium. Oncothermia does not heat the complete tissue in the targeted volume equally.[27] It concentrates the liberation of the absorbed energy to the cellular membranes and to the extracellular electrolytes of malignant cells.[28] The microscopically inhomogeneous heating is far from thermal equilibrium.[29] Oncotherm applies the cellular approach selectively, heating up the malignant cells individually and liberating the incident energy in a nanoscopic range at the cell membrane. The heating energy is not liberated in a sudden single step, but regulated in multiple small energy-absorption processes. This makes it possible to control the energy liberation and to avoid the overheating of the healthy parts.

One technically good parallel example is the difference between the standard incandescent bulb and the energy saving fluorescent ones, using a fraction of the power for the same light. The incandescent bulb creates light by using a high-temperature filament, which heats up the environment, having only 10% efficacy, while the fluorescent bulb has an efficacy of more than 40%. It could be developed further by the more nanoscopic energy liberation, when the electrons, but not the molecules, are directly involved in the light production. These are LED bulbs, having more than 90% efficacy producing light. Following this technically inspired line the keys to success of the proper oncothermia treatment[30] are: (i) accurate selection of malignant cells; (ii) avoiding a gain of the blood flow (which cools, delivers nutrients, and risks dissemination); (iii) using effective cell killing (preferred apoptosis); (iv) acting on the immune system for natural support.

The accurate selection of malignant cells is a key step in proper oncothermia. There are robust electromagnetic differences between the malignant and healthy cells *in vivo*. The biological processes and structures of the healthy cells are distinguishably different from the malignant ones. These differences make it possible to accurately select the cancer cells by their electromagnetic behaviors and actively destroy them without any damage to their healthy neighborhood.

The main physiological differences between malignant cells and their healthy counterparts are

- Differences in the metabolic rate of the malignant and healthy cells (Warburg effect[31])
- Differences in the dielectric constant of the extracellular electrolyte and membrane-bound water of the malignant and healthy cells (Szent-Gyorgyi effect,[32] combined with the Schwan effect[33])
- Structural differences (pathological pattern recognition) between the malignant and healthy tissues (fractal physiology effect[34])

The consequences of these variations are mirrored in bioelectromagnetic properties of these cells and it allows us to distinguish the malignant cells and act selectively upon them.

Metabolic Variations

Due to its intensive proliferation, malignant cells exhaust more energy than do their healthy counterparts. In this aspect, the adenosine triphosphate (ATP) production is crucial. Otto Warburg discovered a type of metabolic deviation of malignant cells,[35] allowing them to produce massive amount of ATPs in a simple way.[36] The process is similar to the exorbitant muscle activity, when the ATP production eludes the complicated and oxygen-consuming Krebs cycle in mitochondria, and uses the simple (but less effective) fermentative method (glycolysis), producing a huge amount of ATPs. Malignant cells use fermentation in utilizing the glucose to produce 2ATPs, while the normal Krebs cycle uses the oxidative way, producing 36ATP with high efficacy.[37] The simplicity of the fermentation and the hypoxic environment favor it, despite the fact that this process produces 18 times less ATP. The reaction rate of the simple fermentative reaction could be 100 times quicker (approximated from the positron annihilation data[38]) than the oxidative way. The large glucose demand intensifies the glucose transport. The end product (lactate) also has to be transported away. According to Warburg theory, the tumor metabolism and its mitochondrial connection are under intensive investigation.[39–41]

Due to the huge ATP demand, high glucose influx is essential for the energy supply of malignancy. This is the basis of positron emission tomography (PET[42]), which is one of the most modern and accurate diagnostics of cancer. As a consequence of fermentation, the extracellular electrolyte in the vicinity of the malignant cell will be rich in glucose and in metabolites, especially in lactate. The ionic concentration of the extracellular solution changes greatly and creates electromagnetically distinguishable differences in the composition of the extracellular electrolyte in the vicinity of the cells by the highly concentrated metabolites.

The composition change is measurable by the conduction of the various liquids, directing the electric current to the more conductive path. This process clearly selects between the cells of different metabolic forms and automatically focuses the RF current on the close extracellular electrolyte of malignant cells (Figure 29.2), and heats microscopically[43] nonhomogeneously, keeping the system far from thermal equilibrium.[28] This automatic focusing makes it possible to follow any movement (breathing, heart beats, muscle movements) in the target tissue and the current density then follows it.

The higher conductivity of the tumor can be measured macroscopically as well. The increase of the current density in the tumor could be visualized by the measurements of real processes by a radiofrequency current density image (RF-CDI).[44–47] The electric impedance tomography (EIT) measures and images the tumor based on the impedance differences.[48] This effect could be applied in prophylactics such as mammography.[49] Further growth of the temperature increases the conduction and the connected selectivity which is a positive feedback process.[50] The measured gain of selectivity is 2% in °C,[51] which means 14% increase from a heating of 36 to 43°C.

Variation of Dielectric Permittivity

The living state exists in aqueous solution. Water content and its structural arrangement dominate the dielectric properties of living matter.[52–53] Living matter exists in aqueous solution, which is partly well ordered,[54,55] and is declared as semicrystalline.[56] Ordered electrolyte states have been suggested to be as much as 50% of the total amount of aqueous solution in living systems,[57] and have been shown to be dominant.[58,59] The water matrix orients the bonds by hydrophobic or hydrophilic properties producing a driving force constructing self-assembly structures, based on electronically driven instabilities.[60]

Rearranging, re- or disordering the electrolyte structure needs energy,[61] similar to melting ice with latent heat. This drastic change (phase transition) modifies the actual physical properties of the material without changing the composition of the medium itself. The decrease of the membrane potential, as in malignant cells, disorients a part of the order[62–64] and increases the electric permeability.[65] The cell–cell adhesion is decreased by the increasing permittivity,[66] which harmonizes with the autonomic malignant cells (disorder in the extracellular matrix[67]) and their decreased membrane potential.[68] The order–disorder phase transition indicates two different states of the cells: their autonomy status (called the α-state) and their connected, collective status (the β-state).[69]

The system (or a part of it) contains cells with high autonomy and high proliferation rate in the α-state. The α-states are metabolizing dominantly in a fermentative way similarly to Warburg's metabolic pathway. Cells in β-states dominantly

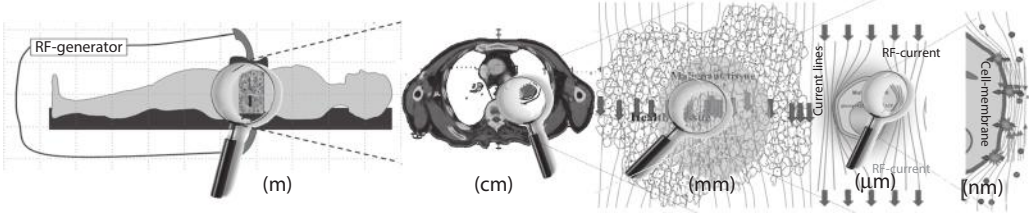

FIGURE 29.2 **(See color insert.)** The concept of the automatic focus of current density on the malignant cellular membrane.

have an oxidative metabolism, where their collective control organizes the distribution of the available sources. Highly organized living objects are based on cells in the β-state, which is 70% of the cells in normal homeostasis. Their cell division is controlled. This control is mandatory, because the division needs autonomic actions; the cooperative intercellular forces slacken, a part of the structure has to be dissolved and rearranged. Therefore, the cell in the division state temporarily became non-differentiated, similarly to the α-state. The actual balance of α- and β-states fixes the actual development status. The balance could be formulated by the cell status of co-operability ($\alpha \leftrightarrow \beta$), formulated by metabolic ways (*glycolysis* ↔ *Krebs-cycle*), or formulated with acting parts of the metabolism (*cytoplasm* ↔ *mitochondrion*).

It is probable that the electromagnetic behavior of the electrolytes in living systems balances the concentration of β- and α-states in highly developed living objects.[69] Cancer cells are in their α-state,[70] mimicking the early development of the cellular evolution.[71] The significantly larger permittivity and conductivity in the tumor tissue *in vitro* is explained on this basis.[72] The high dielectric constant allows the additional selection (focusing): the higher dielectric constant absorbs more from the RF energy, due to their disordered behavior. The ordered structure makes it possible to "channel" the energy flow, while the disordered case absorbs more energy.

The water content of the malignant tissue is an additional modification of the dielectric properties, which is higher than that of their healthy counterparts. The proliferating cells control their cell volume by their water content in the malignant growth.[73] This changes the complex dielectric function and provides more biophysical distinction for properly applied electromagnetic treatment.

The other dielectric selection possibility is based on the characteristic frequency dispersion of various compartments in the tissue. There are various forms of frequency dependent energy-absorption mechanisms that exist,[74] creating variation of the dielectric properties.[75] The β-dispersion[76] (known as the interfacial polarization effect) is between 0.1 and 100 MHz, and it is characteristically determined by the membrane capacities of the cell and the intracellular organelles, bound water to membrane, etc. Responses in this interval are well connected to the cell membrane changes. The β-dispersion of the bound water to the membrane occurs at upper frequency range, denoted by δ,[77] and so this part is well selective for the various cell-membrane states. Selective treatments have to be chosen in the range of β-dispersion.[78] In particular, in the difference between the malignant and healthy tissue, all the electrolyte and membrane properties differ.[79,80] The proper selection uses the dipole relaxation of β-dispersion connected to the membrane bounded water.[81] Rearranging (disordering) the water structure at the membrane needs energy,[61] which is clearly visible in the absorption spectra.

The absorbed bound water on the membrane has an important effect on the SAR and electric field distribution.[82] At low frequencies, the membrane impedance is extremely high, so the electric field in transversal incident is huge. The large β-dispersion in the bound water on the outer membrane (δ-dispersion) was measured at high frequency as well.[83] This has considerable SAR, which could destroy the water structure. The disordered water is one of the important factors of the cellular isolation;[9] therefore, it could lead to the autonomy of the cells, supporting the possible malignant transformation. The δ-dispersion of bound water starts much lower than the GHz region,[84] and is divided into subcategories in the complete range of 1 MHz–10 GHz.[85] The definite peak in the imaginary part of the complex dielectric constant (peak in Joule heat), characterizes the energy absorption in protein and protein bound water structures as well as contains the effect of boundary-interface structures too.[86] A unified model for impedance and induced transmembrane potential has been elaborated.[87] The model uses the electronic circuit schematics such as the three-element model, only all the elements (resistors and capacitors) are calculated as nonperfect (instead of every single element, perfect condenser and resistors are connected in parallel). The numerical evaluation of the model confirms well the specialties of the various measured data around 10 MHz.

Stochastic Selection of the Cells

The morphology is an important factor of cellular organization,[88] and varies between the different kinds of tissues. An experienced pathologist can easily recognize the malignancy in the tissue sample by their deviating structures. The pattern recognition from biopsies or other tissue samples is one of the major proofs of malignancy in oncological practice.

Cellular structures have coordination constrains preferring special coordination arrangements,[89] and form self-organized collectivity.[90,91] The tendency of proliferation is low in populations having small numbers of cells.[92] A critical cell density is necessary when starting significant cell division, similarly to the observed self-synchronization of chemical oscillators.[93] Dominantly, a favorable topological position (cyclic symmetry of the coordination number) chooses the actual division,[94] which is also justified experimentally.[95]

Healthy cells work collectively; their energy consumption as well as their life cycles and the availability of resources are controlled in a collective way by various forms of self-organization.[96] The organization process is governed by special "social" signals[97] commonly regulating and controlling the system. Self-organization in topology is connected to a fractal structure, which also appears in the dynamic self-similar stochastic behavior of the system.[98]

The healthy dynamism fluctuates by a particular identified pattern.[99] Healthy communication has a fractal behavior in both space and time. The healthy time fractal is a scale-independent fractal-fluctuation (pink noise), which can be identified by its dielectric properties.[100,101] The dynamic (time-fractal) behavior is the effective information exchange between the cells in space and time. The social signals and their correlation length are determined by different factors, among which is an energy-pack-like information transfer.[102,105] Consequently, normal (healthy homeostatic)

biological processes could be described by such self-similar function classes, based on the dynamical observations for the long-range correlation lengths.[106,107]

The collective order is different in malignancy than in healthy tissues. The cancerous cells behave dominantly as noncollective; they are mostly autonomic. They are "individual fighters," having no common control over themselves; the available nutrients mainly regulate their life. The order, which characterizes the healthy tissue, is lost in their malignant version, the bonding and junction type cellular communications disappear.[108] The consequence of these morphological differences is the well-recognizable pattern of cancer in pathology. The malignancy has a different fractal structure from its healthy counterpart,[109] causing basic structure-pattern pathologic differences between the tissues. Fractal analysis could be used for better pathologic description[110] and for prophylactics[111, 112] as well. The analysis of the fractal structures of malignancies could even indicate the stage of the disease.[113]

The living systems are open, dynamical structures, performing random stationary stochastic self-organizing processes.[114] The self-organizing procedure is defined by the spatio-temporal-fractal structure, which is self-similar in both space and time.[115] A special noise (called pink-noise, temporal fractal noise)—like a fingerprint of the self-organization[116]—is a typical and general behavior of living biomaterial.[117] The biosystem is based on cyclic symmetry and has infinite degrees of freedom arranged by self-organizing principles. On this basis, a new approach of the living state has been developed: the fractal physiology.[34,118] In the living system, instead of the deterministic actions, stochastic processes occur, so the predictions always have random, unpredictable elements.

This power spectrum characterizes the pink (*1/f*-, or Flicker-) noise. In general, a stationary self-similar stochastic process follows the pink noise when its power spectral density function is proportional to *1/f*. Due to the self-similarity and to the stationary stochastic processes of biosystems, all of those are *a priori* pink-noise generators,[99,119] with definite autocorrelations.

This remarkable result shows that the autocorrelation function of the pink noise of stationary random processes is similar both as a function of time-shift τ and frequency *f*. Therefore, the autocorrelation of living effects is inversely proportional to the time-shift, characterizing the interdependence of the process events. This is a clear fingerprint of the self-organizing structure of living processes.[119] The self-organized harmony could create synchronous oscillations in cell–cell signaling.[120–122] Due to the malignant autonomy, the collective communication signals (called social signals) are broken.[123] The missing information exchange could be reestablished by constraining information exchange from an outside source, the best of which is the modulation of the RF carrier. Stochastic resonances could be introduced for enzymatic processes,[30,124] which can modify the barrier fluctuations of the membrane transport of the cells.[125]

Recently, the research into amplitude modulated RF in human medicine has become very active,[126] and clinical trials have shown its progress.[127,128] Research has shown how an AC electric field inhibits metastatic spread of solid lung tumor.[129]

TECHNICAL REALIZATION OF NANOHEATING IN ONCOTHERMIA

Oncothermia uses the above selection factors targeting the malignant cells with high efficacy, heating them to high temperature very locally (nanoscopic range), and stimulating the immune reactions against the malignant metastases.[30] While the conventional hyperthermia focuses and targets a macro region, the nanoheating (oncothermia) process, the oncothermia solution is similar to the ionizing radiation concept, which also acts nanoscopically on the DNA of cells. The radiotherapy destroys the DNA strands; nanotherapy (oncothermia) destroys the cell membrane of the malignant cell, or, at least, induces apoptotic cell death from there (Figure 29.3).

The applied 13.56 MHz carrier frequency with proper time-fractal modulated current[130] undertakes this role.[131] This applied modulation helps to localize the malignancy in a complex target.[132]

The special selection effects described above are accurately applied in oncothermia, as briefly summarized in Figure 29.4. However, the dose of energy is crucial for all the selection steps. Applying too much energy realizes classical hyperthermia, heats up all components of the target, and the treatment loses its selection ability. The popular wisdom is valid: the difference between the medicine and poison is only the applied dose.

The electric effects are shown on a schematic impedance figure (Figure 29.5). The various actions are not independent, and the effects are overlapping and synergetic.

Heating of the extracellular matrix (ECM) more intensively than the cytoplasm provides a spherical thermal gradient, and consequently, creates heat flow through the membrane of all the selected individual cells. This centrally symmetric effect avoids the thermal limit of the external field application.[133]

This nanoheating is far from thermal equilibrium. According to Onsager's reciprocity relations,[134] the induced heat flow is coupled to the charge current, as well as the other parameters of the complete kinetics of the processes are also coupled.[135] This current is ~150 pA/μm^2.[136] This ionic current creates a zero mode electric current, which in turn induces a zero mode electric field in the cell membrane. Therefore, even small fields with zeroth mode components could elicit biological effects.

The temperature gradient through the cellular membrane pumps the nonequilibrium thermal processes. The gradient is quite large (~0.01°C/nm [≈10^7°C/m]),[134] creating a considerable heat flow (~1.5 pW/μm^2). One of the actions is the change of the intracellular pressure (1320 kPa)[134] by the electro-osmotic conditions.[30] Due to the rigid cell membrane of the cancerous cells,[137] the pressure could be fatal for the cell, which has a maximal tolerable lateral tensile stress of $\sigma_{max} \approx (2–10)10^5$ Pa.[138] The high pressure (when it is not enough to explode the cell) increases the membrane permeability, allowing the internal heat shock protein (HSP)

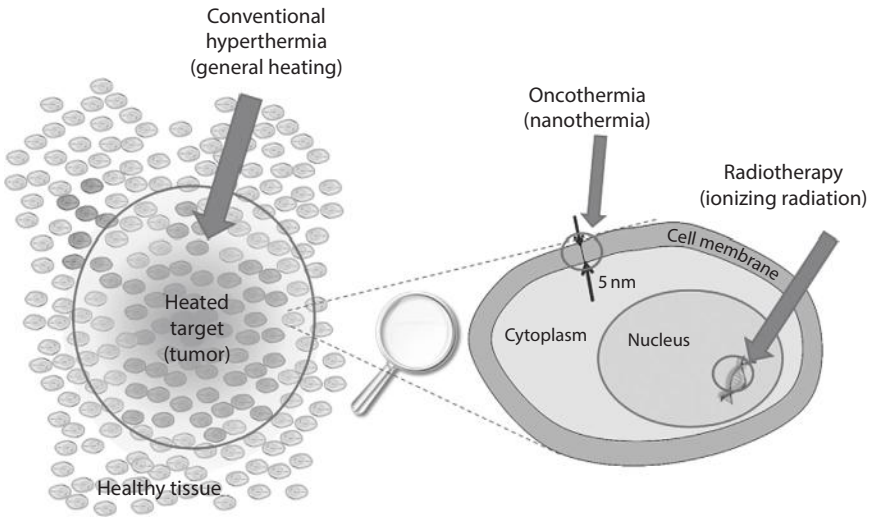

FIGURE 29.3 Oncothermia acts in a nanoscopic range. It is similar to the nanoscopic action of the ionizing radiation, which acts on another point in the cell.

chaperones to be expressed on the outer membrane to ignite immune reactions. This process is promoted by the temperature effect on the membrane permeability.[30]

The RF current has special effects characteristically acting on the membrane of the cells. Its ohmic component directly affects the membrane, while the displacement current (imaginary component) deflects it,[30] causing various mechanical effects on the outer membrane. The effect of the ohmic component is proportional to the square of the RF current (Joule heat) while the capacitive component simply depends on the current itself. A summary of the effects is shown on Figure 29.6.

BIOMEDICAL RESULTS

Oncothermia is well followed from laboratory to clinical bed, showing proofs of the above principles.[139] The effect of modulation is also clearly measured.[140]

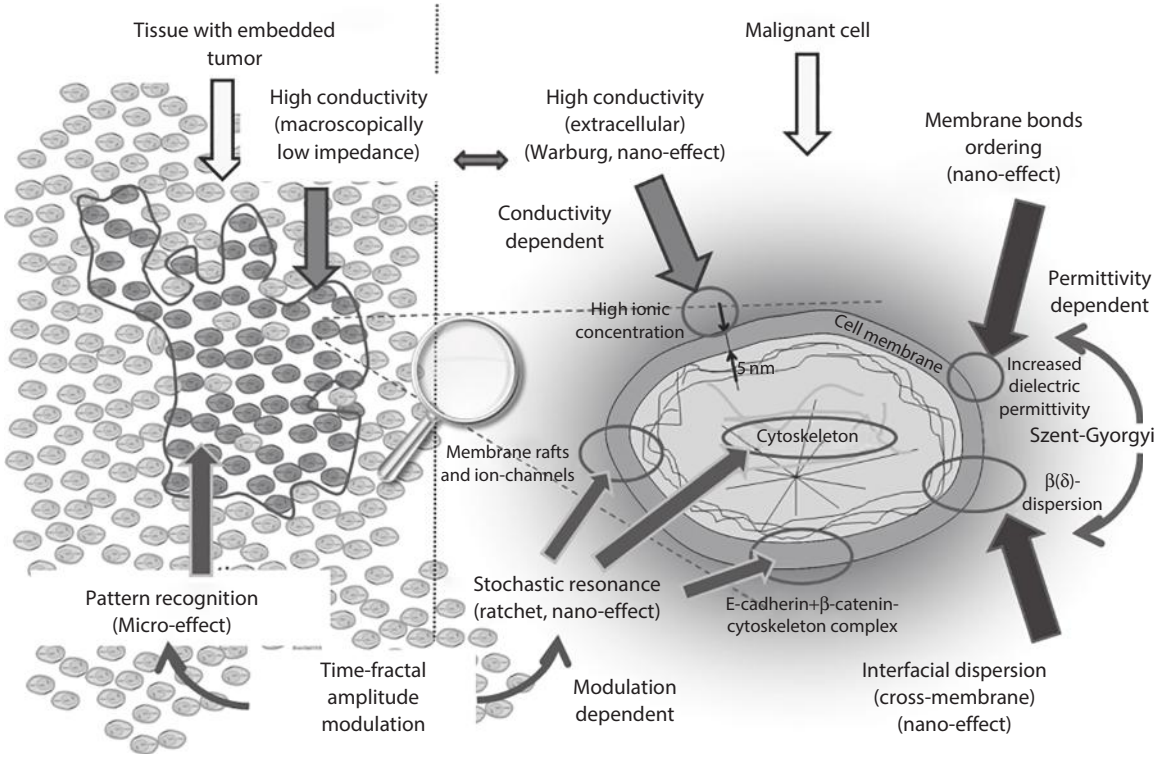

FIGURE 29.4 Main selection factors of modulated electrothermia (nanothermia, oncothermia) method (keeping clarity, only those details are shown that have a role in the processes).

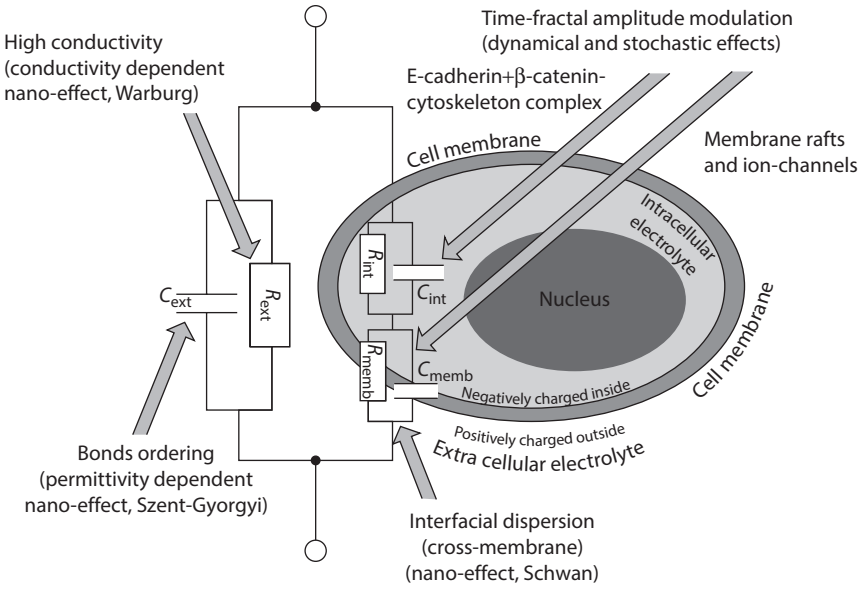

FIGURE 29.5 Action of the various selection factors in nanothermia shown in the impedance schematics of a malignant cell.

The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes, and ignites signal pathways for natural programmed cell death, avoiding the toxic effects of the simple necrosis. The synergy of electric field with the thermal effects selectively acts on the malignant cells.[141] The molecular changes in nanothermia are characteristics of the natural processes and they are dominantly apoptotic.[142] Apoptosis is over in its usual time range in 2 days; it is followed by a transition time, and starts multiple immunostimulation reactions after 72 h. The apoptotic cell death and any systemic immune action following it would be more natural than the necrosis, which is the standard goal of classical hyperthermia dosing the complete problem by the necrotic standard (CEM43°C). The other advantages of apoptosis are that it is free from toxic complications and it fits in well with the complex harmony of the actual system. The thermally induced apoptosis[143] and the activation of natural killer cells[144] are both possible in solving this task. In mammals, temperatures above 41–42°C produce substantial cellular damage,[145] but for the immune actions, the average temperature has to remain under the 40°C limit.[146] This apparent contradiction is solved by oncothermia, where a high temperature exists on the cellular membrane but on average, in a larger volume, the complete temperature remains under the limit, helping the immunoeffective processes.

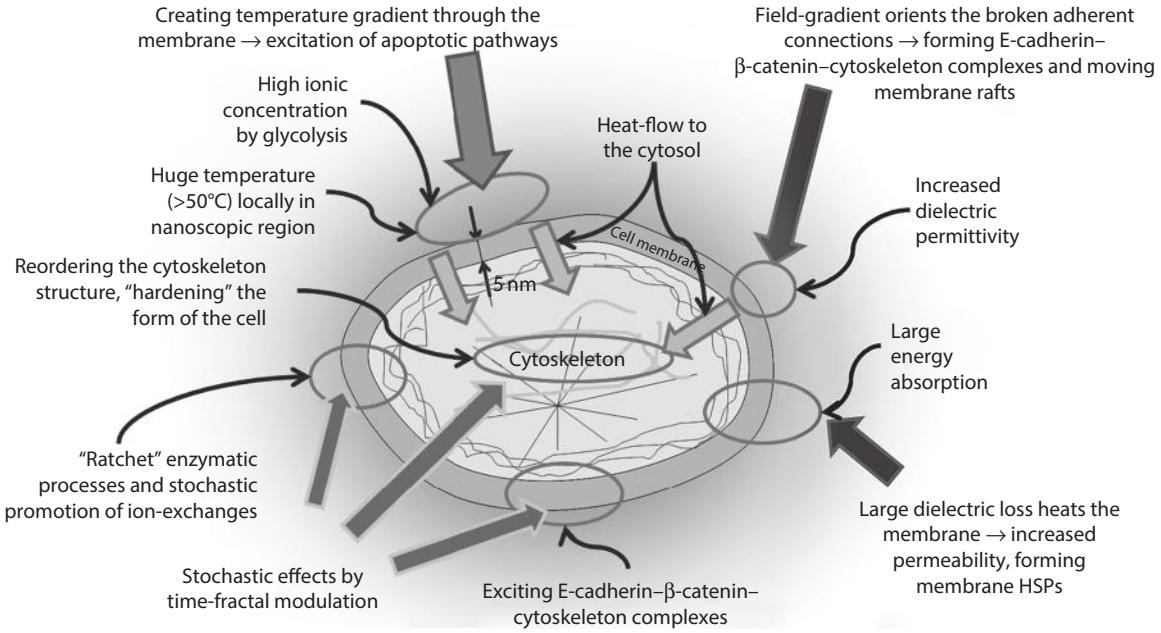

FIGURE 29.6 Summary of oncothermia selection effects on the malignant cell.

In oncothermia applications, the apoptosis becomes robust after 24 h.[147] The complete time-course studies clearly show the details of the apoptotic process,[148] which is measured histochemically with various methods. Measurements in time-course studies show the development of the natural apoptotic processes in a xenograft model (*in vivo*, HT29; Figure 29.7).[148–150] It is important that, after apoptosis, a special invasion ring forms around the treated tumor, and neutrophil and monocytes activity is measured in the region, indicating immune activation of the oncothermia process. The expression of CD3, CD4, and CD8 give enough information in expecting a certain abscopal (bystander) effect by local oncothermia.[151] Massive apoptotic

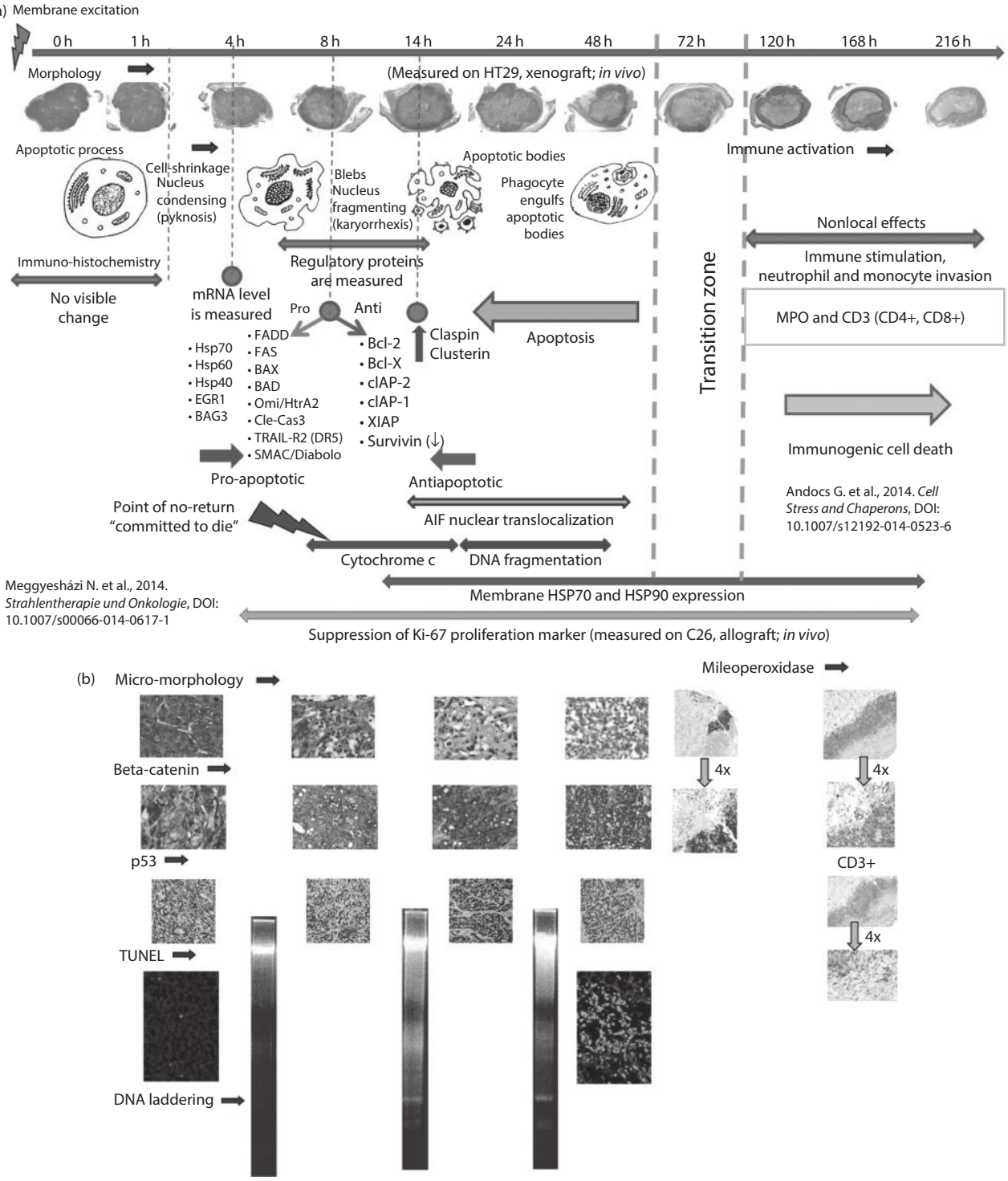

FIGURE 29.7 **(See color insert.)** Developments after oncothermia treatment *in vivo* by elapsed time (h) after a single shot treatment (30 min, 42°) HT29 xenograft model on nude mice.

signal-transduction starts from the membrane by the electric excitation,[152] which is also well proven on the mRNA level.[153] The important results are the possible immune effects of oncothermia, which could lead to systemic action.[154] The time-course investigations of various active compounds on mRNA and on protein levels are summarized in Figure 29.7a and some of their morphology changes on Figure 29.7b. The time delay indicates the long-duration processes, which were identified as programmed cell death (apoptosis), by various investigations: macro- and micro-morphology, enhanced activity of p53 tumor-suppressor, cleaved caspase 3 involvement, Tunel reaction, DNA fragmentation (laddering), etc. was carefully measured.[155] The massive presence of apoptotic bodies can also be observed together with the typical TUNEL reaction.

Furthermore, oncothermia suppresses the proliferation rate in the remaining living part of the treated tumor. Measurement was provided by Ki67 proliferation marker[156]. The surviving, living malignant cells in the treated tumor significantly suppressed the Ki67 marker compared to its untreated counterpart at all the investigated time scales. Together with the certain suppression of the proliferation, the adherent connections are reestablished,[139] blocking the disseminative processes. New connections make the missing signal transmissions possible as well. An important observation is the reestablishment of the E-cadherin bonds between the cells,[139] forming a complex with the β-catenin for signal transduction. This cell–cell connection is not only an effective signal transmitter, but it blocks the cellular dissemination by fixing the malignant cells in a tight connective way.

The research results are applied in the treatment practices. The veterinarian, pre-clinical level,[157] together with a wide range of clinical studies and practical clinical applications show the feasibility of oncothermia[30,156,158–162] as a complementary treatment to multiple other conventional oncotherapies. Its application in monotherapy, when other treatments fail, is also promising.[163] Some nononcological applications are also in progress.[164, 165]

CONCLUSION

Oncothermia uses nanoheating technology to select and heat the membrane of the malignant cells effectively. The heating is concentrated mostly on the cell membranes; therefore, the nanorange energy liberation could be precisely controlled without considerable wasted energy and without having disadvantages because of the heating of the tumor environment. Oncothermia results, and general benefits, open a new kind of local heating and destroy the primary and metastatic tumor lesions.

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30 Tissue Resonance Interaction in the Diagnosis of Prostate and Other Tumors as well as Inflammatory Conditions

Clarbruno Vedruccio and Carla Ricci Vedruccio*

CONTENTS

REVIEW OF SCIENTIFIC LITERATURE

In the past century, a great number of researchers have given their contribution to the study of the interactions between biological matter and electromagnetic fields. Many investigated the dielectric properties of living matter. Some others analyzed the differences between a cancerous agglomerate of cells and homogenous or "normal" tissues.

The period between the First and the Second World War spanned the early days of radio and electronics: vacuum tubes were the radio frequency oscillation generators and the spectrum ranged between a few kHz and 15 MHz. Measurements on biological materials were based on resistivity or impedance and instruments such as the Wheatstone bridge. After the Second World War, investigations on biological materials were extended into the microwave bands.[1]

Among the pioneers in this field, there were H. Fricke[2] and S. Morse.[3] In 1926, in their paper entitled "*The Electric Capacity of Tumors of the Breast*," they reported that "malignant tumors have a greater polarizability than normal breast tissues or benign tumors." They carried out their experiments at low frequencies around 20 kHz. Tissues were cut into small blocks and placed in a conductivity cell for measurement. They claimed that measurements performed on tissues from locations other than the breast convinced them that the method was of general applicability and that in some cases the "measurements may be made directly on the patient." Following the publication of these results, Fricke published a paper in which he declared that: "It seems probable that the measurement of the capacity may provide a very practical method for diagnosing the malignancy of a tumor." These experiences are of a great importance to explain and clarify some aspects that arise in the common use of the Bioscanner/Trimprob device, and it is extremely interesting to read the paper in which the authors wrote: "While the resistance of biologic tissues has been studied by many investigators, little attention has been directed to their capacity." The term "capacity" is to be associated to the well-known property of the tissues, which is usually called its "polarization." Theoretically, we assume two type of electric capacity, the first is the "static capacity" that is independent to the frequency of the alternating current, the second is the "polarization" type that depends upon the inter phases in the tissues and suggest that capacity might have a considerable biologic significance. The "polarization" capacity is related to the alternating current applied or irradiated to the tissue under test. In their paper, Fricke and Morse claim: "It has been a constant surprise to find that the capacity of malignant tumors of the breast is so consistently larger than that of normal tissues in the same location or of benign tumors as to make its estimation in any individual case clearly of diagnostic value."

As above reported, these aspects are important to clarify the mechanism of the nonlinear resonance interaction applied to the diagnosis by means of this technology. It is known by the users that the Trimprob works on three frequencies, and that the first is 462 MHz, while the others are the harmonics of the first ones.

Despite the frequency used for the analysis, but in accordance with the Fricke and Morse paper, the tissue capacity values have to be higher for the malignant tumors, lower for benign, and much lower for healthy ones. The measured values are also greatly different in the order of four times greater for malignancy than for healthy tissues. In other words, we have to expect that a malignant cells agglomerate that it is characterized by a high capacity, must have a nonlinear resonance interaction on the lower frequency of the harmonically related group emitted by the Bioscanner/Trimprob.

Differently, the benign pathologies, such as benign prostate hypertrophy (Figure 30.1) or breast fibromas, will not have the same capacity than a malignant tumor and, of course, the nonlinear resonance interaction could be detected on a higher frequency.

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FIGURE 30.1 Prostate examination.

MATERIALS AND METHODS

The main feature of Trimprob apparatus is a cylindrical probe shown in Figure 30.2, within which, a resonant cavity incorporates a transmission line tuned to the frequency of oscillation, which is in the 65 cm wavelength band (462 MHz).

At the open end of this line there is a semiconductor with nonlinear characteristics, which is activated by a nanosecond electromagnetic pulse. This transient provides an injection of electromagnetic energy into the tuned line, which performs a damped oscillation. This particular tunable amplifier-oscillator represents the core of the Trimprob diagnostic device. It possesses lock-in or synchronization characteristics and, because of its particular construction, it produces a harmonically related group of coherent electromagnetic waves. These oscillations are radiated as a cardioid beam through the oscillator dome at the end of the probe, and is aimed to irradiate the diseased tissues.

The working principle can be explained by considering the equivalent circuit diagram of Figure 30.3. The left part stands for the probe and the right part for the tested biological tissue, while the coupling is represented by (virtual) interrupted lines. Inside the probe, the transistor T activates an electric circuit, which has a natural frequency of oscillation f_1 that is determined by self and capacity of this circuit. The current I passing through T is a nonlinear function of the potential difference V. Actually, $I = -\alpha V + \beta V^2 + \gamma V^3$, where α defines a "negative resistance." It results from a positive feedback, mediated by magnetic coupling with the self of the first circuit. This nonlinear system produces stationary oscillations of well-defined amplitude, but when the probe is brought close to the tested biological tissue, it becomes an "active oscillator" that interacts with a "passive oscillator."

Although the irradiated biological system contains various subsystems that could be set in forced oscillations, their mutual interactions are negligible. It is therefore sufficient to consider the effects of the active oscillator on one particular passive oscillator of given resonance frequency f_2. We can even imagine a circuit, where the self and capacity determine the frequency f_2, while the resistance R defines energy absorption. The probe acts there like an "open capacity" and the tested biological tissue is subjected to the resulting electric field. This type of coupling is unusual. It involves a capacity C that increases when the probe approaches the tested tissue. Since this capacity facilitates the passage of high frequency currents, we can call this a *dynamic coupling*. All these features are taken into account by two coupled differential equations, describing the possible variations of the potential differences V and U. The detailed mathematical treatment is available on the internet,[1] but the basic ideas can be expressed in simple terms. Let us consider the particular case where the active oscillator is unperturbed ($C = 0$). The equation for V reduces then to the well-known *Van der Pol* equation, initially introduced to account for the possible actions of a triode. Even when the amplification coefficient α is very small, the rest-state ($V = 0$) will be unstable. The slightest perturbation will be amplified and the capacity will

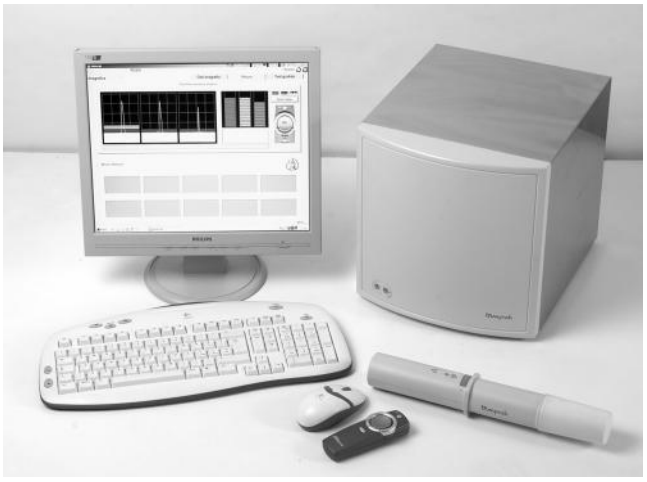

FIGURE 30.2 The Trimprob equipment is composed of the Bioscanner probe and a computer based spectrum analyzer.

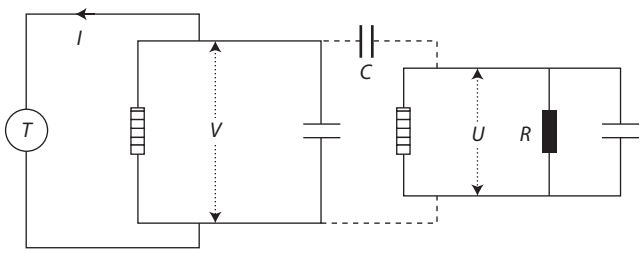

FIGURE 30.3 Coupled active and passive oscillators equivalent electric circuit.

accumulate charges, but when they increase, there will be also a greater tendency towards discharging. The system will end up with a stationary harmonic oscillation of frequency f1 and given amplitude for the potential difference V^3. For larger values of α, higher harmonics will appear, as the equation for V contains terms that vary like V^2 and V^3. This remains true when the active oscillator is coupled to a passive oscillator.

We can thus adopt a solution for V that accounts for the existence of oscillations at a fundamental frequency f and its harmonics, 2*f* and 3*f*. The value of *f*, as well as the amplitudes and phase factors of all these components can only be specified, when we take into account the fact that V produces forced oscillations for U and that this has an effect on V, because of C. The result can be summarized in the following way: the active oscillator is able to "feel" what happens inside the tested biological tissue, as it has to transfer energy to the passive oscillator to produce forced oscillations of the hidden entities. The active oscillator is also able to "tell" us how the passive oscillator is responding, as the amplitude of its own oscillations is strongly reduced when there is a large energy transfer. This is revealed, indeed, by a reduction of the amplitude of the emitted wave, displayed on the screen of the spectrum analyzer. The mathematical treatment reveals that the active oscillator draws more energy from the batteries when resonance is achieved, but its own energy is reduced, as if it had to make a "big effort." This mechanism is the essence of the nonlinear resonance interaction.[1,4,5]

Although the values of f^1 and f^2 are fixed, it is possible to achieve, or at least to approach, ideal resonance where the "dip" of a given spectral line is strongest, by changing the value of C through a modification of the distance between the probe and he tested tissue. The first spectral line is very sensitive to the existence of a resonance, when the negative resistance α is small, but a higher value will allow for a simultaneous search of resonance phenomena at the fundamental frequency f and its harmonics 2*f*, 3*f*, etc.

The effect of this interaction is easily detectable by means of a spectrum analyzer placed in the far field area, feed by a small antenna. At the resonance, on one or more of the spectral lines, two effects are detectable: the first is related to the transfer of an amount of radiofrequency from the generator probe to the diseased tissue that absorbs a part of the signal on the proper frequency line (dynamic resonance), while the second effect it is related to the deformation of the electromagnetic pattern emitted by the probe, due to the interaction with a resonating diseased tissue, that produces in the "near field" a sort of parasitic resonating element able to deflect the waves in other spatial directions, in the same way that beam antennas for radio communications works.

The subject under test must be further from the probe, in the "near field," while one or more multiplexed spectrum analyzer antennas are in the far field. The spectrum analyzer or equivalent device, represents the detecting part of the system. Using this arrangement, it is possible to observe an effect that appears as absorption of one or more of the spectral lines radiated by the scanner. This is observed on the spectrum analyzer display that transforms the received signal into a fast fourier transform (FFT). These lines are specifically tuned to the "biology" of the tissues to be investigated. Three spectral lines are used: the first, corresponding to the wavelength, responds specifically to calcifications and agglomerates of cancer cells; the second line responds to parenchyma (soft tissues) diseases; the third line responds to anomalies of the lymph and vascular system (Figure 30.4).

The interaction between a nonlinear active oscillator and an ordinary (linear) passive oscillator leads to the peculiar phenomenon of "nonlinear resonance interaction." A similar behavior is known as a grid-dip meter (g.d.m.). Initially, it contained a triode[6] that was associated with an oscillating circuit in such a way that it delivered a stationary oscillation at one particular, easily tunable frequency. The tunable active oscillator could be coupled by magnetic induction with another oscillating circuit, containing a real coil.

When such a grid-dip meter is tuned, so that its natural frequency is identical to the natural frequency of the passive oscillator, there will be a resonance. As the active oscillator is transferring energy to the passive oscillator, the oscillating current passing through the coil of the active oscillator is reduced, and an ammeter, included in the grid circuit, will indicate this effect. At resonance, there appears a "grid-dip," but to avoid ambiguities, the active generator should produce no harmonics. When a spectrum analyzer is used to monitor the far field as well as the near field emitted by the g.d.m. coil in the free space, while interacting with a tuned for resonance, passive *L*/*C* simple circuit, we can observe some interesting and not commonly investigated effects.

Figure 30.5 shows the setup for this experiment: A Millen mod. 90651-A g.d.m. is placed on a laboratory wooden table, near a passive oscillator composed of a U shaped coil

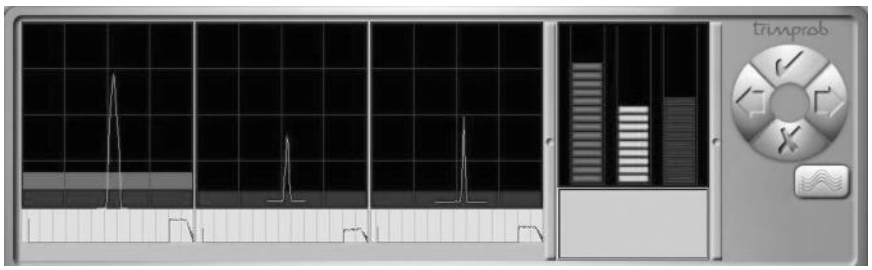

FIGURE 30.4 **(See color insert.)** Visualization of the three spectral lines on the display.

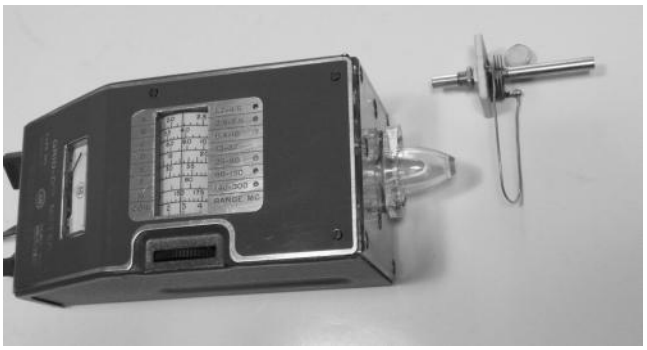

FIGURE 30.5 The grid-dip meter and the passive *L*/*C* oscillator simulating an investigated biologic tissue.

paralleled by a 30 pf variable air spaced capacitor. The circuit is tunable in frequency around the 140–170 MHz, these frequencies were used to facilitate the passive circuit realization as well as a proper coupling with the g.d.m. The passive oscillator U coil is placed in the near field of the g.d.m. test coil. At a distance of at least 50 cm, just outside the near field, a portable spectrum analyzer with a 1/8 wavelength rod antenna picks up the g.d.m. far field.

A slight tune of the g.d.m., to achieve the resonance with the passive circuit, is evidenced by a sharp dip of the ammeter current. This common and known effect represents the normal use of the instrument. At the same time, the far field received by the spectrum analyzer antenna shows a strong dip of the corresponding frequency line as evidenced in Figures 30.6 and 30.7.

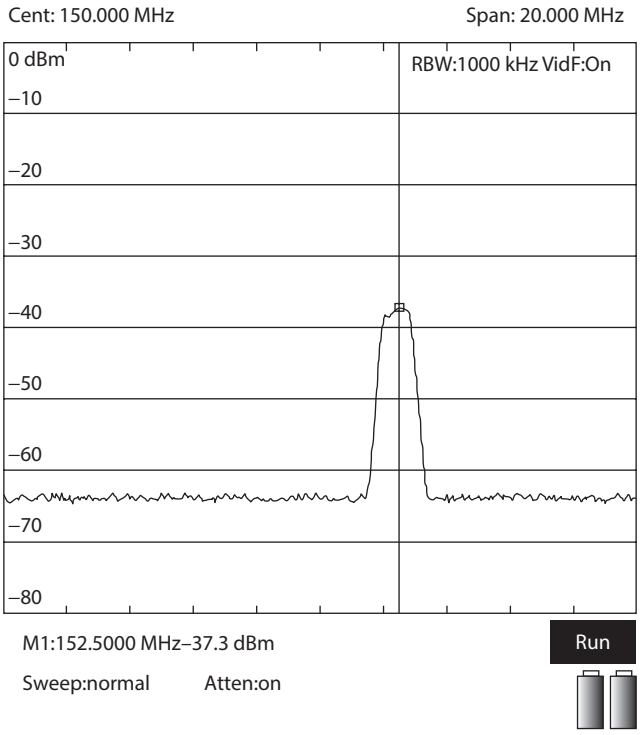

FIGURE 30.6 The grid-dip meter oscillator line out of resonance.

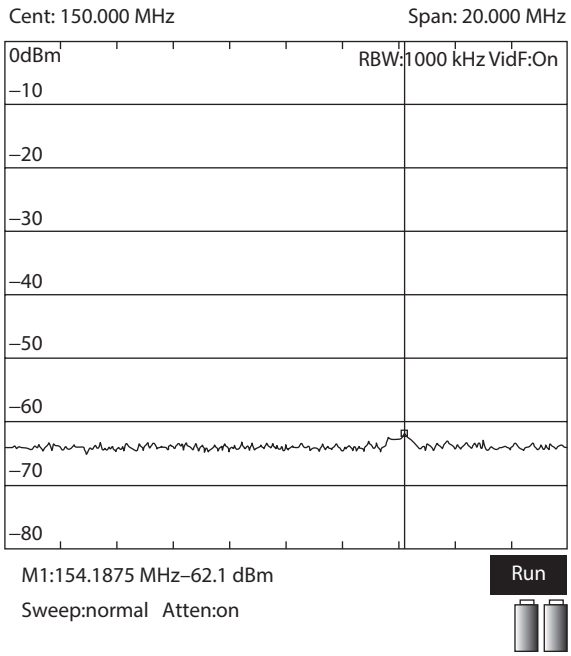

FIGURE 30.7 Frequency resonance interaction, the far, 152.5 MHz, spectral line field is depressed.

The spectral line will drop the amplitude more than 20 dB and could be in the order of 30 or more dB. In other words, the frequency line will disappear from the display. Instead, the near field detection will show a little attenuation of the spectral line in the order of few dB. This far field monitoring, to display the waves propagation of a passive oscillator interacting with an active one, was not previously reported in literature and represents the basis of the Trimprob operations.

The use of a g.d.m. is not used for disease detection but it is used, scaled in frequency, for field modeling purposes and for other experiments and laboratory measurements. It causes the magnetic coupling of the oscillators, although the propagation of the involved radiofrequency field is the same of the diagnostic device, that is, not easily influenced by magnetic-coupled passive oscillators.

The EM cancer detector is different, as it allows for an electric and not magnetic coupling, by means of a quarter wavelength antenna, activating charged particles inside biological tissues or other polarizable materials. Moreover, there are harmonics, which the spectrum analyzer allows for a distinction of possible resonance effects for any one of the frequency components and could be considered as a sort of "electric field capacity coupled grid dip meter" provided of a far field detection. Both g.d.m. and Trimprob are provided with synchronization capabilities that are evidenced by a loop locking of the active oscillator frequency respecting the passive ones. This effect is evidenced by the spectrum analyzer tracking capabilities that measures not only the amplitude, but also the precise frequency at the interaction resonance. It is astonishing to observe the damping force opposite to frequency variations when the two oscillators are in their respective "capture range." To have diagnostic

capabilities, the irradiated radiofrequency of the probe has to be of about 10 milliwatt; instead, the interaction with the tissues will be no more evidenced because of excessive oscillator coupling and other saturation effects. A similar behavior is common with not well designed g.d.m., when these instruments are used to analyze the resonance of passive L/C oscillators, especially when the g.d.m. power output is excessive. By means of the Bioscanner, very low level signals, in the order of microwatts, could still interact with near the skin anomalies on 462 MHz, but a more sensitive spectrum analyzer is required to display the far field. An experimental tunnel diode[28] nonlinear oscillator probe was realized and

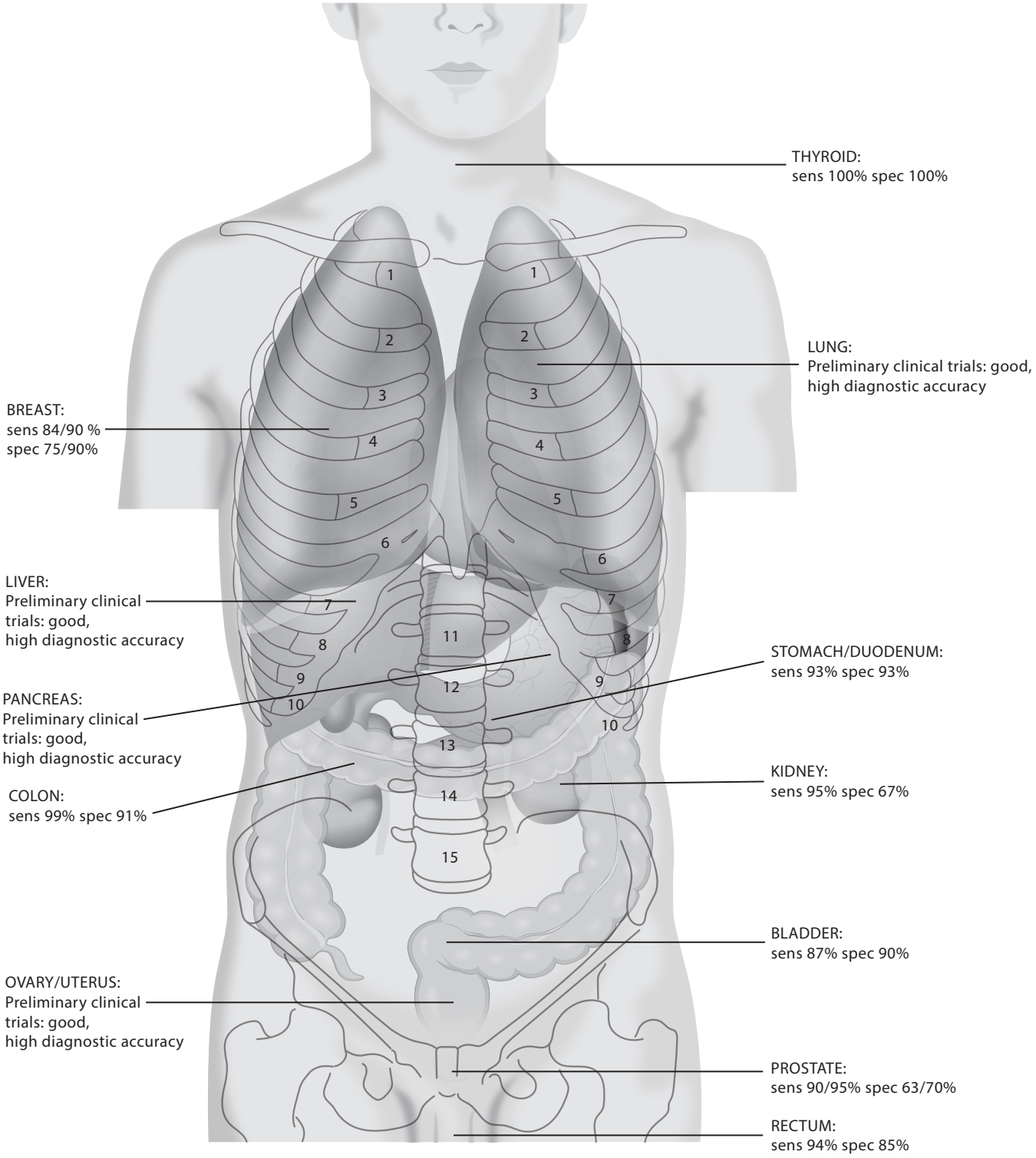

FIGURE 30.8 **(See color insert.)** Clinical trials in several body organs.

laboratory tested by the authors. The lock-in characteristic is also evidenced by the immediate synchronization in frequency of a couple of "Bioscanner" probes when such nonlinear oscillators are in their respective "capture range," that is, about one wavelength wide. Greatest distances are possible with the aid of corner reflectors in focusing both the probe fields. The spectral far field line amplitude, due to the phase synchronization of the oscillators, is greater than for a single oscillator.

Experimental asset: The far-field capturing spectrum analyzer is placed on a table about 50 cm away from the g.d.m and the passive oscillator in Figure 30.5. A small antenna picks up the RF field; when the resonance is achieved, tuning the grid dip meter or the simple *L/C* circuit variable capacitor, the spectral line on the spectrum analysis display is suddenly depressed (Figure 30.7).

OPINIONS AND IMPLICATIONS

The present paper represents an integration of published papers in 2010.[7,8] The first experiments, carried out by the author in the early days of the Bioscanner invention and development, as well as several clinical trials during the last few years have scientifically validated the efficacy of the described low level electromagnetic field (EMF) cancer detector in several body organs such as breast,[9] prostate,[10–13] bladder,[14–16] stomach-duodenum,[17,18] thyroid,[19,20] and colon-rectum[21–24] (Figure 30.8).

A new trial carried out at the University of Sassari, Italy, by M. Tufano et al., was presented at the XVI Digestive Diseases National Congress (Gastroenterology), March 2011 (Figure 30.9).[23]

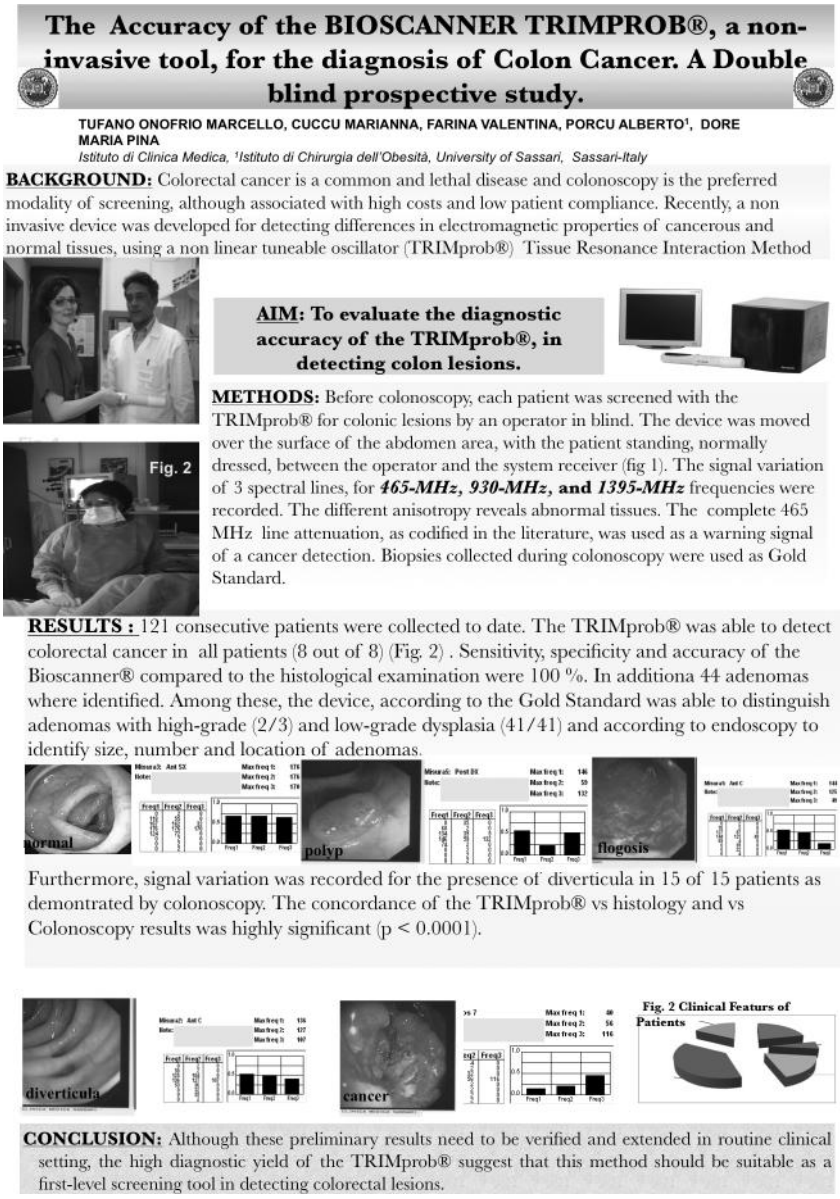

FIGURE 30.9 **(See color insert.)** Clinical trial for the diagnosis of colon cancer.

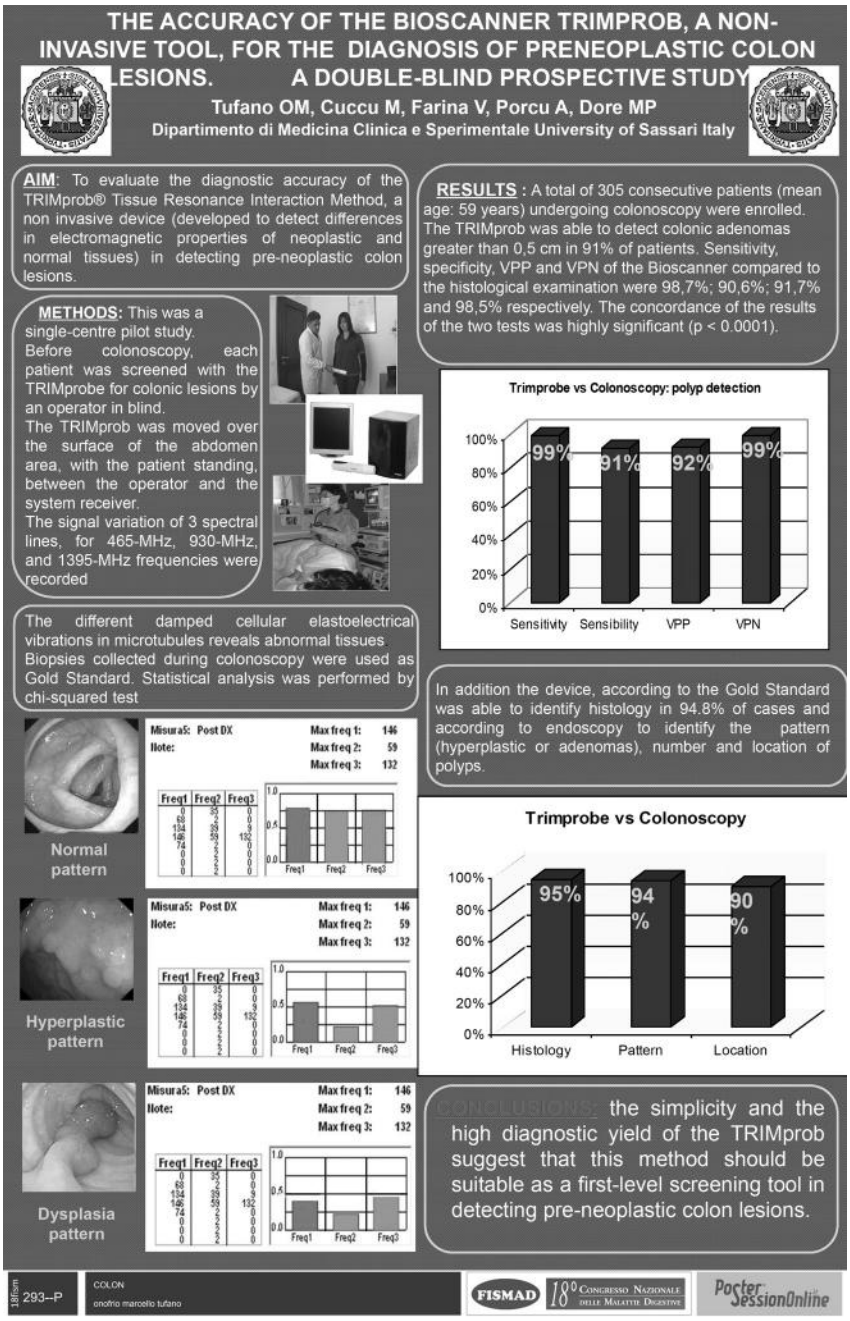

FIGURE 30.10 Clinical trial for the diagnosis of preneoplastic colon.

The first phase of clinical trials by means of the Bioscanner spectrometry demonstrate the elevate accuracy of the method in colon cancer diagnostics: a sensitivity and specificity of 100% and the concordance of the Bioscanner versus the histology and versus colonoscopy results was highly significant ($p < 0.0001$). The second phase of clinical trials was presented at the XVIII Digestive Diseases National Congress (Gastroenterology), Naples, March 2012 (Figure 30.10).

This study, in search of the colon pre-cancerous lesions (double-blind study), a total of 305 consecutive patients undergoing colonoscopy were enrolled. The Bioscanner/Trimprob was able to detect colonic adenomas greater than 0.5 cm in 91% of patients. Sensitivity, specificity, positive predictive value (VPP), and negative predictive value (VPN) of the Bioscanner compared to the histological examination were 98.7%, 90.6%, 91.7%, and 98.5% respectively. The concordance of the results of the two tests was highly significant ($p < 0.0001$).

The overall results of the trial, which lasted 3 years, are being published (www.clarbrunovedruccio.it/eng_pubblicazioni.htm).

A March 2011 paper by Pokorny et al. discloses the mechanism of active grown cancer tissues' interaction with

TABLE 30.1
Principal Clinical Trials Bioscanner TRIMprob™ with Publications

Organ	No. Patients	Sensibility (%)	Specificity (%)	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Accuracy (%)
Prostate						
1. Trial by Prof. Scialpi[5] (Taranto)	43	94	92		96	93
2. Bellorofonte et al.[10] (Milan)	757	95	43		90	
3. Da Pozzo et al.[27] (Multicenter clinical trials in five universities: H.S. Raffaele, Mi, Federico II NA, Careggi FI, S. Orsola-Malpighi BO, Cattinara Trieste)	188	80	51	44	84	60
4. Tubaro et al.[11] (HS Andrea—Univ. Roma)	111	86	63	60	88	72
5. Gokce et al.[13] (Dip. Urologia—Univ. Istanbul)	148	76	61	40	89	
6. Di Vaccaro et al.[12] (Univ. Umberto I Roma)	782	(with PSA >4 ng/mL) 84.1	(with PSA >4 ng/mL) 67.8	(with PSA >4 ng/mL) 61.7	(with PSA >4 ng/mL) 83.8	
1. Leucci et al.[14] (H. Vito Fazzi—Lecce)	114	87.5 (Cohen's K = 0.77)	90.5 ($p < 0.001$)	83.3	91.1	89.5
2. Cormio et al.[16]	125	97.9	89.9	86.8	98.6	93.6
Breast						
De Cicco et al.[9] (I.E.O.—Milan)	101	84	75		80	72
Thyroid						
Sacco et al.[18] (Clinica Chir.—Univ. Catanzaro)	51	100	100			100
Stomach–Duodenum						
1. Vedruccio et al.[17] (Clinica Chir. Osp MM—Taranto)	45	93	93	95	92	
2. Sacco R et al.[18] (Clinica Chir.—Univ. Catanzaro)	43	100	100			100
Rectum						
1. Vannelli et al.[21] (INT—Milan) preliminary study	228	94	85	86	93	89
2. Vannelli et al.[22]—complete results	442	94	84	92	88	90
Colon						
1. Tufano et al.[23] (Univ. Sassari)	121	100	100			100
2. Tufano et al.[24]—second clinical trials	305	99	91	92	99	100
Total	3781					

a nonlinear resonance interaction (NLRI) Bioscanner. This paper represents an important bridge between the technological background of the Bioscanner and the biophysical behavior of cancer cells when irradiated by low level EMF emission.[25] Trimprob clinical diagnostic accuracy as reported in Table 30.1 and in the above mentioned clinical studies,[26,7,16–24] spans several possible applications in the field of characterization of benign versus malignant pathologies, prevention, and screening capabilities, as well as some others not disclosed here.

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Section VI

Ultrasound and Other Applications

31 Holistic Electromagnetic Therapy
The Seqex Approach

Adriano Gasperi, Anna Caruso, Alessandro Greco, and Claudio Poggi*

CONTENTS

ELECTROMAGNETISM AND LIFE

Over the past 70 years, biology and physics have dramatically converged and medicine has benefited from this on both the diagnostic and therapeutic levels. Medical physics, or the application of the concepts, theories, and methods of physics to patient care, is the result of this type of "cross-contamination." An increasing number of patients over the years have enjoyed improved wellbeing and health on the strength of new discoveries and applications. Medical physics is currently applied within a number of medical specialties, both as a diagnostic and interventional tool, with examples including radiology and medical imaging, radiation oncology, and nuclear medicine. Furthermore, a number of physical agents (ionizing and nonionizing electromagnetic radiation, laser light, static electric and magnetic fields, ultrasound, gamma rays, radio frequencies, etc.) are commonly used in official medicine at hospitals and private clinics. Finally, over the last couple of decades and within the framework of the so-called *Epi-biochemical/genetic approach* to medicine, a new field of scientific interest and research has developed. This considers the interactions between extremely low frequency electromagnetic fields (ELF-EMF) and biological matter in order to restore, maintain, and improve health.

The idea that there is an electrical basis for life and health is not new and dates back at least to the middle of the nineteenth century, when the American Electro-Therapeutic Association organized a series of conferences on the clinical use of electricity and electrical devices for the treatment of hysterical pain syndrome. Various energy emitting instruments were used by over 10,000 physicians in the U.S. to treat neurological, emotional, and physical disorders. In Europe, a limited number of medical doctors and researchers made efforts to prove the effectiveness, on both clinical and scientific grounds, of electric and magnetic forces. However, they faced fierce opposition from distinguished members of official medicine, who argued that science would continue to consider a radically new phenomenon as an anomaly, until it was explained within a suitable theory. Then, at the beginning of the twentieth century, the 1910 *Flexner Report on Medical Education*, initiated by the American Medical Association, defined these approaches as abuses in medical practice and banned them from official recognized use. This situation, restricting electromagnetic therapies within the confines of unofficial medicine, remained largely unchanged until the end of the 1900s. However, over the last two decades there has been a strong revival of interest in this area of medicine, resulting from both a wider and greater depth of knowledge in nanoscience, nanotechnology, and molecular biology, and improved digital and communication facilities available to an increasing number of users thanks to new information communication technologies and the internet. Seqex® was designed, developed, and implemented within this rapidly changing environment.

ABRAHAM LIBOFF, STUDYING THE RELATIONSHIP BETWEEN ELF AND BIOLOGY IN DEPTH: THE ION CYCLOTRON RESONANCE-LIKE EFFECT AND PRELIMINARY CLINICAL USE

Professor Abraham R. Liboff was the American scientist who paved the way for a wider acceptance by the medical community of the so-called electromagnetic paradigm in biology and medicine, and deserves recognition for his studies on the relationship between ELF and biological systems, or bioelectromagnetism.[1,2,3] After years of speculation and research, Liboff reached "the inevitable conclusion that living organisms react to imbalances produced by quasi-systemic electric

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changes, while also striving for their own wellbeing either by generating electromagnetic fields (EMF) or through exposure to exogenous EMFs of extremely low frequency and intensity (ELF). These waves, acting in association with the geomagnetic field, induce a physical response on a cellular level, in a phenomenon known as Ion Cyclotron Resonance (ICR)."[4]

While traditional physiology considers bioelectromagnetic interaction to be a kind of stimulation or facilitation of biochemical processes (i.e., increased blood level of serotonin or calcium binding proteins), Liboff introduces the concept that a living system is an electromagnetic system and, as such, is able to respond to electrical and magnetic stimuli according to the principles of physics. Furthermore, Liboff defines living organisms (vegetable and animal) as electromagnetic entities, casting doubts on the granitic conviction shared by the medical scientific community that all vital events (on the physiological, pathological, and therapeutic levels) can be explained in terms of molecular biology. Liboff also clearly perceives how difficult it will be to convince such a medical community who are unaware of the opportunities offered by ELM therapy.

To introduce his paradigm, Liboff classifies three main groups of EMF, according to the intensity of currents generated by the different devices

- Disruptive (electroshock and transcranial high speed magnetic stimulation rTMS)
- Coarse (devices for restoring lost or disrupted physiological conditions, like pacemakers)
- Imperceptible (very low intensity and frequency electric/electromagnetic stimulation, so low that detection is very difficult and impossible to relate to known physiological events)

The Seqex® device belongs to the latter group.

THE ITALIAN WAY TO IMPLEMENT LIBOFF'S DISCOVERIES AND VISION

In 1987, the first medical application of ELF-EMF, to treat bony nonunions, was approved by the U.S. Food and Drug Administration (FDA) and, a few years later, a second medical application was approved to assist spinal fusion.

The medical devices proposed by Liboff were applied locally over the dysfunctional areas. A different type of ELF-EMF treatment was developed in Italy by a group of physicists and biologists convened by Valerio Dallago in the late 1990s. As a financial manager with personal experience of the utility of an EMF device, Valerio was attracted by Liboff's discoveries. His personal views embraced a truly holistic approach to understanding (and ultimately treating) symptoms and diseases using nonconventional approaches, and he decided to invest in this area of knowledge. The group designed and produced a device that was genuinely holistic, using ion cyclotron resonance magnetic fields to treat not just localized body areas, but the entire body. Dallago called his type of treatment endogenous ion cyclotron resonance,

FIGURE 31.1 Abraham Liboff and Valerio Dallago test extremely low frequency electromagnetic fields on Seqex.

extending Liboff's proposal that it was reasonable to assume that all living things must naturally have intrinsic biological ICR properties. The technical development of Dallago's device (subsequently called the *Seqex*® device) is now coordinated by the engineer Claudio Poggi, and regards this intrinsic ICR property as a shared, whole body property. According to this concept, externally applied ICR signals can help restore wellbeing (Figure 31.1).

How can the degree of wellbeing be measured quantitatively? Dallago and Poggi very cleverly made use of total body bio-impedance, a readily measurable quantity commonly used to assess a number of health indicators. Poggi noted that body impedance changes after whole body application of ICR signals, and further, that these changes can be beneficial for the patient. An individual's bioimpedance value is thus referred to as that person's wellness factor. On a molecular basis, it is hardly surprising that ICR magnetic frequencies alter total body impedance, as this impedance includes both resistive and capacitive components. The more important capacitive reactance of the body is mainly due to the double lipid layers of the trillions of cells that constitute the body, and there is general agreement that the site of ICR interaction is most likely at the cell membrane.

In practice, the wellness factor is measured first, and a computer is used to determine which ICR magnetic frequencies are required to adjust this factor, and then these signals are applied. The patient lies horizontally on a bedroll containing sewn-in internal coils designed to produce vertical AC magnetic fields over the entire length of the body. The impedance is measured with a pair of electrodes attached to a wrist and an ankle. Following the test, the personalized treatment profile is stored on a smart card for use in further treatment sessions.

SEQEX: A BRIDGE BETWEEN OFFICIAL AND NONCONVENTIONAL MEDICINE

The history of medicine has reached a critical turning point. The Western medical paradigm with its reductionist,

illness-centered focus, is no longer capable of providing an adequate response to modern patients, who are ever more intent not only on eliminating symptoms but rather on achieving a state of health definable as global wellbeing. A paradigm shift is thus required, a transition from the reductionist model to the holistic view of complementary medicines.

Seqex®, as an instrument for "total body" treatment with consistent information, satisfies this requirement, shifting the attention from an individual illness to the patient. It achieves this by applying two important principles

1. The postulation that everything is information and so any treatment is in reality information given to the organism.
2. The path of innovation in the field of biophysics: starting from studies conducted at the end of the 1900s on the interaction of ELF-EMF with biological tissue, the Seqex® team has developed a non-invasive treatment method that permits the entire organism, rather than just a part of the same, to receive and therefore respond to ICR information.

There is an obvious shift from pharmaceutical-information targeted on a specific molecule (with the known side effects) to EM information that induces the organism towards a biological and physiological restoration of the state prior to alteration by illness.

A fundamental and inescapable aspect remains ongoing dialogue and comparison with allopathic medicine. Seqex® does not aim to substitute pharmacology but to functionally integrate it, providing an additional valid instrument for doctors who today are called on in their clinical practice to apply the axiom that equates energy and material as faces of the same medallion. Dialogue with clinicians is essential to improve and incentivize this approach to integrated medicine, ever more in demand from patients.

The use of EFM instruments in medicine is widespread today, having by now become a transverse approach in various branches of medicine. There are nevertheless three substantial differences between the most widely used machines and the operating principle of Seqex®

- The use by Seqex® of an analogue rather than digital signal, and so more similar to the biological *language*
- The use of ELF-EMF (0.1–0.8 G_ rather than much wider fields) on the entire person and not only on an area of interest
- Application in the field is preceded by an impedenziometric test designed to personalize the individual treatment by identifying the most appropriate waveform, frequency, and intensity for the patient

These differences make it possible to use Seqex® without problems, even at home under medical supervision or outside of medical contexts (Seqex Fam®), increasing patient compliance to treatment. Furthermore, the analogue signal stimulates a more natural response (translating into variable response times depending on the state of health of the patient), and therefore, a biological response that is likely to be more enduring and effective.

THE SEQEX PARADOX: HIGH EFFECTIVENESS VERSUS LIMITED SCIENTIFIC KNOWLEDGE

To date, there are few published studies regarding the use of Seqex®; however, among these, two can be considered particularly important

1. The study by Vallesi et al. on hematic oxidative balancing achieved using the ELF-EMF generated by Seqex®,[5] which demonstrated a statistically significant reduction in malondialdehyde (MDA), this being a marker of the peroxide state of biological tissues (resulting from degradation of plasmatic membranes), caused by endogenous or exogenous stress, following exposure to hydrogen peroxide.
2. The study by Rossi et al. regarding the reduction in oxidative stress in cancer patients obtained using the ELF-EMF fields generated by Seqex®,[6] that demonstrated how the reduction in oxidative stress resulted in reduced myelosuppression from chemotherapy (see Table 31.1).

A study is actually been approved regarding the effectiveness of treatment of headaches with IRC at the University of Milano-Bicocca.

Alongside these studies, there are various case reports and unpublished studies. Among the former, worthy of note is a case of infantile ulcerated haemangioma treated with Seqex® by Covi et al.[7] The patient was a baby girl born at term by eutocic birth on June 28, 2012 and diagnosed on day 10 of life with infantile hemangioma, complicated by ulceration and infection, which extended over the subsequent days to a part of the tongue and gums.

On day 15 of life, antibiotic and antifungal therapy was initiated, but without achieving improvement. On day 21, therapy was initiated with propanolol at a dosage of 2 mg/kg/day to stop the growth of the hemangioma and reduce the widespread ulceration, with the hope of achieving positive results over the next 2 months.

On July 27, 2012, treatment with Seqex® was initiated. After 10 days of therapy with Seqex® and following a dermatological consultation on August 7, 2012, propanolol therapy was suspended because of the initial encouraging results.

The patient demonstrated constant improvement, first with resolution of ulceration, and then regeneration of healthy tissue. After a few days of therapy, appetite improved and normal eating habits resumed. After 40 days, the ulcer appeared to have completely disappeared, with regeneration estimated to be around 90%. The parents reported a significant improvement in sleep rhythms, good appetite, and a lively active child. This report describes a unique case of its type and demonstrates the enormous therapeutic potential of IRC.

TABLE 31.1
Therapy with and without Seqex in Patients with Hodgkin's Lymphoma

Group	Age	Sex	Stage	G-CSF(Mg) Administered	Major Hb Reduction (g/dL)
No. 1	42	F	II A	1200	0.9
No. 2	44	M	III A	1500	1.8
No. 3	45	M	II A	900	0
No. 4	69	M	I A	3900	0
No. 5	38	M	III A	1200	1.5
No. 6	35	F	II A	1200	0.5
No. 7	26	F	II A	1200	0.1
No. 8	39	F	III A	1200	0
No. 9	40	F	IV A	2400	0.6
Mean	**40**			**1200**	**0.3**
No. 10	47	F	III A	5100	3.2
No. 11	26	F	II A	5700	0.4
No. 12	20	M	III A	3600	0
No. 13	27	F	II A	1200	1.2
No. 14	78	F	II A	7500	2.7
No. 15	26	M	IIIA	4800	1.4
No. 16	40	M	II A	6600	1.6
No. 17	23	F	II A	5100	0
No. 18	43	M	I A	4500	1.6
Mean	**27**			**5100**	**1.4**

Note: Patients 1–9 had supportive therapy with Seqex. Patients 10–18 in the second group did not. Age and stage are similar in the two groups. The granulocyte colony-stimulating factor (G-CSF) administered in the two groups is statistically different and is greater for those who did not receive the Seqex treatment. The group of patients not receiving the supportive treatment tended to have a larger decrease of hemoglobin, but this decrease was not statistically significant.

Another very interesting study is that of Mario Betti, an MD, specialized in psychiatry, who investigated the therapeutic potential of ICR in psychiatric pathologies.[8] He assessed the effects of Seqex® therapy on 33 chronic psychiatric patients resistant to pharmacological treatment (e.g., psychosis, neurotic disorders, personality disorders, adjustment disorder). Each treatment cycle involved 20 sessions of variable duration from 18 to 54 min, applying a treatment protocol of 10%–50% of the potential intensity of the device and frequencies from 10 to 40 Hz. Assessments were made according to the Brief Psychiatric Rating Scale (BPRS) with T0, T1, and T2, respectively at the start, after ten sessions, and on completion of the cycle. The results demonstrated improvements in all cases, as illustrated in Figure 31.2.

The study demonstrated significant effectiveness, manifest in particular during the first half of the treatment cycle, and more specifically around the fourth session. Figure 31.3 illustrates the appreciable improvements recorded for all the patient categories.

In conclusion, the work of Betti et al. demonstrates the effectiveness of ICR for treating psychiatric disturbances, and highlights the sensitivity and responsiveness of the CNS to ELF-EMF. An integrated approach would appear to offer great potential for the treatment of patients with psychiatric disorders.

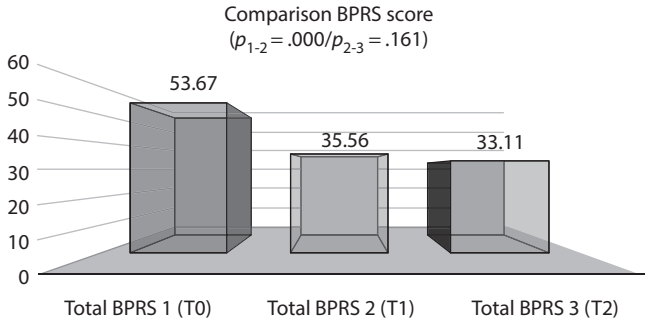

FIGURE 31.2 Graph comparing the Brief Psychiatric Rating Scale results at times T0, T1, and T2. An improvement is demonstrated of statistical significance between T0 and T1.

Alongside these examples, it would be possible to cite dozens of other cases involving a variety of pathologies that are all equally interesting.

THE FUTURE: FROM MEDICAL DEVICE TO WELL-BEING FACILITATOR

Within the medical-academic world there is considerable debate about the effects of ELF-EMF on the human organism. Alongside studies that demonstrate the therapeutic effectiveness[9] or biological potential[10] of ELF-EMF, a lot

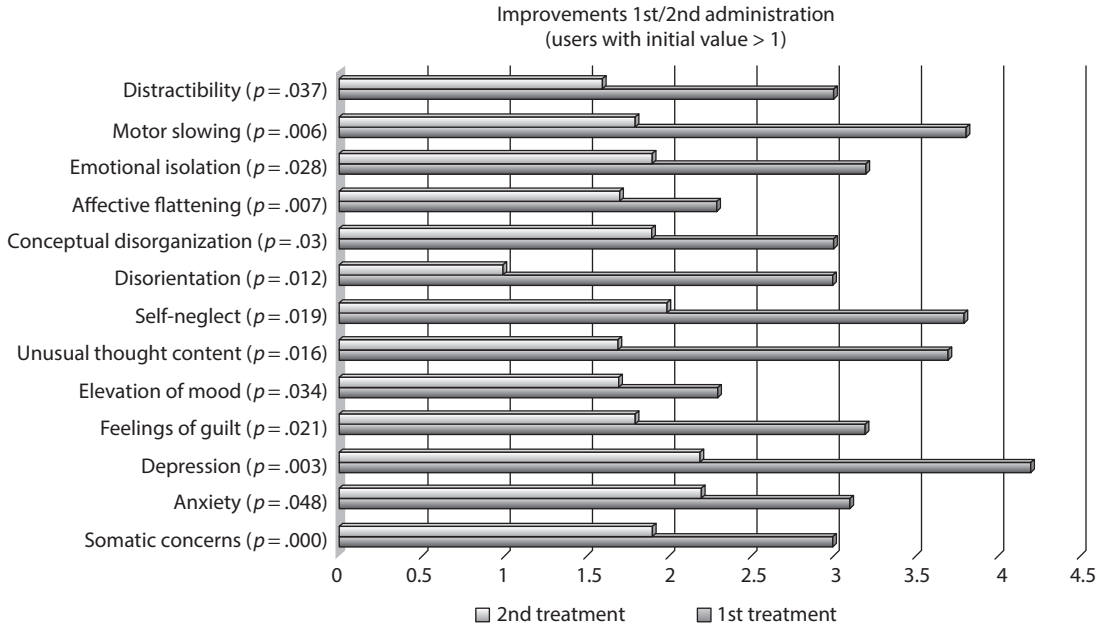

FIGURE 31.3 Improvements in the items assessed by patients.

of attention is directed towards understanding if, how, and when ELF-EMF are involved in the pathogenesis of diseases, for example, in tumors. While there are studies that have linked certain forms of ELF-EMF with particular types of cancer in specific individuals,[11] it needs to be noted that the same researchers are unable to provide a definitive answer to this question, and this remains more of a hypothesis than a certainty. It is also important to underline that many of the studies considered in the cited meta-analysis involved experiments that bore no resemblance to the therapeutic use of ELF-EMF (for example, Loscher and others used DMBA to induce breast cancer in mice, utilizing 50 Hz, 0.2–1 mT, 10 mT, 50 mT, and 100 mT magnetic fields to irradiate mice 24 h a day for 13 weeks!). Thus, it is very important to consider the methods applied in ELF-EMF studies in order to avoid either alarmism or the risk of raising false expectations.

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32 Human Brain Stimulation with Transcranial Ultrasound

Potential Applications for Mental Health

*Joseph L. Sanguinetti, Ezra Smith, John J.B. Allen, and Stuart Hameroff**

CONTENTS

Interest in noninvasive brain stimulation for therapeutic effects on mental health has increased in recent years. The ability to directly modulate brain activity in targeted or diffuse regions noninvasively, that is, from outside the skull, has enormous potential for the treatment of psychiatric and neurological disorders. Brain stimulation also holds promise for the functional mapping of brain systems by coupling stimulation with subjective report and imaging techniques such as functional magnetic resonance imaging (fMRI). A potential advantage of therapeutic brain stimulation over pharmacological intervention is that targeted stimulation of brain circuits implicated in psychiatric disorders might minimize global effects on the brain and body, potentially minimizing or eliminating side effects.

Frequently used noninvasive brain stimulation methods, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have limitations (reviewed below), restricting their scientific and therapeutic applications. Ultrasound is a less frequently used brain stimulation technology, but may have advantages over other techniques. Ultrasound consists of mechanical vibrations above the threshold for human hearing (>20,000 Hz). Ultrasound can penetrate biological tissue, and echo off surfaces to give anatomical images, such as fetuses in the womb. Although primarily used for medical imaging, ultrasound can also modulate neural activity, both peripherally and in the brain. This chapter reviews the history of ultrasound neurostimulation and the first clinical trials in humans. Future directions in this emerging field are discussed.

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INTRODUCTION: BRAIN STIMULATION

There are two broad approaches for human brain stimulation: invasive and noninvasive. Invasive procedures require surgical implantation of a device to a targeted area of the brain or central nervous system (e.g., deep brain stimulation [DBS]). DBS electrodes deliver high-frequency electrical pulses to anatomically selected brain regions with millimeter precision to influence neuronal function and signaling. The ability to electrically stimulate the brain has provided significant benefit for neurological patients[1] and shows promise for psychiatric disorders[2] like depression.[3] Yet the invasiveness of surgical implantation of electrodes and microcontroller devices limits the application of DBS to only the most extreme of cases. Moreover, DBS cannot easily be used with imaging devices, such as fMRI, for brain mapping due to safety concerns and imaging artifact produced by stimulation devices.[4] Therefore, methods that allow noninvasive excitation or modulation of brain activity have been developed.

Among noninvasive methods, TMS and tDCS are the most commonly employed. Each takes advantage of different electromagnetic principles. TMS uses strong magnetic coils

to focus induced currents in the brain via electromagnetic induction. One specific variety of TMS—repetitive TMS (rTMS)—has been shown to excite (~5–20 Hz) or inhibit (~1 Hz) neural activity, and the effects of rTMS can last up to 30 min or more, before neural activity returns to baseline levels.[5] Applying low amplitude (~1 mA) direct current or alternating current to the brain (tDCS and tACS, respectively) can also induce reversible changes in neural activity. Like magnetic stimulation, tDCS and tACS can both excite or inhibit brain activity depending on the cathode/anode configuration of the stimulating electrodes on the scalp.[6]

Both methods are currently used as scientific tools and have shown promising, albeit limited, therapeutic application. Major limitations include the fact that the stimulation fields are relatively nonspecific (1 cm or more),[2] lacking the millimeter spatial resolution of DBS. Moreover, current approaches are incapable of targeting deep brain structures. TMS is relatively expensive, requires specialized facilities, and highly trained staff. Both methods can cause sensations on the skin, creating difficulties for blinding participants to treatment conditions. Finally, a potentially powerful use of noninvasive brain stimulation is the ability to functionally map brain areas by exciting or inhibiting targeted areas to observe the effects on behavior or during brain imaging (like fMRI). However, the ability of both electrical brain stimulation[7] as well as magnetic brain stimulation[8] for human brain mapping may be untenable due to technical difficulties. These issues have motivated researchers to seek alternative technologies for brain stimulation.

Ultrasound can be transmitted through the skull to remotely influence brain activity, known as transcranial ultrasound (TUS). Depending on the focusing beam of the ultrasound, millimeter precision and deep brain structures can be targeted. Clinical ultrasound imaging machines, widely available in hospitals and clinics, can also be used but deliver less focused beams of ultrasound energy. Further, several decades of medical and therapeutic applications has demonstrated the safe output levels of ultrasound on biological tissue. Thus, researchers have begun to investigate the use of TUS in humans for scientific and neurotherapeutic purposes. A brief history of ultrasound for brain stimulation is outlined below, followed by descriptions of the first human studies and a discussion of future directions.

HISTORY

Discovery and Development of Safety Protocols

Ultrasound (U.S.) consists of cyclic mechanical vibrations (acoustic pressure) in a frequency range higher than the upper limit of human hearing (>20,000 Hz or >20 kHz). At high intensity, U.S. can cause tissue heating, but, at lower levels, U.S. is safe for human tissue. U.S. was used for therapeutic purposes (e.g., physiotherapy) before being developed as a tool for medical imaging.[9] Wood and Loomis showed in 1927[10] that high intensity U.S. could produce lasting changes on biological tissue. Shortly thereafter, Harvey and Loomis[11] showed that U.S. could stimulate excitable tissue, including the heart and other muscles. These seminal studies launched investigations into the safety of U.S. for therapeutic applications. In the 1930s and 1940s, researchers realized the potential to use U.S. for medical imaging of brain tumors.[12] Since then, diagnostic ultrasound has developed into an indispensable tool with a wide range of medical applications.

Therapeutic and imaging ultrasound can be generally divided into high and low intensity.[9] High intensity ultrasound can destroy biological tissue by heating or cavitation (the creation of small, gas or vapor filled cavities that may explode[13]). For example, high intensity focused U.S. is used therapeutically for lithotripsy (using shock waves to break apart kidney stones). In contrast, low intensity ultrasound, where exposure is chosen to have minimal lasting effects on biological tissue, has been used for diagnostics and therapeutic applications on the body safely for more than 70 years.[9] Virtually every part of the body, including the brain, has been safely imaged with low intensity ultrasound in humans.[14]

The U.S. Food and Drug Administration regulates the acoustic output levels for ultrasound.[15] Most therapeutic ultrasound is continuously delivered below 1 MHz, whereas ultrasound for diagnostic imaging is pulsed (i.e., cycles of ultrasound separated by brief periods of rest) at frequencies between 1 MHz and 15 MHz. The monitoring and quantification of acoustic output levels allows the ultrasound operator to estimate the temperature changes resulting from ultrasound propagating through tissue or bone (thermal index [TI]) as well as the mechanical pressure induced by ultrasound waves (mechanical index [MI]). Ultrasound exposures can be defined in terms of acoustic pressure or intensity. Pressure in an acoustic field varies spatially, and temporal variation is introduced by pulsing the ultrasound; thus, there are different ways to quantify the intensity output.[9] When calculating intensity, the spatial peak or spatial average of the pressure in the acoustic field can be included, as well as whether the time during the pulse (pulse average) or the total stimulation time including the on/off period of the pulse (temporal average) is included.[9] The current FDA limits for diagnostic ultrasound are limited to an MI of 1.9 and spatial peak, temporal average (I_{SPTA}) of 720 mW/cm^2 (I_{SPTA} will be used when discussing intensity below). At or below these output levels, U.S. applied to biological tissue, including the brain, has been shown to leave no lasting bioeffects.[9,14,16,17]

Early Neuromodulation Studies

A seminal study by Harvey in 1928[18] showed that U.S. could excite nerve and muscle tissue in frogs and turtles. Later, Fry[19] conducted a series of studies showing that high intensity U.S. could lesion brain tissue. Interestingly, this was used to treat Parkinson's disease with some success, but was ultimately abandoned because craniotomy was necessary to deliver the ultrasound to deep brain structures.[20] Fry also found that aiming the ultrasound towards the lateral geniculate nucleus in cats resulted in the suppression of electrical potentials recorded over visual cortex.[20] U.S. modulated the activity of nerve fibers differentially depending on the intensity parameters and size/type of fibers in animals.[21]

Gavrilov and colleagues[22] showed that focused U.S. delivered to nerves in the hand could cause sensory perception in humans. Excitatory and/or inhibitory effects were reported in animal spinal cord[23] and cortex,[24] and in human cranial nerves.[25] There are numerous other early studies investigating U.S. for neural stimulation;[26] for a more extensive review, including a discussion of the interesting work from scientists in the USSR in the 1970s who attempted to introduce auditory information to deaf patients via auditory nerve stimulation. Altogether, neuroscientific evidence from humans and nonhuman animals suggest that U.S. can be used to modulate (stimulate or inhibit) neural activity.

MODERN NEUROMODULATION STUDIES

Recent studies have shown direct effects on the firing rates of single neurons in slice preparations or populations of neurons with brain imaging. Tyler and colleagues[27] reported that focused low intensity U.S. stimulated single action potentials and synaptic transmission in rodent hippocampal slice cultures and *ex vivo* brains. Further, they found that the spatial resolution was on the order of 2 mm. Another study showed that focused TUS (<180 mW/cm^2) was sufficient to elicit motor potentials in intact mouse motor cortex, and caused region-specific muscle contractions after motor cortex stimulation (e.g., tail, forepaw, and whisker movements; see supplemental Movie S2 in[28]). Importantly, remote stimulation affected hippocampal activity, suggesting TUS is capable of targeting deep subcortical structures.[27]

Min and colleagues[29] showed that low intensity U.S. pulsed at a rate of 100 Hz (130 mW/cm^2) could suppress epileptic activity in an animal model. Yoo and others[30] recently demonstrated region specific increases (1.6 W/cm^2) or decreases (160 mW/cm^2) of brain activity in anesthetized rabbits by coupling focused ultrasound with fMRI. Tsui and colleagues[31] found that shorter durations of U.S. pulses led to excitation and longer durations to inhibition of action potentials in peripheral nerves, suggesting that U.S. pulse duration is important for stimulatory or inhibitory effects of U.S. Finally, Min and colleagues[29] recently showed that focused U.S. stimulation of the rat thalamus increased neurotransmitter (dopamine and serotonin) in the frontal cortex. The ability to modulate region specific brain activity along with the modulation of neurotransmission demonstrates that TUS can be used as a brain mapping technique.[29] Indeed, given that U.S. energy is mechanical rather than electromagnetic, several researchers have noted that U.S. is well suited to complement brain imaging techniques, such as fMRI, for functional brain mapping without causing significant artifact.[32,33]

Searching for Mechanisms

The mechanisms by which ultrasound modulates neural activity are poorly understood. Tyler and others[34] proposed that ultrasound excites neural activity by mechanical stretching of membrane lipid bilayers, membrane proteins (integrins), and extracellular proteins that causes membrane depolarization. Indeed, voltage-gated ion channels on neurons and neurotransmitter receptors possess mechanosensitive properties that make them susceptible to mechanical forces. Tyler and colleagues[27] showed that voltage-gated sodium and calcium channels were activated by focused U.S. Moreover, U.S. can reversibly induce increases in calcium uptake in fibroblasts[35] and modulate potassium influx and efflux in rat thymocytes.[36]

Ultrasound may inhibit neural activity by disrupting synaptic signaling possibly via thermal effects (i.e., heating)[37]; however, inhibitory effects have also been found with low intensity U.S. that results in almost no thermal effects (160 mW/cm^2), leading others to propose that higher pulse repetition frequency may lead to inhibitory ultrasonic effects on neural tissue.[30,31]

Another view is that U.S. affects neural activity through resonant vibrations in microtubules, major components of the cytoskeleton. Microtubules grow, organize and regulate neurons and synapses, and have been implicated in mood, memory, and conscious awareness.[38] Composed of the brain's most prevalent protein, microtubules have resonance frequencies in the MHz range,[39–41] making them susceptible to U.S. vibrations affecting neural activity and mental states.

TRANSCRANIAL ULTRASOUND IN HUMANS

Skull Penetration

The evidence reviewed so far points to the possibility of using noninvasive U.S. to modulate human brain activity. Ultrasound can be focused to penetrate targeted areas as small as 2 mm[27] and metamaterials for focusing U.S. may increase spatial resolution even further (<1.0 mm). Focused TUS is also capable of stimulating deeper brain structures than other stimulation methods like TMS and tDCS.[33] Thus, it has been proposed that U.S. could mitigate the need for invasive DBS implants for the treatment of refractory psychiatric disorders (e.g., depression, obsessive compulsive disorder), Parkinsonism, and other disorders that are currently treated via this method.[28] However, the skull reflects, refracts, absorbs, and diffracts the U.S. field, thus presenting a major obstacle for transcranial U.S.

Transcranial Doppler ultrasound (TDU) is used frequently in clinical procedures to measure blood flow velocities in brain arteries,[42] and is capable of penetrating the skull through the trans-temporal window or other areas where the skull is thinnest (Figure 32.1) with low intensity U.S. (~100 mW/cm^2).[43] Many TDU devices use the standard "b-mode" (found on many hospital grade ultrasound machines) in which a linear array of transducers emit ultrasound to scan a plane through the brain or body. As TDU must penetrate the skull and reflect back to the transducer to produce an image, this *prima facia* demonstrates that imaging U.S. can penetrate the skull at intensities under the FDA limit. Mathematical modeling, along with experimental data, shows that the optimal gain for focused U.S. transmission through the skull and for brain absorption occurs at frequencies below 0.70 MHz.[44,45] In fact,

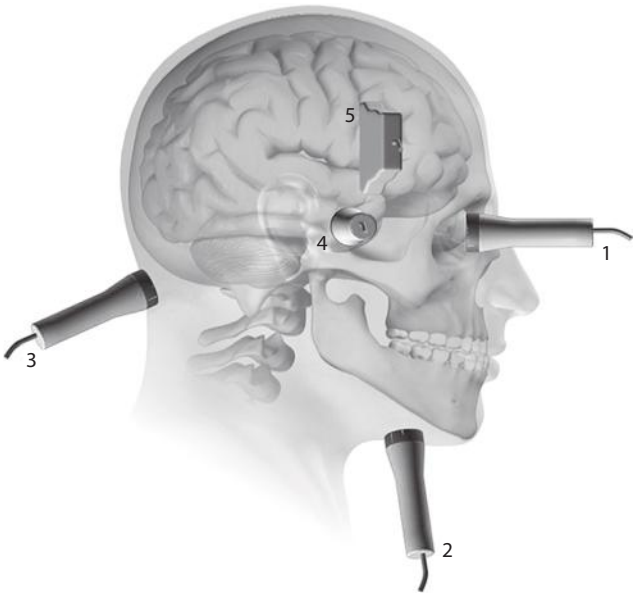

FIGURE 32.1 Typical locations used for transcranial ultrasound in medical imaging 1–4. The fifth location was the stimulation site in Hameroff et al.[56] Stimulation was on the opposite side to where the patient experienced chronic pain. (Adapted with permission from Hameroff S et al. *Brain Stimul* 2013;6(3):409–15.)

Hynynen and colleagues[46–48] have developed a technique for precise targeting of focused ultrasound from outside the skull (magnetic resonance guided focused ultrasound [MRgFUS]). The feasibility of using this method for low intensity neuromodulation is not yet clear, yet the fact that ultrasound can penetrate the skull with such precision is encouraging. Indeed, research groups are currently working on designs for low intensity TUS arrays for the treatment of refractory psychiatric disorders.[49,50] Functional studies must be now performed that examine how U.S., at varying output parameters, affects intact brain circuits and behavior in humans.

Safety Considerations

The major biohazard to consider when directing U.S. into the brain is tissue heating and cavitation. At high intensities, U.S. can cause thermal effects and damage due to explosions of microbubbles. Indeed, high intensity focused U.S. (usually > 1000 W/cm^2) is used for tissue ablation in many areas of the body[51] including noninvasive cancer treatments,[52] whereas U.S. intensities below 500 mW/cm^2 can produce biological effects without damage.[9,16] Recall that the FDA regulates the output level of diagnostic and imaging U.S. (I_{SPTA} 720 mW/cm^2). These guidelines are based on decades of animal and human research showing that acoustic energy at or below these levels is safe for human adults, including the brain.[14] Histological analysis of animal brains that underwent U.S. stimulation at intensities well below the FDA limits (e.g., ~50 mW/cm^2–250 mW/cm^2)[27] show no detectable signs of biological damage. In fact, U.S. effects at intensities higher than the FDA limits also show no histological indicators of damage to the animal brain (e.g., ~3 W/cm^2).[30] It should be noted, however, that U.S. may have detrimental effects on developing brains: neuronal migration is affected when rat fetus is stimulated with U.S. for 30 min or more for at least two exposures.[53–55] Nonetheless, results from adult animal brains, and the fact that U.S. is used routinely in medical procedures with no appreciable detrimental effects, suggests that low intensity U.S. is safe and reversible for neuromodulation in adults.

Given the potentially wide ranging therapeutic application of TUS for the treatment of brain based mental disease, and the fact that low intensity U.S. does not appear to cause biological damage in adults, the first human studies are warranted. The long-term effects of repeated low intensity U.S. in humans have not been examined. Until the proper studies are conducted, these first TUS studies should take precaution to use only intensities that are known to be safe in the brain and to use the smallest exposure duration possible for effects.

Human Transcranial Ultrasound

The first published study attempting to use TUS to manipulate mental states in humans was a double-blind, placebo-controlled experiment testing whether low intensity TUS (at 8 MHz) could alter self-reported pain and mood in an older population of chronic pain patients.[56] An FDA approved medical-grade imaging U.S. device (General Electric LOGIQ e; GE Healthcare, Little Chalfont, UK) that emitted pulsed U.S. in a scanning sequence (described above) was used. This device was chosen because it is used routinely for diagnostic imaging and the intensity output is well below the FDA guidelines. Thus, it presented little risk to the patients in regard to long-term effects. Participants received a single 15-second dose of TUS delivered to the temporal window opposite to the side of reported pain (Figure 32.1). Hameroff and colleagues collected self-reported pain (numerical rating scale for pain) and mood data (Visual Analogue Mood Scales) in 34 patients. Although self-reported pain did not significantly decrease, patients in the TUS group reported an improvement in mood compared to the placebo group at 10 min and at 40 min after TUS stimulation. As ultrasound images from each patient were collected, it could be verified that ultrasound had indeed penetrated the skull sufficiently to image brain tissue (Figure 32.2). These are the first TUS results in humans and, although preliminary, suggest that TUS can improve mood.

A follow-up report by Sanguinetti and coworkers[57] replicated these mood-altering effects in a healthy population of undergraduate students at the University of Arizona. TUS at lower frequencies should have a more robust effect on neural activity than TUS at higher frequencies insofar as lower frequency TUS is better at penetrating the skull.[44,45] Thus, Sanguinetti and colleagues examined self-reported mood following stimulation with either 2 MHz or 8 MHz TUS. Whereas Hameroff et al.[56] stimulated the contralateral side of the frontal cortex to where patients experienced pain, Sanguinetti et al.[57] applied stimulation to participants' right temporal window (Figure 32.3). Self-reported affect increased

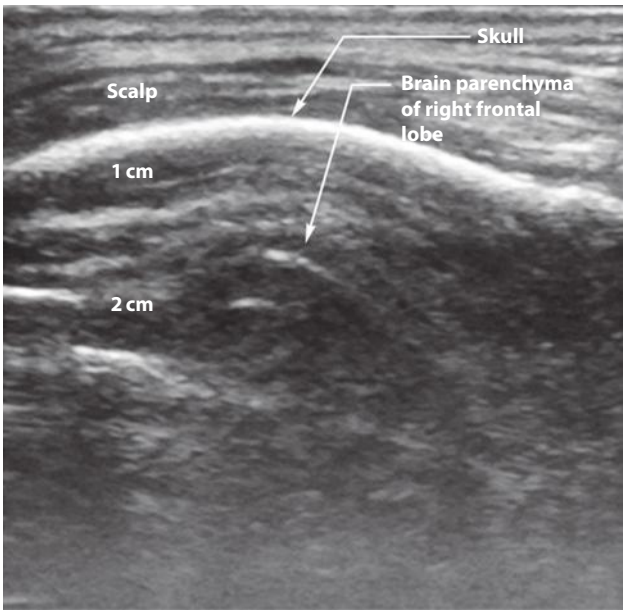

FIGURE 32.2 Example of image taken from a chronic pain patient. Longitudinal gray scale images taken from a session of transcranial ultrasound. Scalp, skull, and brain tissue are visible in the image. (Adapted with permission from Hameroff S et al. *Brain Stimul* 2013;6(3):409–15.)

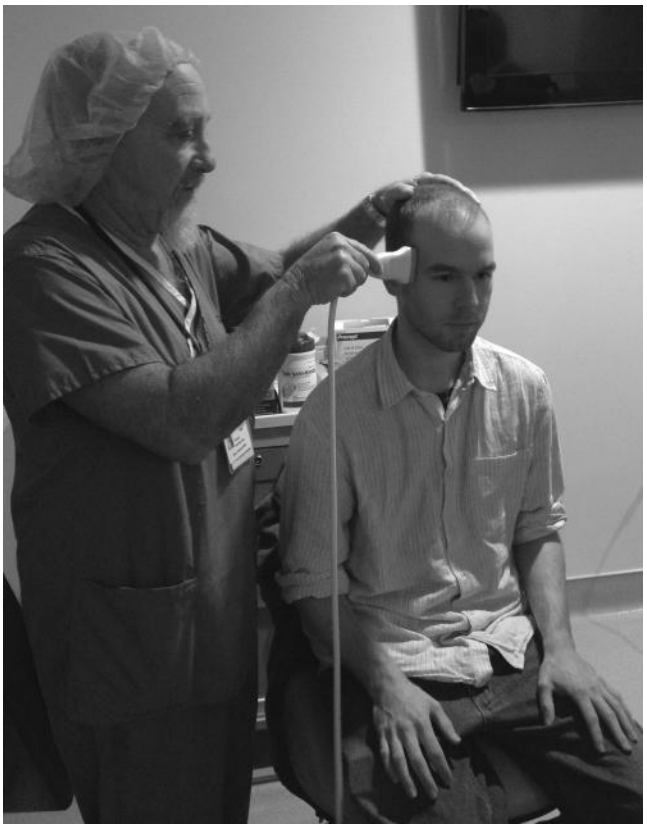

FIGURE 32.3 Example of stimulation to right frontal cortex with the GE LOGIQ e 12R transducer probe (GE Healthcare, Little Chalfont, UK). (Photo courtesy of J. Sanguinetti.)

(i.e., became more positive) following right frontal-temporal TUS stimulation at 2 MHz, but 8 MHz stimulation had no effect on mood relative to baseline. Interestingly, improvements in mood also appeared to be dose dependent: There was a greater improvement on mood following 30 s of stimulation than 15 s of stimulation. The effects on mood in these studies lasted more than 30 min, and it remains to be seen whether multiple stimulation sessions would lead to longer effects on mood. Taken together, these first two preliminary human studies suggest that TUS can affect mental states through frontal cortex stimulation. However, these experiments in humans do not demonstrate direct effects of ultrasound on the brain, therefore future studies in humans should combine TUS with imaging methods (e.g. fMRI).

FUTURE DIRECTIONS

Much remains to be understood about the neurobiological mechanisms of TUS before it can be routinely used therapeutically in mental health fields. However, this should not prevent researchers from investigating the clinical applicability of TUS. Most of the noninvasive brain stimulation methods—TMS and tDCS, for example—were developed for scientific and clinical applications before extensive research on animal models to understand the biological mechanism were conducted.[2] This is due in part to the noninvasive nature of these techniques but also because the necessary work was done in animals to show these methods do not pose significant bioeffects and that the potential benefit outweighed the risks. There is a growing literature on the bioeffects of U.S. at low and high intensities,[9,14,16,17] and low intensity U.S. has a proven safety record in over 50 years of medical diagnostic applications. Thus given the extant evidence that TUS can stimulate brain activity in animals, and the pilot work in humans suggesting promise for elevating mood, researchers should cautiously proceed to investigate the applicability of TUS for mental health conditions. Although research to date suggests that mood can be increased acutely following TUS, whether repeated delivery of TUS can lead to sustained mood change in psychiatric disorders remains an important and unexamined question.

When conducting TUS on humans, the most important safety consideration is the acoustic output levels of the transducer. As mentioned above, the FDA limits the acoustic output to a MI of 1.9 and the spatial peak, temporal average (I_{SPTA}) of 720 mW/cm^2. Researchers should do the necessary background reading to understand what these outputs mean and they should only use equipment in which these outputs can be clearly read out or controlled with high certainty. Hameroff et al.[56] and Sanguinetti et al.[57] chose to use FDA approved medical imaging devices in which the acoustic output cannot be set to dangerous levels. These devices are prevalent in hospital and clinics, giving interested researchers and clinicians easy access for future TUS studies. However, these systems emit U.S. in scanning beams of several centimeters (depending on the selected probe). Furthermore, many of these devices emit U.S. at frequencies greater than1 MHz.

If researchers desire greater spatial precision, and wish to emit U.S. at lower frequencies that will penetrate the skull better, then devices will need to be designed specifically for human TUS. These devices should be designed in such a way that they can only emit low intensity U.S. Such devices are being developed, for example, by a pioneering team at Virginia Polytechnic Institute and Arizona State University.[23,55]

There appears to be an almost unlimited parameter space for researchers to explore TUS in humans. The optimal frequency for TUS transmission and brain absorption is ~0.5 MHz,[44,45] narrowing the parameter space considerably. But many unknowns remain. For example, much of the U.S. brain stimulation results in animals have been on motor areas with focused U.S. (with millimeter precision). It is unknown whether focused U.S. or unfocused scanning beam (like that emitted from medical imaging devices) is best for therapeutic effects. Although the animal research has primarily investigated U.S., researchers and clinicians who have access to medical grade imaging U.S. devices might find that scanning beams are sufficient for many purposes.[56] For example, depression has been linked to alterations in lateralized frontal activity,[58] and it might be sufficient to stimulate the frontal cortex with unfocused U.S. as global effects might be more effective than localized effects.[57] For functional brain mapping, however, focused TUS will be necessary to linking changes in electrical or hemodynamic activity following TUS stimulation with behavioral changes.

Different properties of the U.S. waveforms might affect how effective TUS works as a brain stimulation method.[28] The length of the stimulation pulse (pulse duration), how often the pulse is repeated (pulse repetition frequency), and the overall intensity (peak and temporal average intensities) might alter the effect of TUS on neural tissue. Lower pulse durations have been shown to stimulate brain activity (<50), whereas longer pulse durations (>100) have been found to inhibit.[30,31] However, it is not known which pulse durations give the strongest inhibitory/excitatory effects in human brain tissue and whether different cortical areas respond similarly to the same TUS parameters. The overall exposure duration will also affect stimulation efficacy as well. Given that Hameroff et al. and Sanguinetti et al. found effects of frontal cortex TUS stimulation on mood at 15 s and 30 s, respectively, it is recommended to start with the lowest exposure duration possible where an effect can be seen. The effects in these studies lasted more than 30 min. However, it is unclear whether multiple stimulation sessions would lead to longer effects. In addition to replication studies, and examining the impact of TUS on a variety of emotional disorders, future studies should also examine the parameter-space of TUS waveforms to increase therapeutic effects.

SUMMARY

Over 50 years of animal research suggests that U.S. can stimulate or inhibit neural activity. Low intensity U.S. is safe for use in adult humans and can be effectively transmitted through the human skull and absorbed by the brain. TUS has several advantages over established noninvasive magnetic and electrical neurostimulation methods. It can be focused with millimeter precision or unfocused to stimulate larger brain areas. TUS can easily be coupled with imaging techniques, such as fMRI, for brain mapping studies, and it is capable of targeting and stimulating subcortical brain structures. Two initial reports support the use of TUS for elevating mood in humans and future work will investigate mood-elevating properties of TUS with psychiatric patients (e.g., depression). Looking ahead, future studies will need to examine the TUS parameters most amenable for neurostimulation.

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33 MRI-Guided Focused Ultrasound
A Method for Noninvasive Surgery and Other Clinical Applications

*P. Jason White and Ferenc A. Jolesz**

CONTENTS

INTRODUCTION

The notion that acoustic energy could be used as a modality for delivering therapy was noted as early as 1927, when the interaction of *in vivo* anatomy (an investigator's finger) with high intensity ultrasound generated sensations of heat and subsequent tissue damage.[1] Key studies performed in the following decades had developed transduction technologies[2] and established the basic principles for using focused ultrasound (FUS) to predictably generate deep-set lesions within biological tissue.[3–5] Several attempts were made to devise clinical systems for this new technique, dubbed "high intensity focused ultrasound" (HIFU), notably including a method for treating hyperkinetic and hypertonic disorders by HIFU sonication of the pallido-pallidofugal complex of the human brain.[6] Recognizing that the skull bone presented a substantial obstacle to the effective delivery of ultrasound energy, the initial delivery of FUS into the brain required an acoustic window by craniotomy. It would be several decades before technological developments would allow HIFU to be performed through the intact skull.[7,8]

More significantly, clinical application of HIFU for therapy was not readily adopted early on because of the need for imaging to provide target definition and a reliable treatment monitoring method. In order to use transcutaneous FUS as a surgical tool, imaging is necessary to actively plan, target, monitor, and assess the evolution of therapy. In the early 1990s, magnetic resonance imaging (MRI) was proposed as a modality that can be integrated with HIFU devices.[9–11] These early developments became a driving event in the subsequent resurgence of interest in HIFU for numerous applications, including the treatment of benign tumors such as breast fibroadenomas[12] and uterine fibroids[13]; malignant tumors such as breast,[14] liver,[15,16] prostate[17] cancers, and bone metastases[18]; functional neurological disorders such as neuropathic pain[7]; and movement disorders such as essential tremor,[19] and Parkinson's disease.[20–22] Although active clinical investigations continue into the use of ultrasound imaging as both the targeting and monitoring modality,[23–26] the advantages that MRI offers in soft-tissue contrast and thermometry[27,28] will likely guarantee its continued use as a best available planning, monitoring, and assessment tool in HIFU procedures.

Unlike MRI, the state-of-the-art in ultrasound imaging does not perform sufficiently (especially through the skull bone) in that it is not able to clearly delineate tumor boundaries in most organs, and cannot provide quantitative thermometry. The use of pre-, intra- and post-procedural MRI overcomes these limitations, and allows for detailed visualization of treatment margins and surrounding anatomical structures. This level of detail not only improves treatment outcomes by ensuring sufficient coverage of a targeted tumor or anatomical structure, but also ensures the safety of the procedure by minimizing damage to surrounding healthy tissues. Advanced developments in MRI thermometry have

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produced a method for monitoring and controlling HIFU procedures with high temporal, spatial, and temperature resolution.[10,29–32] Unmatched in efficacy by any other radiological modality, intra-procedural MRI thermometry can generate quantitative temperature maps for planning sonications (even for nonthermal therapies, low intensity sonications with small temperature changes can be used to localize targets) and for monitoring in real time the temporal evolution of spatially isolated temperature gradients.

As an effective imaging method for planning, delivery, and assessment of HIFU therapy, the incorporation of MRI marked the beginning of a substantial increase in research and development of focused ultrasound technologies for a number of potential clinical applications. The ability for tumor margins to be clearly visualized has led to active investigations of MR-guided focused ultrasound (MRgFUS) for various benign tumors like breast fibroadenomas and uterine fibroids. This led to the U.S. Food and Drug Administration (FDA) approval (2004) of a system to treat uterine fibroids.[33] With FDA approval and a substantial number of completed and ongoing clinical studies, the development of MRgFUS treatments of uterine fibroids represents a (more-or-less) complete story of the progression of an idea into a finalized solution.[33] MRI tissue characterization has also been used to detect cancers (e.g., brain,[8] breast,[12] prostate,[27,34,35] pancreas,[36] liver,[37] and metastatic malignancies in the bone[38]). In addition, MRI's ability to depict intracranial anatomical structures with high resolution and contrast has led to investigations into its potential use in treating neurological (e.g., Parkinson's disease,[7] Alzheimer's disease,[39,40] essential tremor,[19,41] neuropathic pain,[7] and obsessive compulsive disorder[42]) and vascular (e.g., stroke[43] and atherosclerosis[44]) disorders with MRgFUS. This mostly preclinical research and development also manifested as a number of improvements in ultrasound transduction techniques and technologies for effective integration into an MRI environment,[10,45] and for a clinically viable method to deliver ultrasound through the intact skull.[46–54]

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

Although soft-tissue imaging is the most common medical application of ultrasound,[55] its therapeutic potential has been known and explored since the early 1900s.[56] In fact, one of the early proposals for its application was for cancer therapy[57] after a heating effect was observed with ultrasound exposure.[1] This observation precipitated a number of investigations into the physical principles of ultrasound and its interactions with biological media. With concurrent technological developments in transduction materials and transducer designs, many of which were built upon technologies developed for military and industrial applications, the controlled delivery of high intensity ultrasound for medical applications became possible. The subsequent investigation and exploration of bioeffects associated with ultrasound have continued to the present day, all in an effort to maximize the potential therapeutic benefits of ultrasound-tissue interactions.

Principles of Ultrasound

Ultrasound can be described as the transfer of mechanical energy through space via particle oscillations that vary temporally and spatially at base frequencies beyond the upper detection limit of human hearing (approximately 20 kHz). Within a lossless homogeneous medium, ultrasound waves are self-propagating with pressure amplitudes that change only according to propagation geometry. In biological media, which is typically resistive and heterogeneous relative to the time and geometric scales, respectively, of ultrasound waves, the interaction between a propagating pressure wave and tissue leads to physical effects that are useful for imaging and therapy.

The interactions between ultrasound and the tissues in which it propagates are often broadly categorized into two fundamental mechanistic categories: scattering and absorption. Ultrasound scattering arises from discontinuities in mass density or compressibility within tissues, and become the post-interaction signals that are used to reconstruct and yield information about tissue structure. Functionally speaking, scattering processes are a more significant effect for ultrasound imaging. For HIFU, ultrasound absorption is a more significant effect than ultrasound scattering. This is the conversion of the coherent energy of a propagating acoustic wave into heat via various physical and chemical relaxation mechanisms. These mechanisms of absorption are numerous, varied, and complex; as such, they remain poorly understood.[58] In fact, attempts toward a comprehensive theory of ultrasound-tissue interaction by reductionism and categorization, although useful in many scenarios, have overly simplified the complexities inherent in real materials and nonideal geometries. To deduce fully the correlation between tissue heating (this being the key effect for HIFU thermal therapies) and ultrasound parameters such as frequency and intensity, one must not only consider the fundamental interaction mechanisms that account for ultrasound attenuation, *viz.*, scattering and absorption, but also recognize that these mechanisms are not necessarily functionally separable. While efforts are continuing to formulate such a model, empirical studies have provided the necessary starting points for the design, construction, and testing of HIFU devices.

HIFU applications that are designed to induce a thermal effect in tissue rely on accurate, controllable, and predictable conversion of acoustic energy into heat. The parameters that affect the ability of ultrasound to generate a given temperature rise include the sonication intensity, duration, and frequency. The delivery of a specified time-averaged energy within a localized target (i.e., intensity) is effectively determined by transducer design, and will be discussed in section "Transducer Design." Bioeffects largely dictate the required sonication durations to maintain temperature elevations; these effects will be discussed in section "Bioeffects." The dependence of tissue heating on the ultrasound frequency is governed by fundamental physical principles and will be discussed here.

When a unit of tissue experiences a change in pressure (i.e., a force) from a passing ultrasound wave, intrinsic viscoelastic

forces counter and resist the force in proportion to the tissue strain (elasticity) and the first temporal derivative of the tissue strain (viscosity), respectively. These relations can be described in a simplified form (neglecting shear stresses and in only one dimension) with the equations,

$$F_E = kx \tag{33.1}$$

and

$$F_V = \delta \frac{dx}{dt} \tag{33.2}$$

where F_E and F_V are the restoring and resistive forces due to elasticity and viscosity, respectively; k is a constant of elasticity; δ is a constant of resistance; and x is the tissue strain. Equation 33.1 is commonly referred to as Hooke's law and it describes linear elasticity. Equation 33.2 describes a resistive force that acts against the first temporal derivative of strain (dx/dt) and dissipates energy from the original wave. An additional relation between strain (x) and its temporal derivative (dx/dt) gives rise to a characteristic relaxation time, τ_R, which is an intrinsic property of a given tissue or combination of tissues. Because each ultrasound cycle is hysteretic due to this relaxation time, energy is dissipated and transformed into heat over each ultrasound cycle. As ultrasound frequency is increased, the combination of more cycles per second and an increasing dx/dt (Equation 33.2) leads to an increase in energy dissipation and hence, higher attenuation. This mechanism is partially responsible for the increase in attenuation with increasing ultrasound frequency. The exact relation between ultrasound frequency and attenuation is a topic of ongoing investigation and debate.[59–65]

The dissipation of coherent ultrasound energy into heat is a process that transfers the energy of waves into incoherent vibrations that exist and can be categorized in many mays (e.g., translational versus rotational motion, molecular versus lattice structural energy, physical versus chemical energy states). Due to the inherent complexity of biological tissues and the multiplicity of energy coupling pathways, empirical studies have generated a substantial collection of data[62,66–82] that, when analyzed according to

$$\alpha = Nf^m \tag{33.3}$$

where α is attenuation, f is frequency, and N is the constant of proportionality, the power-law exponent, m, is found to be close to unity for most soft tissues,[58] indicating a more-or-less linear relation between attenuation and frequency below 10 MHz. But m is not constant over the entire range of ultrasound frequencies, tending toward 2 with higher frequencies because the absorption of water (which follows an f^2 relation) becomes a significant contributing factor above approximately 10 MHz. These relations for the respective tissues play an important role in designing the ultrasound specifications for the intended purpose of a HIFU transducer. Along with the properties of the targeted tissue, those of intervening tissues and tissues distal to the focus must also be considered.

Beyond absorption mechanisms, nonthermal effects of FUS, such as scattering and cavitation, are also being investigated for clinical application.[83–96] Although beyond the scope of this chapter, which focuses on thermal therapies, it should be noted that the secondary processes of nonthermal effects are significant contributors to temperature rise in ultrasound attenuation, and, when considered in conjunction with absorption, substantially affects the accuracy of HIFU thermal models.[58]

Transducer Design

The discovery by Jacque and Pierre Curie in 1880 of natural piezoelectricity in quartz[97] marked the beginning of ultrasound transducer development. Although other instances of natural piezoelectricity were subsequently discovered (e.g., potassium sodium tartrate, berlinite, and topaz) and used to generate ultrasound, the development of artificial piezoelectricity in polycrystalline ferroelectrics led to shapeable materials with high electromechanical coupling that were well-suited for FUS production.[98–102] These materials, especially the lead zirconate titanates ($PbZr_xTi_{1-x}O_3$), have become the mainstay of the HIFU device industry. (Polyvinylidene difluoride [PVDF], a piezoelectric thermoplastic fluoropolymer, is limited to use as a detector due to its relative thermal fragility and substantially lower electromechanical coupling coefficient.) Nonetheless, there have been a number of obstacles that have been addressed to arrive at the present state-of-the-art HIFU transducer designs.

Lead zirconate titanate (PZT) has a mass density of 7500 kg/m^3 and an acoustic wave speed of 4530 m/s (PZT-4), together giving it an characteristic impedance of 34.0 MRayl.[103] When contrasted with the same for soft tissue (ρ = 1000 kg/m^3, c = 1540 m/s, Z = 1.5 MRayl), the first drawback of PZT becomes evident: the large impedance mismatch prevents the efficient delivery of ultrasound energy from the transducer into soft tissue. Two methods to mitigate this large impedance discontinuity include the implementation of physical quarter-wave ($\lambda/4$) matching layers[104,105] and the use of composite transduction materials.[106] For narrow-band operation, a $\lambda/4$ layer with characteristic acoustic impedance

$$Z_M = \sqrt{Z_1 Z_2} \tag{33.4}$$

has been shown, in conjunction with air backing, to substantially increase the efficiency of energy transmission into the targeted tissues.[107] Also, specific configurations of PZT rods as embedded in relatively compliant passive polymer matrices have been investigated as composite transduction materials that can more closely match the characteristic impedance of soft tissue or the coupling medium.[108] To date, most HIFU transducers are constructed with these "piezocomposite" materials, but it should be noted that a new class of ultrasound generators, capacitive micromachined ultrasound

transducers (CMUT), have recently been proposed for high power applications.[109] The proposed advantages of CMUTs over piezoceramics (e.g., reduced self-heating, direct electronic integration, and physically compact) could have a significant impact on future transducer designs.

To produce the focused ultrasound field that is required for HIFU, various designs have been proposed and tested. As discs with parallel surfaces were easiest to fabricate and their radiating fields were relatively predictable, early designs incorporated reflectors[110,111] or refractors[112–114] with planar sources to produce focused fields. Geometric constraints also brought about some effective designs for focusing ultrasound fields from a planar source.[115,116] Today, HIFU fields are typically generated with geometrically curved sources[117] that produce focal zones suited for specific applications. With the advent of modern electronic circuits and their subsequent miniaturization, the possibility of multiple-source phased arrays transformed the design options for HIFU transducers. With designs that incorporate hundreds of independently controlled sources, the latest HIFU transducer systems allow for high levels of control, including electronic beam steering and aberration correction.[118,119] Presently, transducers designed for HIFU applications deliver focal intensities on the order of 100–10,000 W/cm^2, with peak compression pressures up to 70 MPa and peak rarefaction pressures of up to 20 MPa.[120]

With the proposition that MRI could be used for intraprocedural guidance in HIFU,[11,121] transducers and systems were devised to be compatible and operable within the high magnetic field of clinical scanners and to be minimally interfering to MRI scanning.[10] This development led to the first clinical application[122] and eventually the first FDA-approved application of MRgFUS.[123,13,33]

Bioeffects

Local strains produced by ultrasound waves passing through biological tissue have the potential to induce a number of bioeffects. Most notably, thermal rise stemming from the dissipation of coherent wave energy is one of the principal mechanisms for delivering HIFU therapy. Although the physical mechanism may be different, the spatial and temporal evolution of temperature elevation with HIFU follows the same pattern as with any other modalities of thermal therapies (e.g., RF, microwave, and laser), the primary determinants being the intensity and exposure duration. But an important advantage that HIFU offers is the delivery of thermal therapy without the percutaneous insertion of a probe. This not only reduces the invasiveness of the procedure, but also allows for extended spatial coverage and the targeting of complex geometries. When monitored with MR thermometry, in particular, FUS has been shown to be an effective and efficient modality for thorough coverage of large and geometrically complex tumors.[33]

The threshold for causing irreversible damage in tissue via thermal mechanisms varies according to tissue type and is defined by a combination of temperature and sonication duration. Evidence has shown that short exposures (a few seconds) that raise tissue temperature beyond approximately 57–60°C lead to protein denaturation and irreversible damage.[124] There is also evidence that sustained (several minutes) temperatures of 43°C likewise leads to irreversible tissue damage.[125] Temperatures beyond 100°C induce tissue boiling at atmospheric pressure, which leads to complex behaviors for FUS since the ultrasound field will interact strongly with the generated gas bubbles. For this reason, 100°C represents the upper temperature threshold for HIFU thermal therapies.

Sonication parameters for the generation and maintenance of temperature elevation at a targeted site must be adapted according to multiple influences, including the tissue's absorption coefficient, the geometric arrangement of anatomical structures, and the effects of blood perfusion on local heat transfer. During HIFU sonication, the interplay of the tissue's intrinsic ultrasound absorption with the complex concurrent dynamic of heat diffusion and vascular perfusion creates a scenario in which energy has to be constantly and consistently delivered into a volume to maintain the target temperature. As a consequence, for a given time-averaged delivery of acoustic power, shorter sonication durations lead to better-defined treatment margins by minimizing the time-dependent effects of heat transfer.[33] Monitoring and responsive control (see section "MRI Guidance") is especially crucial in highly vascularize organs and organ systems as excessive heat can be inadvertently delivered outside the targeted region.

Irregularities in anatomical geometry (whether normal or pathological) further contribute toward deviations from the expected thermal behavior because, unlike many other modalities, ultrasound energy is redirected by mass density and elastic discontinuities within the medium. In certain cases, obvious boundaries, such as bone or bowel interfaces, can be accounted for in the pretreatment planning phase and sonication protocols adjusted accordingly. Otherwise, the cumulative effects of smaller scattering structures can be accounted for *in situ* by noting their secondary effects (i.e., temperature elevation due to energy redirection) with an effective monitoring method such as intraoperative MRI.

Nonthermal bioeffects of FUS are cellular, tissue, or organic responses that can be largely attributed to the mechanical action of ultrasound, which includes not only the force from pressure gradients, but also cavitation and nonlinear streaming. They include blood-brain barrier disruption,[126] cellular permeability modification,[89] and biochemical activation.[127] Because of the inherent difficulty in separating thermal from nonthermal actions—in fact, cavitation enhances tissue heating—the basic mechanism for eliciting these bioeffects are not fully understood, but are attributed predominantly to nonthermal pathways.

MRI GUIDANCE

Clinical application of FUS languished for most of the twentieth century because, although it was understood that ultrasound could be used for thermal therapy, there was no

effective method for monitoring the subcutaneous deposition of energy during treatments. Plain film x-rays were used in early attempts to guide the treatment of neurological disorders with FUS,[4,6] but images could only be used to establish anatomical landmarks relative to the high-contrast signal of the skull bone. With the advent of electronic, computer, and materials technologies in recent decades, several imaging modalities, including ultrasound, have been explored or are presently being investigated as HIFU guidance tools.[23] MRI, with its superiority in soft-tissue contrast[27] and its ability for real-time thermometry,[29,31,32] has emerged as the dominant modality for treatment planning, *in situ* monitoring, and post-procedural assessment of HIFU treatments.

For treatment planning, a significant advantage that MRI has over other imaging modalities is soft-tissue differentiation. For outlining the extent of tumor treatments for targeting therapy, in particular, only MRI provides sufficient conspicuity of margins between healthy and pathological tissues. Even with these advantages, the continued development of novel scanning techniques and the use of higher field magnets could improve the identification of tumor margins, especially for infiltrating malignant tumors. In addition to defining treatment boundaries, MRI provides a sensitive and detailed view of critical anatomy within the FUS beam path. Tissues proximal and distal to the target site may have enhanced ultrasound absorption (e.g., scar tissue and bone) and must be allowed extra time to dissipate heat between serial sonications. Alternatively, MRI images can be used to identify these tissues, and the treatment plan can be adjusted to avoid them.

Along with structural imaging, MRI can also be used to generate *in situ* temperature maps of HIFU treatment zones.[8,33] MRI thermometry can be used for tracking, in near real-time (3-s resolution), with high temperature sensitivity (±1°C), and with high spatial resolution (1 mm),[120] the temporal and spatial progression of localized HIFU thermal ablations. The visualization of evolving temperature maps allows for a systematic control of energy deposition at the targeted site according to live feedback, and allows for concurrent thermal monitoring of the neighboring nontargeted tissues for safety. Along with a level of spatial and temporal discrimination for MRI thermometry that is unmatched by any other imaging modality, the specific method of measuring proton resonance frequency (PRF) shift adds a high level of measurement consistency to the list of advantages.[128–132] This measurement is possible because there is an inverse relation between tissue temperature and PRF. Upon raising the temperature of water, the increased kinetic energy disturbs electron bonds, returning the hydrogen nuclei to a more magnetically shielded state, and hence, decreasing PRF on the order of 0.01 ppm per degree Celsius.[128] Although other MRI parameters have been shown to exhibit temperature dependence,[133] the relationship of PRF with temperature is less sensitive to tissue type[132] and coagulation status.[131] Despite sensitivity to motion and inconsistent performance in adipose tissues, this method of MRI thermometry remains the most successful *in situ* method for monitoring the spatiotemporal deposition of heat during HIFU thermal therapies.

After HIFU sonications, the sensitive and accurate assessment of treated tissues has likewise been demonstrated with MRI. Typically, a contrast-enhanced T1-weighted image is used to identify nonperfused tissues as a result of HIFU thermal coagulation.[134] These images have been especially useful in studies to improve the predictive capabilities of inline MRI-HIFU thermal dosimetry to predict coagulation status of treatment sites.[135]

CLINICAL APPLICATIONS

As a method that uses nonionizing radiation delivered noninvasively for percutaneous surgery, HIFU is an appealing alternative to existing techniques such as radiosurgery, RF- and cryo-ablation. MRgFUS is now being actively investigated for treatments of a number of clinical conditions. However, significant experiences to date have been accumulated in three clinical application areas: uterine fibroid, bone metastasis, and functional neurosurgery. This chapter examines in detail the application of MRgFUS for these three clinical conditions: uterine fibroids, bone tumors, and for functional diseases of the brain.

Uterine Fibroids

Uterine fibroids are noncancerous tumors of the smooth muscle (a.k.a. leiomyomas) that arise within the myometrium. They occur singularly or as a collection of multiple tumors and can variably cause mild or severe symptoms, including urinary urgency, heavy menstruation, and intense pain.[136] The current treatments for symptomatic uterine fibroids include uterine arterial embolization, RF ablation, myomectomy, and hysterectomy.[13] Today, HIFU has been successfully performed under ultrasound[23] and MRI[33,137] guidance, and has been demonstrated to be an effective alternative treatment modality for uterine fibroids that is noninvasive and preserves the option of pregnancy.[134] The entire procedure, as performed with the FDA-approved ExAblate 2000 system (InSightec, Haifa, Israel), is performed in an outpatient setting and lasts approximately 3 h (two treatment sessions over 2 consecutive days may be required for patients with large or multiple fibroids). The only invasive element of the treatment protocol is the preparation of an intravenous line that is required for administration of moderate sedation and post-procedural MRI contrast agents. The patient can return to normal activities after a brief post-procedural monitoring period and is offered over-the-counter medication for the relief of minor treatment-related discomfort.

To sonicate within the uterus under MRI guidance, the patient lies prone on a scanner table atop an integrated HIFU transducer that is positioned to sonicate upward through the abdominal wall. Prior to sonications, a series of steps are taken to establish safety parameters and plan the treatment in detail. A T2-weighted MRI image is used to define the targeted volume and to evaluate neighboring structures for interference potential with the intended ultrasound beam path. Specifically, the beam path is verified to not intersect

with scar tissues, bowel loops, or the bladder (this is exempt from some protocols), and that it remains a specified distance from the sciatic nerve and branches anterior to the sacrum. These limits are in place to reduce the risk and/or reduce the severity of side effects such as mild skin burns and transient sciatic nerve palsy.[138,139]

For each planned sonication, which produces a roughly ellipsoidal lesion (approximately $1.5 \times 1.5 \times 15$ mm) with its major axis collinear to the ultrasound propagation direction,[140] safety measures are reevaluated and verified. The treatment procedure consists of sequential sonications to cover the extent of the targeted area, each separated by sufficient time for prefocal tissues, which are exposed to low intensity ultrasound for each sonication, to dissipate heat. Spatial and temporal thermal evolution is monitored with MRI thermometry during each sonication period at a temporal resolution of approximately 3 s, allowing for real time closed-loop control. As the typical treatment requires between 60 and 90 sonications, leading to an overall treatment time of approximately 3 h when performed in this fashion, sonication interleaving and clustering techniques are being developed that will substantially shorten the treatment time by spatially separating the dose accumulation zones.[141] The use of FUS to generate microbubbles for enhancing thermal rise is also being explored as a way to improve treatment efficacy and shorten the treatment time.[142–144]

Treatment is assessed using contrast enhanced T1-weight MRI images to demonstrate nonperfusion within the treatment zone. In this fashion, residual tumors can be identified and sonicated before ending the treatment session. The current recommendation to optimize outcomes in uterine fibroid HIFU treatment is to achieve at least 60% nonperfused volume in the original tumor.[33] The volume of nonperfused tissue post-HIFU has been linked to long-term overall fibroid volume reduction,[145] which was shown to lead to sustained symptom relief in a 12-month follow-up study of 160 patients.[138] As the FDA has relaxed guidelines for maximum treatable volumes, studies have been able to demonstrate improved overall outcomes (level and duration of symptom relief) with larger treatment volumes.[138,139,146] Outside of the United States, similar findings have been shown, with centers in Germany and South Korea creating average nonperfused volumes of well over 80%.[147,148]

Research on MRgFUS for uterine fibroids has been continuing with the development of next generation devices that incorporate technologies to reduce treatment times while increasing treatment volume (ExAblate 2100 and Philips Sonaleve). Studies to evaluate long-term outcomes,[149] post-treatment pregnancies,[150] and efficacy predictors[151] are ongoing.

Bone Tumors

Bone is one of the most common sites for cancer metastasis, with occurrences in 90% of breast cancer patients[152] and 30% of cancer patients overall.[18] Of these cancer patients with bone metastases, 50%–70% suffer from significant pain.[120] As medical advances have increased the survival time of cancer patients, there has been a growing population of people who are living with metastatic pain, which, when localized to specific sites on bone tissues, is often quite debilitating and leads to a substantial reduction in quality of life. A number of localized treatment options are available for palliation, including surgery, laser ablation, radiofrequency percutaneous ablation, and the current standard of care, external beam radiation therapy (EBRT). However, EBRT treatments have failed to relieve pain in 20%–30% of patients[153,154] and have led to pain recurrence in 27% of cases.[155] Repeat treatments are precluded in these scenarios due to ionizing radiation dose accumulation.

With the demonstration of MRgFUS efficacy in the treatment of uterine fibroids, it was proposed that bone tumors could be similarly treated. The most immediate advantage of MRgFUS over EBRT is the use of nonionizing radiation, which would allow for repeat treatments. Just as with uterine fibroid treatments, MRgFUS is a localized thermal ablation method that is planned, monitored, and assessed with MRI structural, physiological, and thermal measurements (see section "Uterine Fibroids"). In the case of treating lesions on or adjacent to bone tissues, the higher acoustic absorption of bone (as compared to soft tissue) allows for higher temperatures to be generated with lower ultrasound power.[156,157] The use of a lowered overall acoustic power to deliver the equivalent therapy as in soft tissue means that safety parameters for nontargeted tissues can be more easily achieved. In addition, the low thermal conductivity of bone tissues means that the time-averaged thermal build-up tends to remain on the cortex, next to the periosteal layer. This leads to preferential ablation of this periosteal layer and should result in pain relief since this layer is highly innervated and is postulated to be the major source of bone metastases pain. Unfortunately, this low thermal conductivity has also been an obstacle to treating tumors that are deep within the bone. This difficulty has been shown to be resolvable by lowering the frequency of sonication and increasing the acoustic power and sonication duration.[158,159]

Since the first reported clinical investigation of MRgFUS for bone metastases in 2006,[18] a multicenter study with 31 patients has demonstrated its effectiveness in relieving pain over a mean follow-up time of 4 months.[152] Out of the 25 patients that were available for follow-up assessment, 72% (18/25) reported significant pain improvement. Pain relief was reported as early as 3 days after treatment and lasted for at least 3 months. In addition to the need to examine the durability of treatment and tumor site-related outcomes, ongoing efforts have been focused on performing randomized controlled studies on large patient populations.[160]

Other bone-based pathologies that have been investigated for MRgFUS include osteoid osteoma[161] and lumbar facet arthropathy.[162] Technologically, there is interest in the development of versatile device designs to accommodate varied treatment geometries according to the anatomical locations of bone metastases.[152] Also, efforts are continuing on the development of specialized MRI techniques for thermometry within the bone.[163]

Thalamotomy for Functional Neurosurgical Applications

One of the earliest attempts to produce lesions with FUS was performed within the deep-set tissues of the brain.[3,6] Although the concept was demonstrated, clinical application languished until solutions were proposed and examined to address the acoustic window craniotomy requirement[50,51,118,164] and the need for effective intra-procedural guidance.[129,165] To mitigate the effects of skull-related heating and focal aberration, large-scale hemispherical transducer arrays with precise phase and amplitude control were developed.[50,119,166] Advanced techniques for MRI thermometric mapping with high spatial and temporal resolution were also developed for integrated treatment planning, guidance, and assessment.[135,167] With the advent and development of these technologies, the first clinical applications of transcranial MRgHIFU in the brain (treatment of deep-set glioma) were demonstrated in 2005 at the Brigham and Women's Hospital (Boston, MA, USA).[8] Subsequent clinical applications have included the focal thermal ablation of thalamic nuclei to treat neuropathic pain.[168]

The delivery of acoustic energy into the intracranial space with sufficient coherence and intensity to create a thermal lesion requires powers on the order of 600–1200 W delivered over a sonication period of approximately 10–20 s.[8,168] Three strategies are used to mitigate the heating of the skull bone due to the absorption of this acoustic energy: (i) distribution of energy across the maximal area of the skull surface;[45,48,50] (ii) minimizing shear mode transmission through the bone;[54,169] and (iii) the circulation of cold water over the scalp surface during the procedure.[8,170] Even with sufficient transmission of time-averaged power into the brain, the intra- and inter-patient variation in skull bone geometries and local morphologies decohere the signals at the focus, leading to a highly distorted thermal energy deposition map.[118,171] To reestablish phase coherence at the focus, spatially registered CT images of the patients are used to predict the local skull-induced phase aberration for each transducer element's trajectory toward the focus, and a calculated phase correction factor is applied to each element.[119,172,173] Low power sub-ablative sonications are applied to establish geometric accuracy using MRI thermal mapping, after which therapeutic sonications that induce temperatures between 56°C and 62°C are applied.[8,168] If multiple sonications are required, they are performed sequentially with a separation of several minutes between sonications to allow tissues to cool. During these periods, the patients, who are lightly sedated, are examined for adverse effects and assessed for therapeutic effectiveness.

A number of studies are ongoing or have been performed to evaluate the clinical application of transcranial MRgHIFU for noninvasive functional neurosurgery, including treatments for neuropathic pain,[174] essential tremor,[175,19,176] and obsessive compulsive disorder.[177] For tremor-dominant Parkinson's disease, similar studies targeting different structures within the diencephalon have likewise been performed or are ongoing. The first nine patients to undergo transcranial MRgFUS treatment for Parkinson's disease received unilateral pallido-thalamic tractotomies via HIFU-induced thermocoagulation.[20,21] No adverse events were reported for all cases. Eight patients were evaluated 3 months after treatment[20] and one patient was evaluated 6 months after treatment.[21] The results from functional neurosurgical applications and early clinical provided initial confirmation that MRgFUS can be a safe, accurate, and overall effective method for treating movement disorders and neuropathic pain.

CONCLUSIONS

Given the multiple instances of demonstrated clinical utility of MRgFUS and the volume of research that is currently taking place in the field, this technology will likely substantially alter the fields of surgery and radiation oncology. Studies that are examining action mechanics beyond thermal coagulation (e.g., drug delivery,[87,94] blood-brain barrier disruption,[178] and cavitation-mediated histotripsy[179]) will dramatically contribute to the potential therapeutic applications of FUS. When integrated with MRI, the potential for HIFU as a noninvasive alternative to traditional surgery and radiation therapies becomes substantially enhanced, as demonstrated by the current successful clinical applications.

For more information, see: http://www.youtube.com/embed/IfJemqkby_0?rel=0.

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34 Electromagnetic Therapy
A Primer

*Abraham R. Liboff**

CONTENTS

INTRODUCTION

Electromagnetic (EM) signals are increasingly used in both systemic and local medical applications. We attempt here to provide an outline of the types of signals currently in use. This also necessitates a general introductory classification of EM signal types, based on how each signal varies in time.

Although EM medicine includes both diagnostic and therapeutic applications (Figure 34.1), the medical community is far more familiar with the former, especially with magnetic resonance imaging (MRI), electromyography (EMG), electroencephalography (EEG), electrocardiography (EKG), and magnetocardiography (MKG).

There are historical reasons for the medical unfamiliarity (even antipathy) with electromagnetically based therapies. One has only to look at the beginnings of modern medicine in the United States, specifically the 1910 Flexner report[1,2] that provided the basis for medical education today. Prior to this report there was widespread use of electromagnetic techniques in medicine, often little more than late nineteenth century versions of snake oil cures. In great measure, the present aversion to electromagnetic therapies built into modern medicine is a direct result of Victorian age quackery. This century-old prejudice has carried though to today even as it becomes clearer that weak (low intensity) magnetic fields exhibit physiological effects that must be considered separately from those caused by high intensity fields. Although the effects related to exposures at large fields are, as a rule, readily explained by known physical interactions, usually Faraday induction or joule heating, the weak-field effects, often rather robust, remain mostly unexplained. This has unfortunately opened the door for many electromagnetic nostrums of dubious value.

A few of the examples we mention below illustrate the useful therapeutic delivery of heat by electromagnetic means. The most interesting applications are, however, nonthermal. Further, we exclude from our discussion treatments that involve signals directly applied to specific regions of the body by subcutaneous means, such as pacemakers, defibrillators, deep brain stimulators (DBS), etc. Unlike electromagnetic applications, which are mostly unexplained, these represent techniques for replacing or enhancing faulty existing physiological electrical stimulations.

FIELD PARAMETERS

Whether one employs magnetic or electric fields, it is still necessary, when defining a given therapeutic procedure, to specify the waveshape, that is, how the signal develops in time. The question of waveshape can add greatly to the potential complexity that accompanies different electromagnetic applications. It is critical to realize that electromagnetic therapies are intrinsically far more complicated than pharmaceutical treatments. Many clinicians fail to appreciate this complexity, applying electric or magnetic fields as they would a pharmaceutical regimen whose outcome is solely dependent on titer. It is important to remember that there is no such thing as a little or a lot of magnetic field. For example, one can find high frequency signals that have miniscule intensity, low frequency signals with large gradients, or high intensity magnetic fields with low duty cycles. Each of these might produce different physiological responses and different therapeutic usefulness. The clinician must be aware of the various factors, or metrics, the sum of which is used to describe a given field.

One such factor relates to the vector nature of magnetic and electric fields. The characteristic of field uniformity has no analogue in pharmacy. Yet the interactive capabilities of

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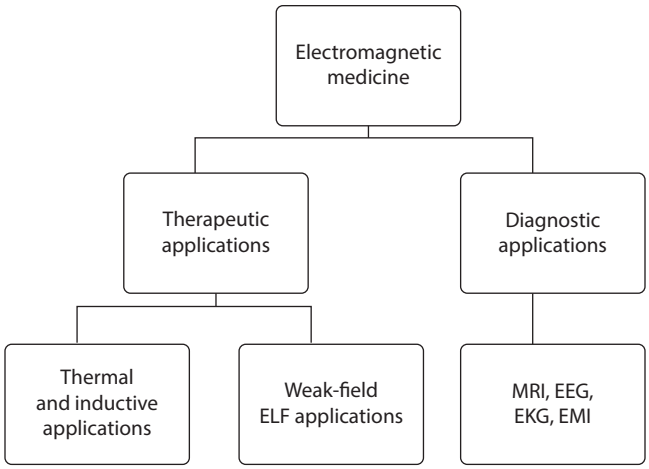

FIGURE 34.1 Clinical applications in electromagnetic medicine. Diagnostic applications are more acceptable than therapeutic and weak-field applications are less acceptable than thermal and inductive.

a magnetic field are definitely a function of its uniformity. A uniform field is one that has the same intensity and direction everywhere over the region in question. As a rule, this is a very difficult condition to maintain in any given application. Figure 34.2 compares the lines of force in a uniform field to those in one that is very nonuniform.

In laboratory practice, specially designed coils (e.g., Helmholtz or Merritt coils) are often used to maintain a certain degree of magnetic field uniformity within the active volume of application. However, it is usually the case that the volume within which uniform field conditions are actually achieved is but a small fraction of the total volume enclosed by the coils. One notable exception to this is found when using a properly designed solenoid (Figure 34.3).

It can be taken as a rule of thumb that none of the devices actually used for electromagnetic therapy achieve any degree of field uniformity over the treatment volume. This is especially true for field applications that utilize permanent magnets. Further, considering the wide range of dimensions and designs, it is very likely that no two therapeutic devices are strictly the same when considering the fields that are used.

One important classification of therapeutic EM signals is based on how the applied signal varies with time. These can be grouped into DC signals, trains of sine wave signals, and a wide variety of repetitively applied pulses. Signal trains can take on various forms, as shown in Figure 34.4. Signal intensity can be measured in different ways depending on the parameter that is considered essential to the therapeutic application, for example, voltage, current, and magnetic field intensity. These are, in turn, expressed in terms of specific units such as volts, millivolts, milliamperes, microamperes, microtesla, milligauss, etc.

SINE WAVES

Of the various time-varying signals utilized in EM therapeutic applications, the sine wave shape is the simplest to deal with and the easiest to generate (Figure 34.5). The frequencies

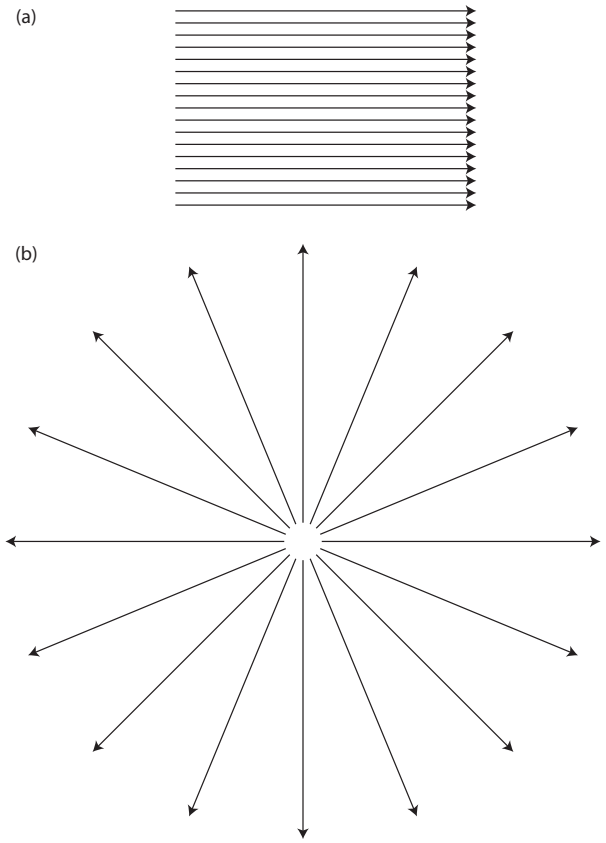

FIGURE 34.2 (a) A uniform field (electric or magnetic) is one in which everywhere within the region of interest there is the same intensity and direction. (b) Example of a very nonuniform electric field, namely that produced by a single positive charge. The lines of force drawn here are shown in two dimensions but in reality should always be thought of as three-dimensional. Thus, the lines of force in (b) are not only in the plane of the page but also point upwards and downwards.

of sine wave signals used in EM therapy can be ultralow, to about 1 Hz, and extend upwards to 50 GHz or more (1 GHz equals 1×10^9 Hz). At the lower extreme, a number of clinical applications utilize the extremely low frequency (ELF) region, which includes frequencies up to 300 Hz. These

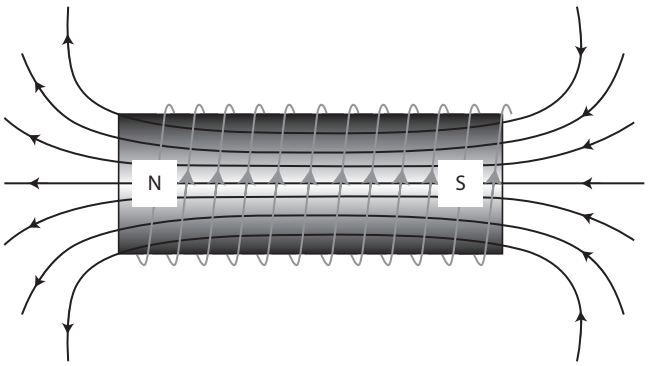

FIGURE 34.3 Excellent field uniformity is achieved inside a solenoid that is much longer than its diameter, say by a factor of 7 or greater.

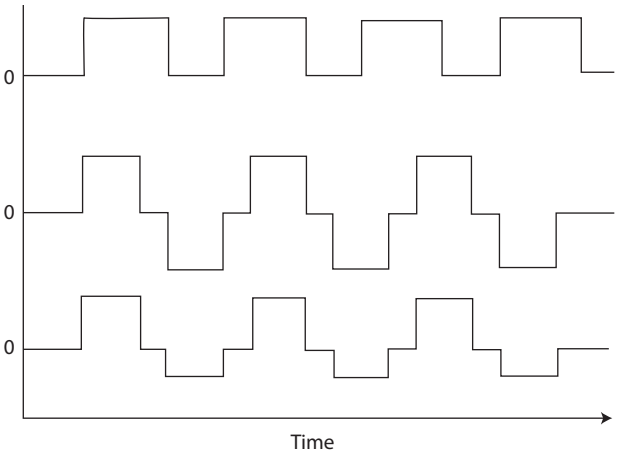

FIGURE 34.4 Three different pulse trains. The pulses at the top are monopolar, all positive. The lower two sets are bipolar, such that in each cycle both polarities are obtained. The bottom set of bipolar pulses show that positive and negative amplitudes need not be the same.

frequencies appear to be physiologically interactive, presumably because they couple to processes in the body that naturally occur at similar frequencies. Additionally, living tissue is transparent, not only to static (DC) magnetic fields, but also to ELF magnetic fields. Further, in some cases the ELF therapeutic application has been designed to take advantage of the easily available (and reliably constant) power line frequency, which, depending on the region, is either 50 or 60 Hz.

At higher frequencies, choices are limited to those permitted by the Federal Communications Commission (FCC) to avoid interfering with existing broadcast frequencies. Three such allowed frequencies are 13.56, 27.12, and 40.68 MHz (1 MHz equals 1×10^6 Hz). A number of EM therapeutic devices utilize the 27.12 MHz frequency. Needless to say, there is nothing biologically interesting about these specific frequencies. They are used solely because they are available!

Because sine waves are easiest to generate, these shapes have found extensive use in the design and implementation of electromagnetic therapy devices. This is especially true for those devices that are strictly electric in character, where signals are delivered through electrodes. Electrically based therapies can be more straightforward compared to magnetic applications operating at the same frequencies, because magnetic interactions can readily result in different effects in tissue, especially for higher frequencies and intensities.

Additionally, the medical community is more at ease with electrical applications in clinical procedures, even to the point where magnetic therapies are often viewed suspiciously.

Apart from the limited education of the average American doctor in the physical sciences, this suspicion of electromagnetic medicine closely follows the fact that no reasonable explanation has yet been found to explain those observations showing that therapeutic benefit does indeed result from specific applications of certain electric and/or magnetic signals.

A good example of a clinical application that utilizes sine wave signals that are purely electrical in nature is found

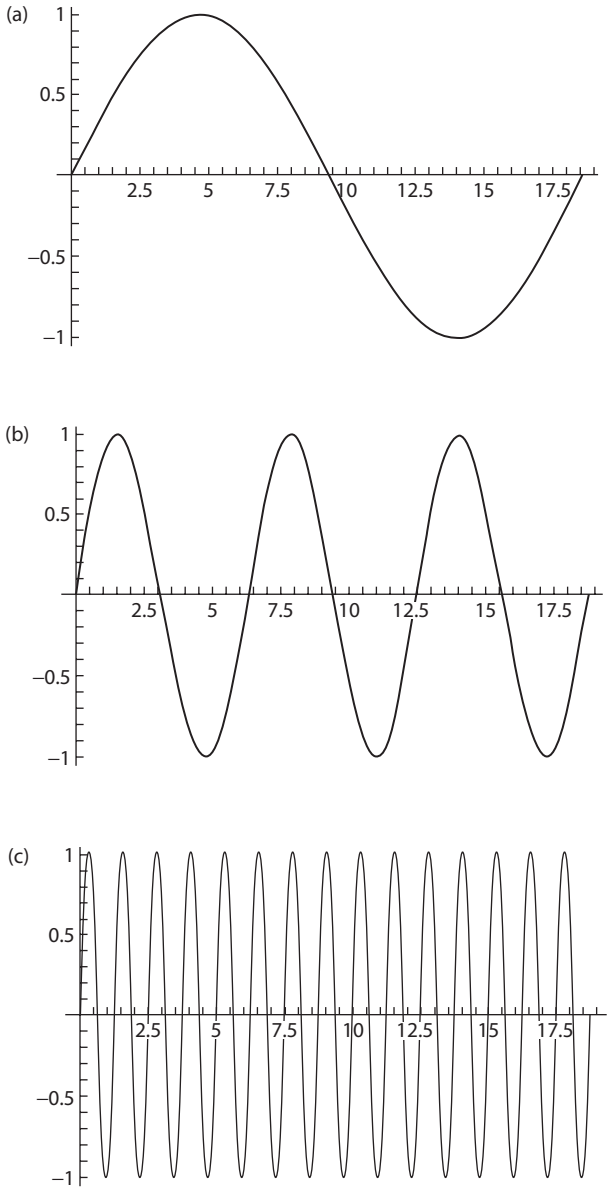

FIGURE 34.5 Three sine wave signals differing in frequency, but each having the same amplitude of 1.0 and plotted over the same 18 s time span. Frequencies are (a) 0.053 Hz, (b) 0.159 Hz, and (c) 0.79 Hz.

in the tumor-treating fields (TTF)[3,4] used to fight cancer in devices designed by the Novocure Corporation (Portsmouth, NH, USA). Distinctly nonthermal signals, ranging between 100 and 200 kHz, are applied to the body using skin electrodes supplied by portable battery-powered generators, allowing patients freedom of movement even away from the hospital environment (Figure 34.6). This treatment covers a range of illnesses, including brain and lung cancer, and, in a number of instances, is Food and Drug Administration (FDA) approved.

Many therapeutic applications utilize signal shapes that, although based on sine waves, are somewhat more complex. Three such shapes are those that are modulated, rectified, and biased signals (Figures 34.7 through 34.10).

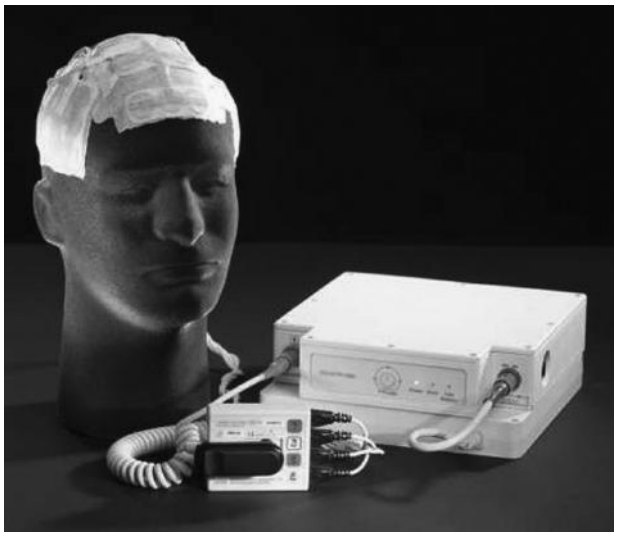

FIGURE 34.6 As a treatment for glioblastoma, the portable Novocure device supplies sine wave signals at frequencies ranging from 100 to 200 kHz to electrodes on the scalp.

An example of a procedure that uses modulated electrical sine waves (Figure 34.7) to treat liver cancer is found in the TheraBionic device (Mountain Brook, AL, USA).[5] The clinically effective frequencies, varying sequentially between 100 Hz and 21 kHz, are applied by means of a 27.12 MHz carrier signal. One rather unique aspect of this treatment is the electrode arrangement, one of which, spoonlike, is located sublingually (Figure 34.8).

In AC interferential therapy (Figure 34.9) electrodes are used to apply two separate AC signals with slightly different frequencies to the tissue in question, thereby creating a means for treating tissue with a low frequency electric current that may be difficult to achieve if applied directly. Rectified wave shapes of the form shown in Figure 34.10 for example are used in a device sold by the EMF Therapeutics Corporation (Chattanooga, TN, USA).[6] This operates at a frequency of 120 Hz, indicative of the fact that the base frequency before rectification is the power line delivery frequency of 60 Hz.

One can add a DC component (also called a bias) to any sine wave, thus shifting its zero point (Figure 34.11). This is the basis of magnetic therapies employing ion cyclotron resonance (ICR), also referred to as CMF (combined magnetic field).

In practice, the two components comprising this type of signal are often not applied directly as shown, but are instead obtained using two separate coils to generate superposed magnetic fields that are then added to give the same result. Another variation of ICR, termed ion parametric resonance, maintains the fundamental ICR relationship but in addition also fixes the ratio between the DC and AC values in the total signal. A number of therapies have been designed using ICR, with the oldest (from the 1980s) the FDA approved treatment for pseudarthroses[7] (Figure 34.12).

FARADAY INDUCTION

Since the middle of the nineteenth century, it has been known that a changing magnetic field can induce an electrical potential in nearby conductors. A generalized way of looking at this is given in Figure 34.13. The actual principle says nothing about current, but, rather, it is stated in terms of the electrical potential. We can readily extend this in living tissue to current, because tissues are relatively good conductors. The basis for a great number of magnetic therapy devices entails

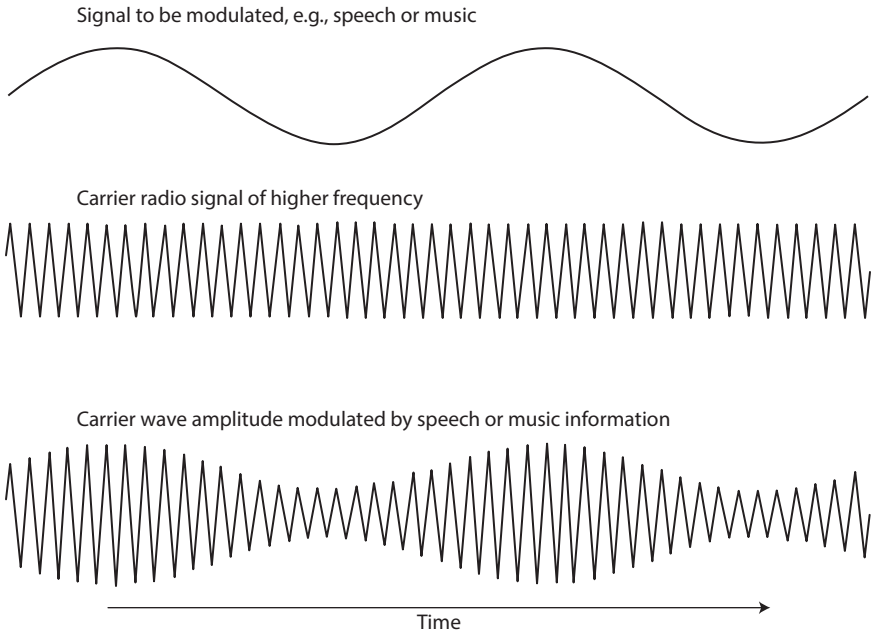

FIGURE 34.7 Adding a low frequency wave to a high frequency carrier wave results in the modulated signal below.

generating currents in tissue that is exposed to externally changing magnetic fields.

One of the pioneers in utilizing this concept in a clinical procedure was the orthopedist C. A. L. Bassett,[8] who, with Pilla in the 1970s, designed a system that supplied pulses to nonunions, discontinuities in bone that are either congenital or fail to knit following fracture. This followed the discovery[9] that subcutaneous application of small DC currents, on the order of microamperes, was capable of nonunion repair. Bassett was able to provide such currents to the defect noninvasively by making use of Faraday induction. This FDA approved procedure is still used, with the signal type universally referred to as PEMF, or pulsed electromagnetic field.

FIGURE 34.8 The fully portable TheraBionic device (Mountain Brook, AL, USA) uses a range of modulated radiofrequencies to treat liver cancer.

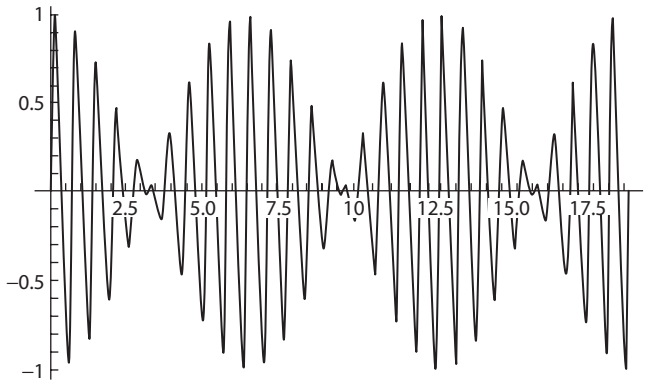

FIGURE 34.9 The phenomenon of "beats" is a special type of modulation, obtained when two sine waves equal in amplitude are added with frequencies close to each other. In this example, the original frequencies are 0.008 Hz apart.

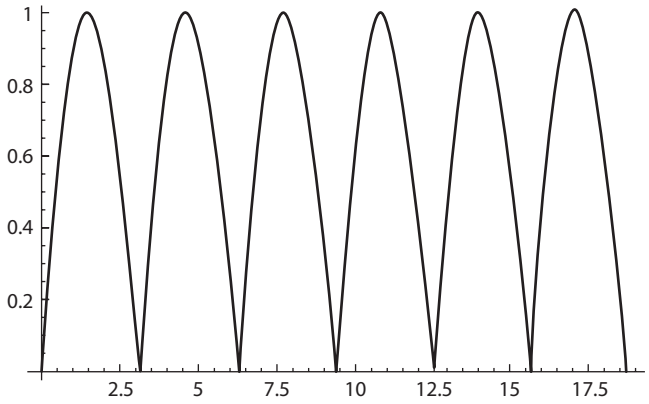

FIGURE 34.10 Rectified signal, as constructed from the sine wave shape given in Figure 34.5b. The negative parts of the original wave have been flipped, resulting in a signal that is everywhere positive. Note that the rectified signal repeats itself twice as fast as the original signal, such that the new frequency is now doubled to 0.32 Hz.

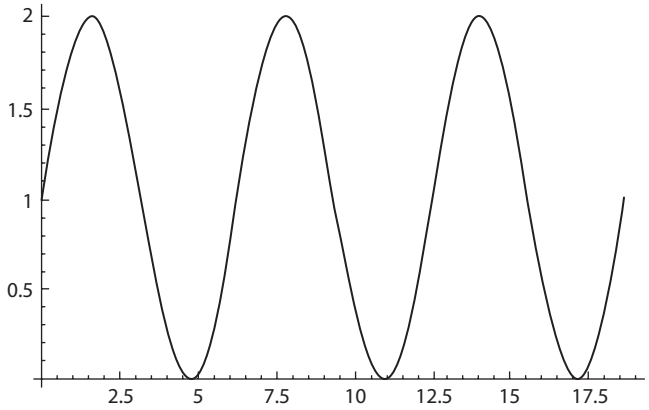

FIGURE 34.11 Example of a biased sine wave, obtained by adding a constant (DC) signal of one unit amplitude to the sine wave shown in Figure 34.5b. Pictured is only one very specific choice (1.0 units) for the added DC signal.

FIGURE 34.12 This Food and Drug Administration approved ion cyclotron resonance device manufactured by DonJoy to treat nonunions in bone is worn directly on the affected limb. Another version of this design is used as an adjunct to enhance spinal fusion.

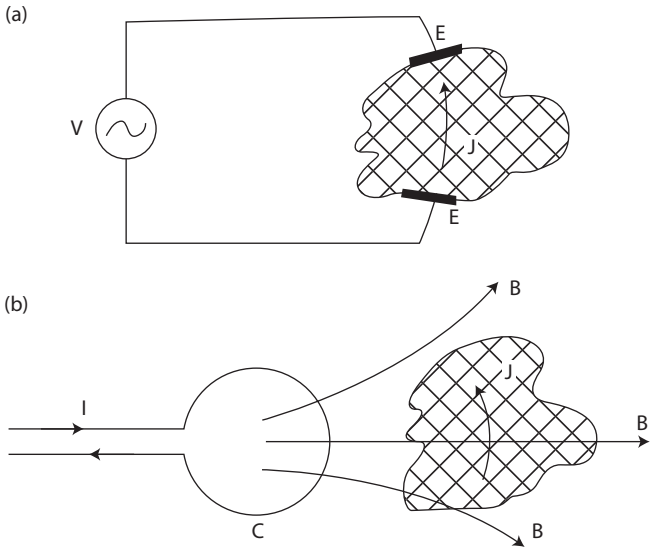

FIGURE 34.13 Electrical current J can be introduced into tissue in two ways, (a) by applying a voltage V through electrodes E (Ohm's Law), or (b) applying a changing magnetic field B from a coil C energized by a current I (Faraday induction). The change in field can occur if the current I is changing, or if there is relative motion between tissue and coil.

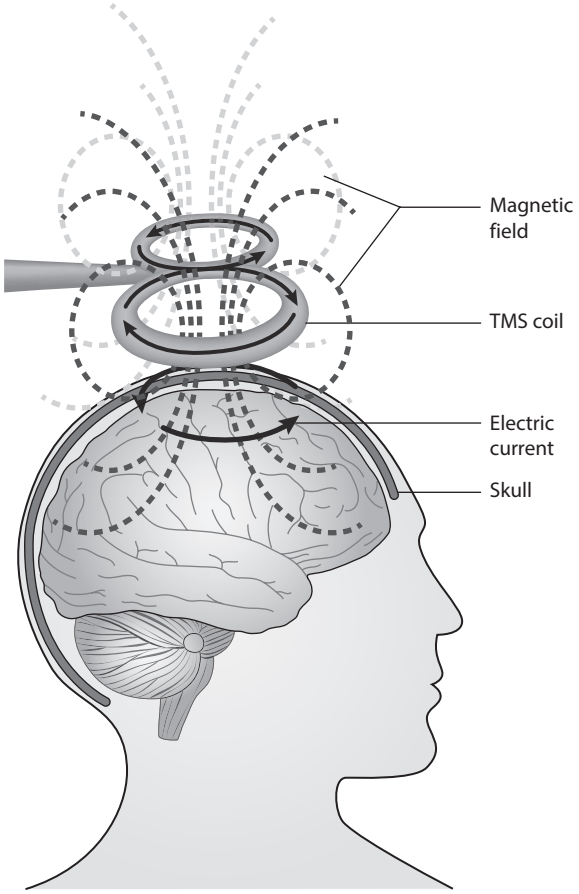

FIGURE 34.14 The repetitive transcranial stimulation coil (in a figure-of-eight configuration) is pulsed with very large currents to produce a rapidly changing magnetic field, thereby inducing currents in the brain.

More recently, Faraday induction has been used in a different context, namely to induce currents in the brain (Figure 34.14), as a means of treating depression. The repetitive transcranial stimulation (rTMS) procedure[10,11] is often compared with the older treatment for bipolar disorder, or electroconvulsive therapy (ECT), which is purely electrical in nature.

Although the means of delivery for rTMS is very different from Bassett's PEMF signals, and the focus is on the brain instead of the skeletal system, it is important to realize that Faraday induction is being employed in both cases. Both PEMF and rTMS are magnetic therapies whose utilization derives from inductively generated currents that were found earlier to be clinically efficacious when these were previously used in older, electrically based therapies.

PULSES

Pulses are signals that last for short lengths of time, often taking a square-like shape as in Figure 34.15. Although there are well recognized methods for analyzing any type of magnetic pulse, one can readily tell a good deal about the pulse by direct examination. The shorter the pulse, the higher the frequency content. One can say, for example, in very rough fashion, that microseconds-long pulses are equivalent to frequencies on the order of MHz, while nanosecond pulses correspond to GHz frequencies. This follows from the mathematical breakdown of any pulse into its equivalent: the sum of sine waves of different frequencies, a process known as Fourier analysis. In this sense, pulses can always be described in terms of sine waves.

Pulses are very effective in generating high frequency currents in tissue. This follows the fact that very short magnetic signals represent a rapidly changing magnetic field, which in turn creates through Faraday induction a large degree of voltage change, or, in tissue, a correspondingly large current that changes at the same rate. Yet another type of fast-changing magnetic signal that can be applied to tissue to induce an electrical change is found in the sawtooth shape, shown in Figure 34.16.

The sawtooth signal as externally applied in repetitive fashion is able to treat nonunions in bone because of the electrical waveshape that is induced within tissue as shown in Figure 34.17. The adjustable amplitude of this induced train of pulses is given in terms of the electric field and ranges from 1 to 100 mV/cm. In use, this pulse application is repeated periodically at repetition rates of 15 Hz or higher. This fact has led some to suggest that the rate of repetition itself may be of some consequence in assessing the reasons for the efficacy of treatment using PEMF devices, inasmuch as the repetition rates that are used fall within the ELF range.

A novel change in the way the PEMF signal is applied is shown in Figure 34.18, which illustrates the pulsed signal therapy (PST) approach[12] to magnetic therapy. Instead of a steady train of identical pulses, there is a random generation of successive pulses with different intensities and widths. This means that the tissues under treatment are exposed to a

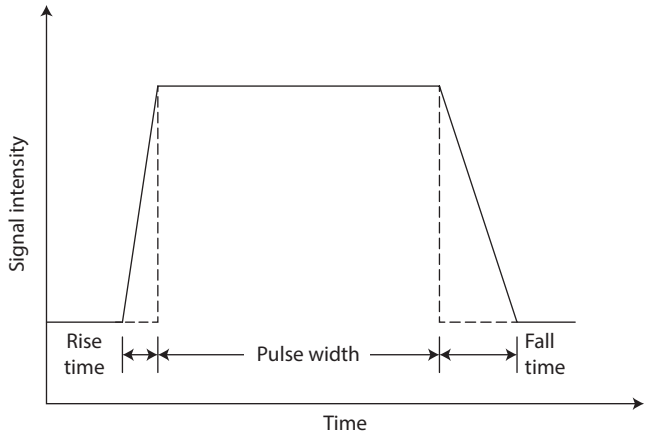

FIGURE 34.15 Typical square pulse, showing limitations on the electronics generation process that make it difficult to achieve very short rise and fall times.

spectrum of various magnetic intensities as well as more than one distribution of frequencies. This feature helps cover the problem that different patients with various medical histories may require differing types of electromagnetic treatment. In effect, it represents an attempt to cover all bases, an approach similar to what we have already seen in the TheraBionics therapy.

A bipolar equivalent to PST, one employing electrical pulses instead of magnetic, is found in the α-stim technology (Figure 34.19), and is used to treat anxiety, depression, and insomnia.[13] Electrodes directly attached to the scalp supply currents on the order of hundreds of microamperes directly to the brain. Yet another approach to treating the brain electrically for depression is found in transcranial direct current stimulation (tDCS),[14] which applies milliampere-level currents to the scalp.

The Seqex device (Pergine Valsugana, Italy; Figure 34.20) makes use of the ion cyclotron resonance physiological interaction,[15,16] but in a totally different way from that shown in Figure 34.12 for treating bone disorders. Instead, the ICR signal characteristic is obtained by combining 30 magnetic

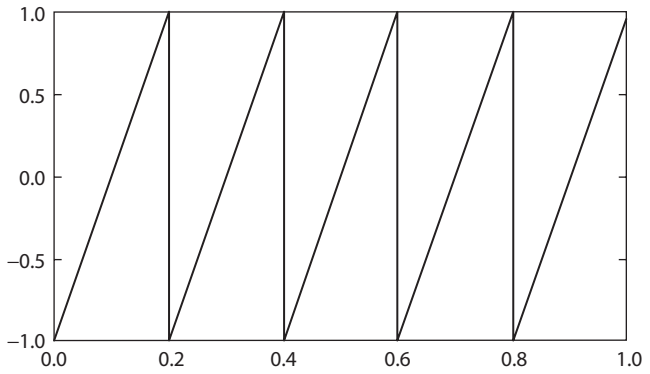

FIGURE 34.16 Example of sawtooth wave. Vertical axis in arbitrary units, for example, milligauss. Horizontal axis is time. For example, milliseconds.

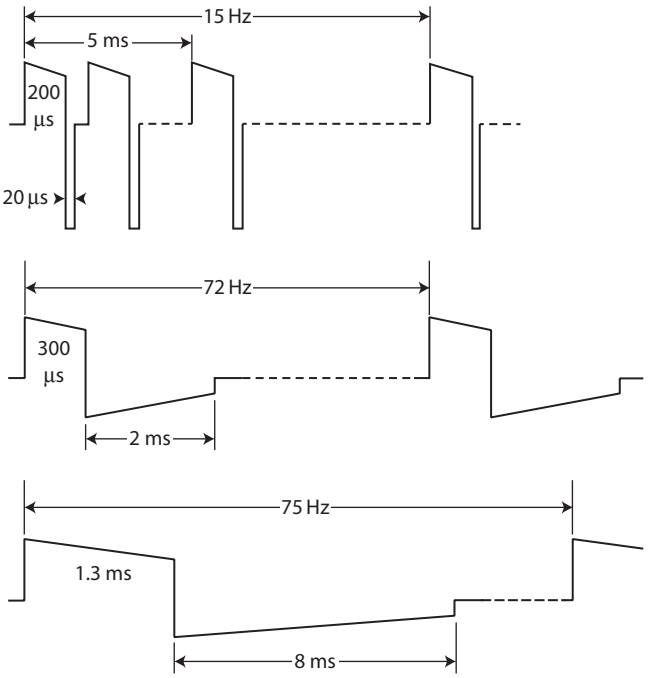

FIGURE 34.17 Train of electrical pulses induced in tissue by a sawtooth signal. Note that the pulsed electromagnetic field signal as shown here is applied repetitively, often at a 15 Hz rate.

field frequency distributions with the ambient vertical geomagnetic component, and then selecting that combination for which the tissue bioimpedance becomes anomalously low. In addition to this unique type of application, the Seqex technique represents a new, holistic approach to magnetic therapy, as the magnetic field application covers the patient's entire body. This device is currently being used clinically as an adjunct to chemotherapy and for treatment of neurological and musculoskeletal disorders.

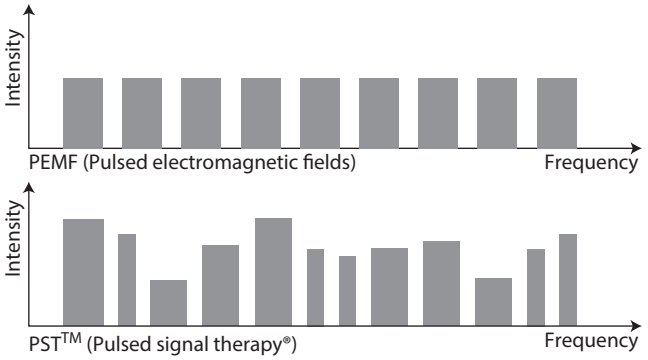

FIGURE 34.18 Comparison of the sequence of pulses in pulsed signal therapy (PST) therapy to the usual delivery of pulsed electromagnetic field signals. The upper pulse train is equivalent to what was shown in Figure 34.17. The lower, PST train consists of various heights (magnetic intensities) and widths (time spans). The different widths correspond to different frequency distributions, narrow widths implying higher frequencies and wider widths lower frequency groupings.

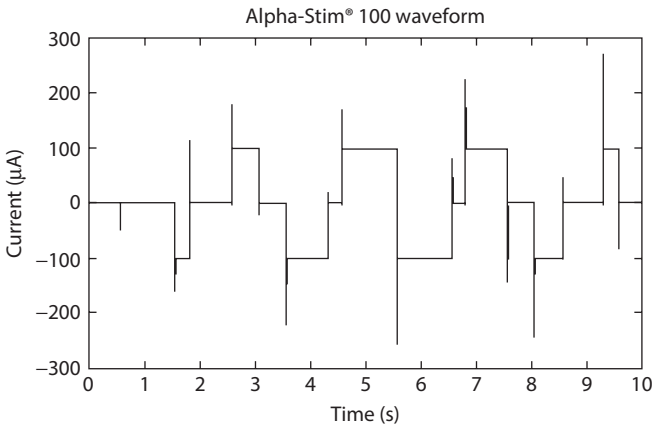

FIGURE 34.19 Electric pulse sequence applied during Alpha-Stim treatment. Pulses are bipolar with repetition rates of 0.5, 1.5, and 100 Hz, and currents developed range from 10 to 600 μA. Note the high frequency spikes at the leading and falling edges of each pulse, typically seen when pulses are switched on and off rapidly.

THERMAL APPLICATIONS

For the most part, electromagnetic therapy is nonthermal in character, that is, not dependent on heat generated by the applied fields. However, there are exceptions to this rule. Figure 34.21 shows a typical pulse train generated for the purpose of diathermy treatment as manufactured by the Diapulse Corp (Great Neck, NY, USA). The 27.12 MHz signal is used to treat soft-tissue injuries.[17] This approach clearly substitutes electromagnetic energy for the much older thermal treatments that directly applied heat packs to afflicted tissues.

Another, very different type of electromagnetic therapy is found in the Oncotherm device (Oncotherm GmbH, Troisdorf, Germany), which uses a modified version of hyperthermia to help destroy malignant tumors (Figure 34.22). A frequency of 13.56 MHz is used to treat a variety of cancers, including liver, brain, lung, pancreatic, breast, and prostate, among others.[18] It has been estimated that upwards of 100,000 such treatments are conducted annually. By taking advantage of differences in cancerous and normal tissues, this therapy selectively overheats the tumor without affecting the surrounding normal tissue.

TRENDS

Many ELF magnetic interactions have been observed in the laboratory, but have yet to be clinically exploited. One excellent example is the ICR stimulus of cardiac stem cells that advances differentiation to the degree where successful regrowth of damaged heart muscle is now likely.[19] In another case it has been found that low energy protein hydrolysis is possible using weak magnetic fields,[20] and, in follow-up studies,[21] it has also been shown that resonance magnetic applications in mice brain can dissolve the β-amyloid plaque that is characteristic of Alzheimer's disease, and, further, that these same ICR magnetic fields can significantly reduce cancer growth in mice.[22]

Equally important, it is probable that future advances in electromagnetic medicine will follow the remarkable discovery[23] by Mikhail Zhadin that vanishingly small magnetic intensities are biologically interactive. This work represents the successful extension of ion cyclotron resonance interactions, already regarded as occurring at "impossibly small" μT levels, to even smaller intensities in the nT range, down by a factor of 1000 times! This could have enormous consequences for clinical applications. Many of the therapeutic devices mentioned here may turn out to be even more efficacious when smaller intensities are used.

However, applications at these vanishingly small intensities are rather difficult. Proper use requires special shielding

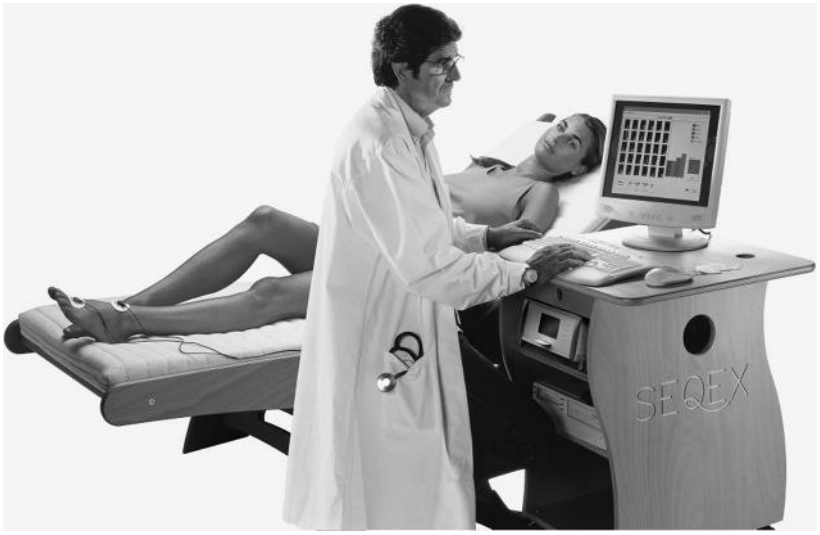

FIGURE 34.20 The Seqex magnetic therapy device (Pergine Valsugana, Italy). One signal shape is selected from an array of 30 wave shapes, the choice depending on the whole-body impedance of the patient. This low frequency signal is repetitively applied by means of coils within specially designed pads that treat the entire body.

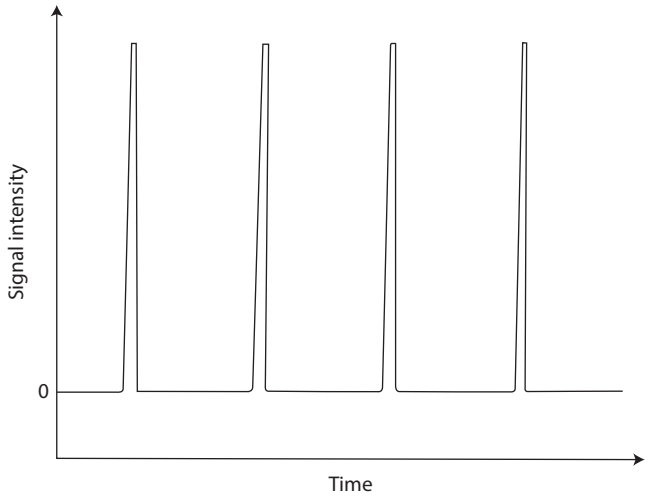

FIGURE 34.21 Illustrating the train of monopolar pulses used by Diapulse (Great Neck, NY, USA), applying the short microwave bursts that are used as a diathermy treatment. In this example the pulses are extremely short (about 65 μs) and the time between pulses rather long (1600 μs).

from local AC magnetic sources such as the omnipresent 60 Hz current-carrying wires in building walls, often presenting the researcher with laboratory fields greatly in excess of nanotesla intensities.

These advances and opportunities also have a dark side, providing new areas for quacks and charlatans that specialize in electromagnetic "cures" to prey on the sick. For example, we have already seen devices based on "picotesla stimulation" marketed without regard to the need to shield or correct for more intense, local magnetic fields. Electromagnets directly purchased from physics supply houses have been touted as "molecular energizers" to help combat brain cancer. Furthermore, in the longest-lived scam perpetrated on the sick and dying, the role of frequency in promoting wellness has been repeatedly misstated by some for more than 50 years.

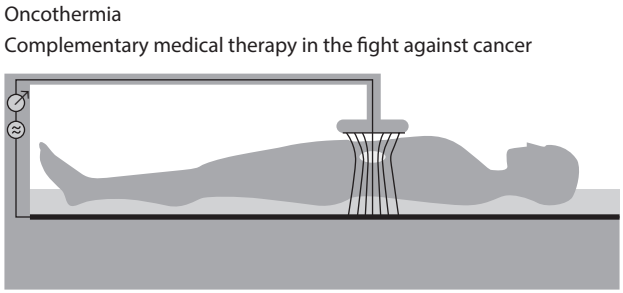

FIGURE 34.22 Schematic showing the basic way in which Oncotherm (Oncotherm GmbH, Troisdorf, Germany) treatments are conducted. High-voltage 13.56 MHz electromagnetic radiation is directed to the tumor, making use of the self-focusing that occurs because of the intrinsically higher conductivity of cancer cells. The patient lies on an electrode bed while the moveable upper electrode is deployed to computer-directed positions determined by the size and location of the tumor.

The recognition of the importance of frequency in electromagnetic medicine that we have outlined here is a far cry from nonsensical claims that diseased cells can be "blown up" at certain frequencies, or that the entire array of human disease is traceable to specific parasites, each of which has its own unique susceptibility to a given frequency.

Unfortunately, we note that the recent successes obtained by "traditional" clinicians in using electromagnetic techniques, for example, Novocure, TheraBionic, to treat cancer have not carried over to their admitting that there is a profound puzzle connected to the full understanding of these therapies. They give inadequate explanations for the robust efficacies that are observed, using traditional bioengineering language that fails to explain how cells are actually affected. This lack of real explanation mirrors the experience of many laboratory researchers who repeatedly reported on electromagnetic effects in living systems, but discovered that their efforts were not considered credible without a reasonable explanation based in molecular biology. It is hoped that the clinical results will serve to provide greater credibility for those studying weak-field effects in less clinical settings.

It is a fact that resonance studies clearly indicate that living systems are sensitive to selected frequencies with observed efficacies, probably related to existing physiologic events involved in the various activation pathways one uses to describe pharmaceutical medicine.[24] Successful treatment resulting from application of a given frequency at a given intensity appears to mimic the positive actions of otherwise prescribed biochemicals.

In short, it is our view that electromagnetic medicine functions as a substitute for the pharmacopeia.

GLOSSARY

Angular frequency: Usually symbolized as Greek letter ω. Related to linear frequency through the formula $\omega = 2\pi f$, measured in terms of rad/s (radians per second).

Athermal signal: Same as nonthermal signal.

Beat(s): The new frequency that results from adding two sine waves of equal amplitude but slightly different frequencies. Equal to the difference between the two original frequencies. Sometimes called the *interference frequency* or *AC interferential frequency*.

Bipolar signal: Signal composed of both positive and negative components. Sometimes called *biphasic signal*.

CES: Cranial electrical stimulation.

CMF: Combined magnetic field, formed by adding DC magnetic field to sinusoidal magnetic signal. Same as ICR when appropriate values of DC magnetic field and AC magnetic frequency are used.

Constant current amplifier: Electronic circuit that automatically adjusts the output voltage of a given power supply to maintain a constant current.

Current density: Electrical current per unit cross-sectional area, measured, for example, in terms of microamperes per centimeter squared ($\mu A/cm^2$).

Duty cycle: Measure of the energy supplied over a given length of time. Increases with the intensity of the pulsed signal and decreases with the increased time between pulses.

ECT: Electroconvulsive therapy.

Electric field: Measure of the electric field intensity. Often symbolized as E and specified in terms of V/cm, mV/cm, or V/m.
Electrostatic field: An electric field that does not change in time.
EMF: Two meanings: Electromagnetic field, also (less used presently) electromotive force, an older term for electric potential difference.
Fall time: Time interval over which a pulsed signal falls from its maximum value.
Faraday's Law of Induction: A changing magnetic field can create an electrical potential difference. If this occurs in an electrically conducting material, a current density results within the material.
Giga: Prefix meaning one billion times, or 10^9 times larger, as in gigahertz or GHz.
GMF: The geomagnetic field.
ICR: Ion cyclotron resonance.
Helmholtz coil: Parallel array of two circular coils connected in series-adding configuration where the separation between the coils is equal to the coil radius. Commonly used to obtain uniformity of field near the center of the array, along its axis.
Hertz (Hz): Measurement unit for frequency of sine wave or any periodic phenomenon. Appears often with appropriate prefix, for example, kHz, MHz, GHz.
Kilo: Prefix indicating a factor of 1000 (10^3) larger as in kV, kG, and kHz.
Magnetic gradient: A description of how much the magnetic field changes in any one direction, measured for example, in terms such as microtesla per meter (μT/m).
Magnetostatic field: Magnetic field that does not vary in time.
Mega: Prefix meaning one million times (10^6) larger, as in MHz.
Micro: Written as Greek letter μ. Commonly used prefix in electromagnetic measurements, same as one millionth, or 10^{-6}, for example, μT, μA, μV. In biology, 1 μm (1 micron) is often used as a measure of diustance.
Milli: Prefix in electromagnetic measurements. Equals one thousandth (10^{-3}). for example, mT, mV, mA.
Modulated signal: Result of adding two sinusoidal signals, usually with very different frequencies. The higher frequency signal is the carrier, and the lower signal, the modulation frequency.
Monopolar signal: Signal that is always positive, sometimes called monophasic.
Nano: Prefix meaning one billionth, or 10^{-9} times smaller, as in nV, nA, and nT.
Noise: Unplanned variation in voltage or current signal that can result from random perturbations in electronic or electric components, mostly due to thermal effects.
Nonthermal signal: Signal that does not result in increased temperature within tissue.
Observable: Parameter used as a measure of a physical state, for example, magnetic field, voltage, current, temperature.
Oscillatory: Same as periodic.
Parallel plate capacitor: Pair of parallel electrical conducting plates where the diameter of each plate is much greater than the separation between the plates. Used to obtain highly uniform electric field between the plates.
PMF: Pulsed magnetic field. Same as PEMF.
Peak value: Maximum amplitude of sinusoidal signal.
Peak-to-peak value: Total swing in signal intensity, measyred from negative minimum of sine wave to maximum positive, or simply twice the peak value.
Pico: Prefix meaning one million million times (10^{-12}) smaller, as in pV, pA, pT.
Pulsatile: Same as pulsed.
Pulse height: Maximum amplitude of pulse.
Pulse train: Sequence of pulses in one cycle. Same as pulse burst.
Pulse width: Interval of time over which a single pulse is applied.
PST: Pulsed signal therapy.
Rectified signal: Modified sine wave, always positive, either as halfwave rectification, skipping any original negative components, or full-wave rectification, where the originally negative parts of the wave shape are flipped up into the positive region.
Repetition rate: Frequency, in cycles per second, (or Hz) with which a periodic signal repeats itself. Typically used to describe nonsinusoidal signals that are repetitive.
Rise time: Time it takes for a pulsed signal to reach its maximum value.
rms value: Root-mean-square of maximum intensity of sine wave. Equal to 0.7071 times the maximum amplitude of the sine wave. Same as effective (eff) value.
rTMS: Rapid transcranial magnetic stimulation.
Sawtooth signal: Waveform similar to saw blade, either rising slowly to a maximum and falling rapidly or rising rapidly and falling slowly.
Signature: Same as waveform.
Solenoid: Closely wound coil on long cylinder that can provide excellent field uniformity within the cylinder volume.
tDCS: Transcranial direct current stimulation.
TENS: Transcutaneous electrical nerve stimulation.
Transient: A single pulse, usually nondescript and the result of a switching problem or unexplained perturbation such as a temporary loss of power or remote lightning stroke.
TTF: Tumor treating fields.
Uniform field: Electric or magnetic field that is everywhere within a given region constant in direction and intensity.

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Section VII

Environmental Influences

35 Influences of Space and Terrestrial Weather on Human Physiology and Pathology

Germaine Cornelissen, Yoshihiko Watanabe, Kuniaki Otsuka, and Franz Halberg*

CONTENTS

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Dedicated to Earl Bakken on the occasion of his 90th birthday.

INTRODUCTION

Interactions between electromagnetic fields and living matter are at the interface of biological and physical sciences. In 1985, Schwan[1] presented a summary of various biological effects that can be induced by alternating fields external to the cell. Alignment of particles in the direction of the field to form "pearl chains," orientation of nonspherical particles in relation to the field direction, and particle movement resulting from inhomogeneous fields are just a few illustrative biological manifestations of ponderomotoric forces observed with alternating fields. Natural AC electromagnetic oscillations of living cells are reportedly maximal at or near mitosis, accounting for their importance in relation to growth, as during embryonic growth, usual body cell replacement, wound healing, and neoplastic growth.[2]

The study of electromagnetic effects in mammals, however, remains controversial. To a large extent, this may be because underlying mechanisms are not fully understood. In the experimental laboratory, effects may vary greatly depending on whether static or changing fields are applied, the intensity and duration of exposure, and, in the case of alternating fields, the frequency of their oscillation. An important and interesting concept in studying the potential health effects of electromagnetic fields is that of a "biological window," introduced by Ross Adey,[3] who showed that calcium output of brain cells in rabbits could only be triggered by using very low magnetic field intensities and a specific low frequency. More generally, a biological window is an electromagnetic signal that only has a biological effect if it is of the right intensity in the pertinent frequency range.

Whereas some studies found only weak or no statistically significant links between biomedical and helio-geophysical data,[4] other biological experiments[5,6] and clinical investigations[7–10] yielded results suggestive of a close correlation with solar activity.[11] These contradictory results have given rise to a generally skeptical attitude toward geomagnetism and biota. Several arguments against an influence of space-terrestrial weather on biota have been voiced. First, helio-geophysical variations on earth are of exceedingly small magnitude as compared to other technogenous and social influences. Possible electromagnetic field effects at the cellular level are weaker than the electromagnetic noise of biological origin.[12] Second, different studies often report only weak and/or inconsistent statistical associations, stemming mostly from correlation analyses between biological measurements and electromagnetic parameters in the environment. Among several statistical limitations of these studies, the brevity of the records may account for the difficulties encountered in replicating results from a variety of laboratory experiments.[13]

A better understanding of the behavior of complex nonlinear open systems, to which biological systems belong, especially but not exclusively those near a threshold of

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instability, such as a morbid body, suggests that they may react globally to external perturbations. This may also be the case for disturbances whose energy is many orders of magnitude below the free energy available in the system, provided the parameters of the input fall into some critical ranges or "windows." In other words, they must bear some spatial and temporal coherence over a large ensemble of the system's components.[14,15] Far from thermodynamic equilibrium, the influence of weak environmental elements can become decisive.[16]

As reviewed by Breus et al.,[11] magnetite biomineralization and magnetoreception found in different organisms, including humans,[17] suggest that biosystems may have adapted to variations in the geomagnetic field induced by variations in the solar wind and the interplanetary magnetic field (IMF). Magnetocytes, loaded with crystals of biogenic magnetite, have been found in the human brain and may characterize the adrenal glands.[17,18] These biological functions, while unknown, may detect the geomagnetic field, as do magnetostatic bacteria, protozoans, and migratory fish and birds.[19] Magnetic crystals could be biochemically important, for example, in spin states of reaction intermediates, controlling the decay path of a triplet state, as suggested by McLauchlan.[20,21] According to his theoretical estimation, fields of a few milliteslas (mTs) generated by solar activity can affect the rate of chemical reactions when some bonds break and reform.

Another important factor often overlooked underlying the lack of reproducibility of results relates to the presence of multi-frequency cycles characterizing both biological and environmental variables. As extensively shown by Franz Halberg,[22–27] the stage of broad biological time structures (chronomes) can account for dramatically different outcomes in response to a variety of stimuli, including differences between life and death. Taking into consideration the rhythmic nature of most biological and environmental variables is critical in avoiding controversy and gaining a deeper understanding of ways in which biota are influenced by space-terrestrial weather.

METHODOLOGIC CONSIDERATIONS

Living matter is variable in time and space, as is weather.[28] Cycles in a very broad frequency range are ubiquitous. Nevertheless, they are often overlooked in investigations examining the effect of space weather on physiology and/or pathology. Often, analyses are limited to calculating the simple Pearson product-moment correlation coefficient when testing for associations between effects of geomagnetic activity or space weather more generally on human physiology[29] or on mortality from various causes.[30–32] Correlations without considering cycles in examining associations in phenomena characterized by rhythms can be spurious, with statistically significant positive or negative correlation or no correlation found, depending solely on the phase relation between the two variables sharing the same periodicity.[33] In the presence of cycles, and they are ubiquitous, methods other than the Pearson product-moment correlation are advocated.

Cross-spectra and coherence spectra are one option.[34] Superposed epoch analysis is another option.[35,36] Yet another method is the remove-and-replace approach,[37] so named after the precedent in endocrinology where a gland or organ (such as the pancreas) is first removed to determine what the resulting health problems are, and its hormone (such as insulin) or other secretion is then administered to find out whether health can thus be restored. In studies examining the effect of space weather, the environment is doing the removal and replacement. It can be the presence versus the absence of a given condition, such as a magnetic storm, or of a given spectral component (such as the week).[38] Biological states during spans corresponding to the presence or absence of given environmental features can then be compared by an armamentarium of standard statistical tools.[37]

Spectral components shared between physics and biology (coperiodisms) serve as an important complementary approach, itself amenable to further sophistication. Coperiodisms are assessed by a measure of congruence, where congruence is defined as overlapping 95% confidence intervals (CIs) of the periods estimated nonlinearly[39] for a given cycle common to biology and its environment. Within a given spectral region, it is then possible to calculate the probability of occurrence of coperiodisms by odds ratios.[40,41]

Cycles shared between physics and biology include the well-known about-daily (circadian) and about-yearly (circannual) variations. These cycles are photic in origin. They are now broadly recognized as partly built-in entities in biota. Other cycles are not directly perceived. They are nonphotic components found in particle radiation from the sun and the galaxy, partly in helio-geomagnetics, gravity, UV flux, and/or possibly in other measurable weather in extraterrestrial space.[42] Nonphotic cycles are notoriously wobbly, their periods and relative prominence showing nonstationary behavior, seen for instance in solar wind speed, a feature that led Franz Halberg to refer to them as being "Aeolian."[43]

The wobbliness of nonphotic cycles can be an advantage in assessing physical-biological associations. Indeed, as nonphotic environmental cycles undergo changes in cycle duration and in their relative prominence, the observation of similar changes in period and amplitude of corresponding biological cycles lends further support for the detected association to be factual rather than mere happenstance or outright spurious.[44] In view of the nonstationarity of nonphotic cycles, it is desirable that data be analyzed both globally (considering the time series as a whole) and locally (over an interval shorter than the entire observation span that is progressively displaced throughout the time series). In other words, in addition to global spectra, short-time Fourier spectra[45] or gliding spectral windows[46] can be computed to provide information about the time-varying characteristics of the variables investigated. Provided drifts in period remain small, this approach can be complemented by the chronobiologic serial section[47] applied at the average common period for a refined analysis of changes in phase as a function of time. This combined GLObal and loCAL analysis of data has been referred to as a "GLOCAL" approach.[48]

SPACE-TERRESTRIAL WEATHER EFFECTS ON HUMAN PHYSIOLOGY AND PATHOLOGY

Early Pioneers

Vallot et al.[49] reported a larger incidence of symptoms in the presence versus absence of sunspots. Symptoms included those of various diseases of the heart, vessels, liver, kidney, and the nervous system. Whether all or only severe symptoms were considered, a meta-analysis shows the difference between days with or without sunspots to be statistically significant.[33] Using superposed epochs by stacking their data over an idealized 27-day (Bartels) cycle, Düll and Düll[50] unveiled solar influences on neural and mental disease. They studied how space-terrestrial weather may differentially influence human mortality from various causes, the 27-day mortality pattern being different whether death was from cardiac or respiratory disease, or from suicide.[33]

The work of Chizhevsky,[51–53] who devoted his lifetime to the study of subtle environmental influences, cannot be ignored. He investigated the influence of the rhythms of solar activity on mass manifestations in human life, from epidemics to wars, riots, and other phenomena. His data on cholera and diphtheria remain relevant today, as cholera has yet to disappear.[54]

Moscow Database of 6,304,025 Ambulance Calls (1979–1981)

The 1979–1981 Moscow database of 6,304,025 ambulance calls included 85,819 cases of myocardial infarctions, 98,625 cases of strokes, and 71,525 cases of sudden cardiac death.[55] A statistically significant cross-spectral coherence was found between the local index of geomagnetic disturbance, K, and the daily incidence of myocardial infarctions at a period of about 3.17 days in 1979 and at a somewhat shorter period in 1980, with results in 1981 similar to those in 1979, albeit not reaching statistical significance.[35] The daily incidence of myocardial infarctions is also cross-spectrally coherent at the same 3.17-day period with the vertical component (Bz) of the IMF, with additional cross-coherence found at periods of about 26.9, 14.7, and 7.7 days, likely related to the rotation of the sun around its axis.[35] In the same data set, time-variant coherence and phase synchronization were found independently at the same frequency between the daily incidence of myocardial infarctions and the local K index.[56]

Southward turns of Bz have been associated with aurorae and magnetic storms. Defining a southward Bz turn as a change between a daily average of Bz of ≥1 nanotesla (nT) to one of ≤–1.5 nT, by superposed epochs it is found that there is a statistically significant 7% increase in myocardial infarctions after a southward Bz turn, a result found consistently during all the 3 years when analyzed separately.[36]

This result was independently confirmed by applying a different approach to the same data.[57] An even larger effect was reported in relation to the antipodal index of geomagnetic disturbance $aa > 60$, and to Forbush decreases in cosmic ray intensity >1.5%. Additional evidence was further obtained from a different data base.[58] Investigating relationships between different parameters of the geomagnetic activity and the daily incidence of myocardial infarctions in St. Petersburg, Russia, during the period 1989–1990, Villoresi et al.[59] indicated the need to differentiate between morbidity and mortality data: The about 10.5% increase in mortality from myocardial infarction during big geomagnetic storms (descending phase of cosmic ray Forbush decreases) contrasts with the lack of an effect on the incidence of morbid events.[59]

The Moscow database also included 70,531 cases of sudden cardiac death. Contrasting with other cardiovascular morbidity statistics showing a prominent weekly pattern, sudden cardiac deaths are characterized by an about half-monthly component not found in other cardiovascular events. Its period (and 95% CI) is estimated to average 15.2 days (CI: 15.15–15.30 days).[60] Whereas this period differs from that of local K analyzed during the same 3-year span, estimated to average 14.0 days (CI: 13.94–14.17 days), the half-monthly component shows great wobbliness in both variables when data are analyzed by moving spectra over a shorter interval of 3 months, progressively displaced by 1.5 weeks throughout the time series.[60] Interestingly, a similar half-monthly component was detected in Bz recorded in a magnetometer about 600 km from the nearest human habitat in Antarctica during the span from January 1, 1997 to January 31, 1999.[61]

The half-monthly component in the daily incidence of sudden cardiac deaths is more prominently expressed when it is also more prominently detected in the least squares spectrum of local K, suggesting a possible resonance with occasional frequency trapping between the two variables.[60] A similar resonance was observed in the case of about-weekly variations in mortality from myocardial infarction in Tbilisi (Republic of Georgia) in relation to solar activity.[62] The circaseptan component is more prominently expressed during years of high versus years of low solar activity.[63] More prominent about-weekly circaseptans in human heart rate are also found to resonate with the rate of change in sunspot area.[38]

Mortality (n = 129,205) from Myocardial Infarction in Minnesota (1968–1996)

After removing a linearly decreasing trend, mortality from myocardial infarction is found to follow an about 10.5-year cycle ($p < 0.001$).[10] Categorizing the yearly incidence of myocardial infarction by solar cycle stage (maximum, descending stage, minimum, and ascending stage), there is an excess of 220 deaths per year seen during years of maximal versus minimal solar activity ($p = 0.023$). Separate analyses for the three solar cycles covered by this database show inter-solar cycle differences: statistically significant differences are found both in the average daily number of deaths and in the 10.5-year amplitude, that is in the prominence of the about 10.5-year cycle, the about 10.5-year component being resolved by nonlinear least squares during the first two solar cycles, as well as overall, but not during the 1987–1996 span.[10] Independent studies[64] suggest that the adverse effect

of solar activity on the circulation, gauged by mortality from ischemic heart disease and stroke, may be particularly prevalent in the elderly, perhaps because of an increased susceptibility associated with old age.

The about 10.5-year variation in mortality from myocardial infarction in Minnesota is not the only nonphotic cycle detected in this database. While less prominent than the about-yearly and about-weekly changes, a transyear with a period of about 1.3 years is also detected with statistical significance, as it was in all longitudinal records of blood pressure and heart rate spanning 10 years or longer available to us for analysis.[65] Transyears with a period of about 1.3 years are nonphotic in origin, as they have been detected in the interplanetary magnetic field,[66] in solar wind speed[67,68] and in helioseismology,[69] also leaving their signature in the terrestrial environment.[70] The relative prominence of the transyear by comparison with the calendar year, like circaseptans,[71] is also larger in the elderly and early in life.[72] Albeit of small amplitude, a cis-half-year also characterizes mortality from myocardial infarction in Minnesota, with an estimated period of 0.424 year (95% CI: 0.421, 0.427 year). Cis-half-years are also nonphotic in origin, as they have been reported to characterize solar flares.[73–75]

Heart rate variability may be involved in a mechanism underlying the influence of space weather on myocardial infarction. In 24-h Holter recordings from 50 patients who had a myocardial infarction, heart rate variability (HRV), gauged by the 24-h standard deviation (SD) of heart rate (HR), was reduced by 20% as compared to similar records from 50 clinically healthy men ($p = 0.002$).[76] HRV is also 20% lower in 48-h ambulatory blood pressure monitoring profiles from the 16 initially healthy subjects who were to develop coronary artery disease within the next 6 years, as compared to the other 281 study participants without this condition at the end of study ($p = 0.004$). In this investigation, too low a HR-SD was associated with a 550% increase in the risk of coronary artery disease.[77] In short (about 30-min) electrocardiographic (ECG) recordings from presumably very healthy cosmonauts in space, the HRV was 30% lower in the eight subjects monitored during a magnetic storm as compared to 41 others monitored during quiet conditions ($p = 0.041$).[78]

Geomagnetic disturbance effects on HRV were also found in a 7-day ECG record provided by a clinically healthy man. HRV was statistically significantly decreased during geomagnetically disturbed versus quiet days, notably in spectral regions centered around one cycle in 46.5 s (that may relate to variations in the activity of the renin–angiotensin system and thermoregulation) and 10.5 s (thought to be generated by the baroreceptor modulation of the sympathetic and vagal nervous tone), but not in a region centered around one cycle in 3.6 s (thought to reflect the respiratory modulation of vagal nerve activity).[77] Similar results were obtained in 7 day records from clinically healthy subjects in Alta, Norway, located above the Arctic Circle,[79] where a graded response of HRV was found in association with the severity of geomagnetic activity.[80] These results suggest the involvement of the autonomic nervous system.[81] Signs of reduced vagal activity have been associated with an enhanced risk of sudden cardiac death.[82] Impaired HRV is reportedly also a predictor of mortality among patients with a variety of other vascular diseases.[83] Any physiological mechanism underlying the response to changes in magnetic activity should not involve the parasympathetic system, usually identified with spectral power centered on 3.6 s, a spectral region where differences were not statistically significant.

Sudden Cardiac Death in Minnesota and Other Geographic Locations

Since the 10th revision of the International Classification of Diseases (ICD10), sudden cardiac death (SCD; code I46.1) has been separated from myocardial infarction. SCD is now defined as unexpected death from cardiac causes within 1–24 h of the onset of acute symptoms. It has thus become possible to compare the time structure of SCD and myocardial infarction during the same or similar time spans in Minnesota and in other geographic locations. As seen from Figure 35.1, mortality from myocardial infarction during the span from 1999 to 2003 (10,272 deaths) is characterized by a prominent circannual variation ($p < 0.001$) with a 1.009-year

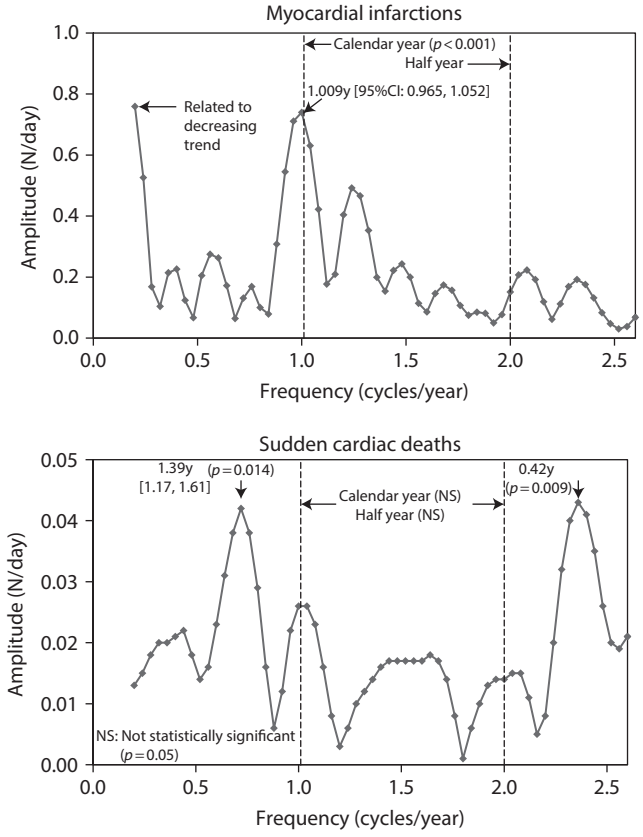

FIGURE 35.1 Mortality from myocardial infarctions in Minnesota during the span from 1999 to 2003 (10,272 deaths) is characterized by a prominent 1-year synchronized variation ($p < 0.001$). By contrast, sudden cardiac death in Minnesota (343 cases) during the same 5-year span (1999–2003) is characterized by a transyear and a cis-half-year, both nonphotic solar signatures.

period and a 95% CI (0.965, 1.052) overlapping the precise calendar year. By contrast, SCD (343 cases) in Minnesota during the same 5-year span (1999–2003) is characterized by a transyear and a cis-half-year, both nonphotic solar signatures. Nonlinearly, the transyear has a period estimated as 1.39 years (95% CI: 1.17, 1.61 years; $p = 0.014$), and the cis-half-year a period estimated as 0.42 year (95% CI: 0.40, 0.44 year; $p = 0.009$).

A transyear is also found to characterize SCD in Arkansas and the Czech Republic, albeit a 1-year synchronized component is also detected at these two geographic locations. A cis-half-year was also detected in the Czech Republic after 1999, as well as in Hungary and Lithuania, whereas in North Carolina, the Republic of Georgia, Latvia and Hong Kong, only a 1 year synchronized component was found.[84] Lending support for an influence by space-terrestrial weather on the incidence of SCD is the report in Azerbaijan of a reduction in SCD in association with solar-geomagnetic activity.[85] Further supporting evidence stems from the presence of transyear and cis-half-year components in 10-year-long records of two kinds of cardiac arrhythmia, namely atrial fibrillation and paroxysmal supraventricular tachycardia.[86] Ventricular arrhythmia have long been associated with the risk of SCD,[87,88] and SCD resulting from ventricular tachyarrhythmia remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States.[89]

Suicide

The fact that there is increased interest in transcranial magnetic stimulation as a treatment for depression[90,91] suggests that depressive disorders and suicide may also be influenced by space-terrestrial weather. Epidemiologic studies indeed yielded positive correlations between magnetic- and/or electric-field strengths in local environments and the incidence of depression-related suicide. A nested case-control study revealed an association between occupational electromagnetic fields and suicide that warrants further evaluation as odds ratios were reportedly increased in association with years of employment as an electrician or line worker but decreased for power plant operators.[92] Melatonin is cited as a plausible underlying mechanism. Disruptions in the circadian rhythmicity of pineal melatonin secretion have indeed been associated with certain depressive disorders in humans.[93] Melatonin has long been thought to be involved in depression.[94,95] In keeping with the proposal of a low melatonin syndrome in depression,[96] melatonin concentrations in the pineal glands of suicide victims were reportedly reduced[97] and post-mortem studies in suicide victims with various psychiatric disorders showed decreased concentrations of serotonin and its metabolites in the brain.[98] Suppression of the nocturnal melatonin metabolite 6-hydroxymelatonin sulfate was reported after exposure to 50/60-Hz magnetic fields as well as in association with increased geomagnetic activity.[99–101] A response of the circadian melatonin rhythm to a magnetic storm has also been described in the pineal and in the hypothalamus of rats sampled at six different circadian stages for 7 consecutive days.[102]

Against this background, it is not surprising that the daily incidence of suicide in Minnesota during the span from 1968 to 2002 (N = 15,881) shows nonphotic solar signatures. As seen from Figure 35.2, in addition to the calendar-year synchronized component, a more prominent transyear with a period of about 1.3 years was detected together with a very prominent half-year with peaks in the spring and fall, as seen for indices of geomagnetic disturbance.[103,104] A near-transyear was also detected with a period slightly longer than 1 year similar to that observed in solar magnetism.[105] Whereas a cis-half-year component is not detected in the data from Minnesota, it is present in statistics from Australia for the 1968–2001 span.[106] Its period is estimated by nonlinear least squares to average 0.422 year (95% CI: 0.419, 0.424).

A cis-half-year is also detected in transverse data on circulating melatonin of 172 patients, each contributing samples every 4 h for 24 h (at 08:00, 12:00, 16:00, 20:00, 00:00,

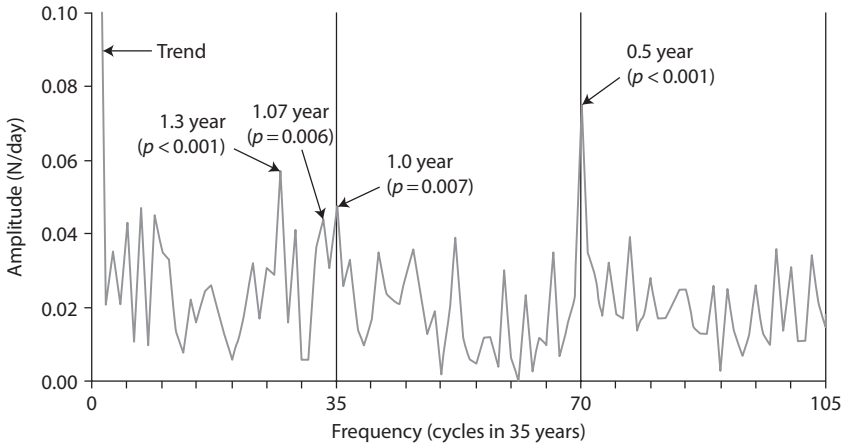

FIGURE 35.2 The daily incidence of suicide in Minnesota during the span from 1968 to 2002 (N = 15,881) shows both photic and nonphotic solar signatures. In addition to the calendar-year synchronized component, a more prominent transyear with a period of about 1.3 years is detected together with a very prominent half-year with peaks in the spring and fall, as seen for indices of geomagnetic disturbance.

and 04:00) between October 1992 and December 1995 in Florence, Italy.[107] A model consisting of a fixed 1.0-year component alone or with an adjustable 0.42-year (cis-half-year) component was fitted to the circadian MESORs (where MESOR stands for midline estimating statistic of rhythm, a rhythm-adjusted mean, usually more precise and more accurate than the arithmetic mean). This model also fits the data collected at each clock hour, except for the data at 00:00 and 04:00, when only the cis-half-year was statistically significant. Nonlinearly, the cis-half-year component was invariably documented for all endpoints considered.[107] Melatonin may thus be a mediator of an informational effect by nonphotics, including particle emissions from the sun acting in part via geomagnetic disturbance and/or directly.

The intermittency of the cis-half-year in solar activity enables the further study of solar-biospheric relations by a remove-and-replace approach, wherein the sun and/or earth implement a subtraction or removal of a component and its replacement. Thus, a cis-half-year was found to persist in the urinary excretion of steroidal hormone metabolites of a healthy man after this component could no longer be detected with statistical significance in geomagnetics.[108] Corresponding changes as a function of time were similarly observed for the prominence of the cis-half-year in human heart rate by comparison with its presence in solar flares.[109] Specifically, a multi-component model consisting of cosine curves with periods of 0.41, 0.50, and 1.00 year (corresponding to major spectral peaks in that frequency region) was fitted to weekly means of heart rate collected about 5 times a day over 39 years by a clinically healthy man. The amplitude of the 0.41-year component, estimated over a 4-year interval displaced in 2.5-month increments, follows an about 11-year cycle similar to the solar activity cycle, also seen in the total solar flare index (from both solar hemispheres). Figure 35.3 shows the superposed time courses of heart rate and the total solar flare index, visualizing the presence of a shared cycle of about 11 years. It can be seen that the cis-half-year in heart rate is more prominent after the total solar flare index reaches its about 11-year peak. The cis-half-year amplitude of heart rate shows a cross-correlation coefficient of 0.79 with the total solar flare index at a lag of about 3.2 years.[109]

Heart rate was only one among several variables self-measured about five times each day by this clinically healthy man since 1967 when he was 20.5 years of age. It was thus possible to compare the time structure of these self-measurements collected over nearly four decades with that of space-terrestrial weather. For comparison, solar wind speed and the antipodal index of geomagnetic disturbance (aa) were analyzed during the same about 40-year span. Least squares spectra were computed for each variable in the frequency range of one cycle in 2.5 years to 3 cycles per year, a range including both transyears and cis-half-years, together with the calendar year and half-year. Each spectral peak was resolved by nonlinear least squares to obtain an estimate of the period with its 95% CI.[40,41] Shared cycles were identified by the criterion of congruence between each of the somatic and mental functions, separately with solar wind speed and with aa, determined by the criterion of overlapping 95% CIs of corresponding periods. Odds ratios served to test for statistical significance.[40,41] The number of congruences found for the estimation of 1 min and for mood in the spectral range investigated more than equalled that of the known association of solar wind speed and geomagnetism (aa). Mental functions showed higher congruence than somatic functions.[40,41]

DISCUSSION

Far from being an exhaustive review of the field, results summarized above represent only a small glimpse of associations between physics and biology encountered within the realm of

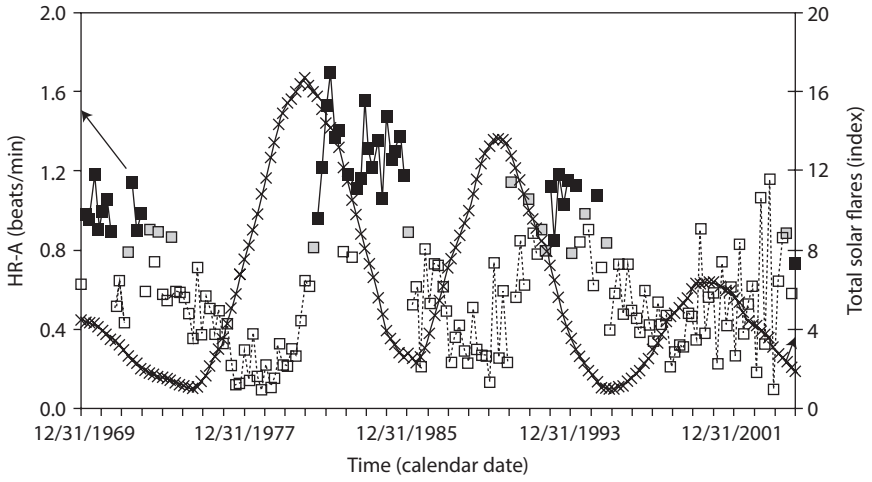

FIGURE 35.3 The amplitude of the 0.41-year (cis-half-year) component in heart rate (self-measured about 5 times a day by a clinically healthy man over 4 decades), estimated over a 4-year interval displaced in 2.5-month increments, follows an about 11-year cycle similar to the solar activity cycle and to the total solar flare index (from both solar hemispheres). The superposed time courses of heart rate and the total solar flare index visualize the presence of a shared cycle of about 11 years. The cis-half-year in heart rate is more prominent after the total solar flare index reaches its about 11-year peak.

research at the Halberg Chronobiology Center. Cycles with periods of about 5 and 16 months, 10.5, 21, 35, and 50 years, all observed in the nonphotic environment, have also been detected in longitudinal records of physiological variables and in patterns of mortality incidence from various causes.[28] In contrast with the relatively stable 24-h day and 12-month year, nonphotic cycles in the environment related to solar-terrestrial magnetism vary as a function of time. They undergo changes in cycle duration and in their relative prominence. These features can be exploited to go beyond the simple observation of cycles shared between physics and biology.[44,108] They can help our understanding of environmental effects, making it possible to predict the future course of the biological variables (such as the incidence of various diseases) by monitoring cycles in the environment, a task which is facilitated by the availability online of comprehensive databases on a variety of environmental factors prepared by physicists.[110]

While results presented herein relate primarily to heliogeomagnetic influences on human physiology and pathology, this chapter would not be complete without mentioning lunar influences that could also act according to gravitational changes, as evidenced by the tides. The lunar month having a period similar to the solar rotation around its axis, separating effects of the sun and moon needs more careful considerations than the mere mapping of about-monthly cycles. Stacking the data according to lunar stage over a long enough observation span may be most informative. For instance, a lunar influence has been reported in relation to paroxysmal tachyarrhythmia[111] and atrial fibrillation.[112] The unusual case of a selenosensitive woman could be studied longitudinally by some of us.[113] This 61-year old woman experienced half-yearly recurrent episodes of adynamia lasting about 2 months for the past 20 years. Extensive around-the-clock monitoring of her mood, vigor, urine volume, wrist activity, blood pressure, heart rate, and several salivary hormones revealed multiple circadian desynchronization during her downtimes.[113] Analysis by the extended cosinor shows the co-existence of a 24-h synchronized circadian rhythm and an about 24.8-h (double tidal) component that alternate in prominence between spans of wellness and adynamia, as illustrated in Figure 35.4 for some of these variables. A stable and robust about 24.8-h "lunar" component with a residual weaker near 24.0-h synchronized cycle were also detected in around-the-clock measurements of blood pressure and heart rate collected automatically during 267 days of isolation in a special habitat (like lunar base) known as Underlab in the Frasassi caves near Ancona, Italy, by a 28-year old woman.[114] Only a strong 24.0-h synchronized circadian rhythm was detected before as well as after isolation.[114]

This review focused primarily on human physiology and pathology. There is, however, one database of the average number of hours per month spent proselytizing available yearly between 1950 and 1999 from 103 different geographic locations[115] that allowed the analysis to go one step further. A common about 21-year cycle detected prominently was validated nonlinearly in 70% of the sites. Lending further evidence for an influence of geomagnetic activity on motivation is the statistically significant regression on latitude of characteristics of the 21-year cycle: the about 21.0-year amplitude was found to be larger at low and middle than at higher latitudes, and the resolution of the about 21.0-year cycle (gauged by the width of 95% CIs for the period and amplitude) was higher (the 95% CIs are statistically significantly smaller) at higher than at lower latitudes.[115] Any planetary geomagnetic influence may be felt more strongly at higher latitudes. Latitude dependence has also been reported for melatonin,[116] which can also be influenced by geomagnetic disturbances, as reviewed above. Interestingly, schizophrenia, a condition associated with motivational deficit,[117] can also reportedly be affected by geomagnetic activity.[118–120] About 20-year and

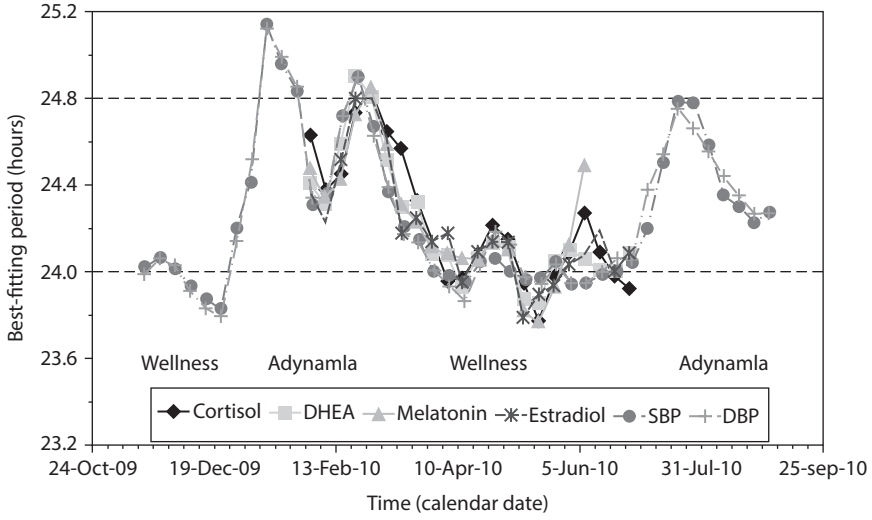

FIGURE 35.4 (**See color insert.**) A 61-year old selenosensitive woman who experienced half-yearly recurrent episodes of adynamia lasting about 2 months for the past 20 years monitored her mood, vigor, urine volume, wrist activity, blood pressure, heart rate, and several salivary hormones around the clock for over a year. A 24-h synchronized circadian rhythm and an about 24.8-h (double tidal) component coexist, alternating in prominence between spans of wellness and adynamia.

about 10-year cycles have further been reported to characterize religious motivation from other churches (approximated by church membership) as well as criminality.[121]

Also of interest is a large database from the Memorial Institute for the Prevention of Terrorism (MIPT) from which the average daily numbers of international terrorist acts each month was derived between February 1968 and March 2007 (approximately 39 years). In the absence of any 1-year synchronized component, a transyear with a period of about 1.3 years was prominently detected and further investigated in gliding spectral windows for comparison with the changing time structure of solar wind speed and the antipodal index of geomagnetic disturbance (aa).[44] Albeit wobbly in frequency and amplitude, the transyear in terrorism remains mostly statistically significant throughout the whole record, but it is most prominent during the years that also show a prominent transyear in solar wind speed and in aa, particularly during solar cycle 22.[122] In this case, there is not only a communality of the major transyear component in the frequency range, there is also coincidence in relative prominence of all three variables in the time domain. This is further documented by the phase behavior at the average common period of 1.33 years: the transyear in terrorism follows with a lag the transyears in solar wind speed and in aa, persisting after 1998 when it is no longer detected with statistical significance in solar wind speed or in aa.[122]

The monitoring of physiological variables, facilitated by the growing availability of sensors for continuous surveillance, can be used not only for primary prevention in healthcare but also as a way to better understand how we respond to our environment. There is even evidence suggesting that subtle physiological changes may occur preceding the occurrence of natural cataclysms. While these changes may not be of sufficient magnitude in any single individual, the question could be raised whether a systematic monitoring of large populations linked to an as-one-goes center for data processing may not someday complement the physical monitoring as a forecasting aid. Taking the example of major earthquakes, abnormal behavior in fish, snakes, dogs, frogs, and mice has been reported before an earthquake.[123–125] While most accounts remain anecdotal, locomotor activity of mice monitored automatically around-the-clock was shown to be dramatically decreased on day 3 before the May 12, 2008 Wenchuan magnitude 8.0 earthquake in China, the behavioral change lasting 6 days.[126] Changes in groundwater chemistry prior to seismic events have been considered to account for their possible effects on animals.[125,127] In humans as well, an increase in systolic blood pressure was observed, starting 2 days before the 11 March 2011 magnitude 9.0 Eastern Japan Great Earthquake Disaster, reaching a peak on the first day after the earthquake ($F = 3.157$, $p = 0.013$).[128]

CONCLUSION

Despite remaining controversies and some skepticism about influences from helio-geomagnetism on human affairs, data start accumulating to constitute evidence that can no longer be ignored. One way to avoid controversies in the future consists of systematically documenting in detail all experimental conditions and to rely on data analysis techniques that are robust. Using complementary approaches can lend further confidence to the results, realizing the severe shortcomings of the Pearson product-moment correlation that is likely to yield spurious results in the presence of ubiquitous cycles.

The evidence presented herein can only provide a glimpse into a new realm open for much further exploration. But we hope that by opening the door to this fascinating new field, as others have done before us, new knowledge will be gained that may become amenable to useful applications in medicine and the earth sciences.

Toward this goal, Franz Halberg first envisioned the building of an atlas of chronomes, that is, of broad time structures, including photic and nonphotic cycles. As seen in a few illustrative examples herein, the presence of nonphotic cycles has been demonstrated, and, in a few cases, their characteristics have been quantified with a measure of uncertainty. Much more needs to be done for these cycles to become truly useful. They need to be systematically mapped and reported in an atlas that is easy to consult, just as astronomers have started the mapping of stars and galaxies, and unmanned vehicles are exploring the terrain on Mars.[110] Connections need to be made between the presence of nonphotic cycles in the cosmos, how they may be affecting the ionosphere[129] and influence weather on earth,[130] and how these changes can, in turn, have an impact on agriculture,[131] nutrition, the presence of pathogens, and overall human health.[132,133] By organizing charts in a way that best conveys sequences of events along a given time scale (i.e., cycle length), it should become clearer how to best utilize the information to the benefit of humankind.

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36 Medical Problems Arising from Solar Storms

*Abraham R. Liboff**

CONTENTS

INTRODUCTION

It goes without saying that the sun has an influence on human beings. It is necessary for life on earth through its gift of warmth. Our evolutionary make-up in large part derives from the physical attributes of the sun. The maximum sensitivity of the eye is adjusted to the green wavelengths that are at the peak of the sun's spectral output. Our kinetic energy expenditures are cyclically apportioned for wakefulness and our sleep is in synchrony with the side of the spinning earth that faces the sun. Metabolic activities are consistent with the range of temperatures on earth from the sun. One of the most frightening doomsday scenarios is that of the solar winter, where an enduring cloud cover would severely interfere with photosynthesis, thereby reducing food production to catastrophically low levels.

It should not be surprising, therefore, to learn that relatively small disturbances in the sun's activity can also affect humans in serious ways. Indeed, a large body of literature has been generated to indicate that there are robust connections between solar activity and human health. Interestingly, this connection is not reflected in the thermal energy received at the earth's surface. Terrestrial temperatures do not scale with solar activity. Rather the effects on human health are due to an intermediary between sun and earth, namely the solar wind that causes perturbations in the earth's magnetic field (geomagnetic field [GMF]).

Although the present work is focused on illness, we should not forget the deep historical context that preceded this, where attempts were made to relate the sun to human behavior. In the 1920s, a Russian school of thought was generated specifically highlighting what was claimed to be the close relationship between solar activity and human events. This work, largely developed by the father of heliobiology, Chizhevsky,[1] argued that the sun is far more important in social affairs than usually acknowledged. Not only were matters of health addressed but also effects on climate and political matters. From a scientific standpoint, however, establishing a connection between solar activity and biological change is difficult enough without venturing forth into the gray areas surrounding societal impact. Much maligned as this research was at the time (and still is), it had the virtue of serving as a springboard for a multitude of Russian scientists that followed, all studying various aspects of the interactions between the geomagnetic field and living things. A more recent version of these studies, somewhat more acceptable scientifically, has been developed by Halberg and Cornellisen.[2] This approach stresses the painstaking delineation of the various frequencies attached to the sun's cycles, coupled to putative cycles gleaned from human medical and social records.

THE NATURE OF SOLAR ACTIVITY

A variety of electromagnetic signals, either as directly delivered radiofrequencies or indirectly as transients caused by solar wind interactions are part of solar storm activity. Magnetic disturbances on the solar surface have been visibly recorded since at least the 1600s, conveniently listed in terms of the number of sunspots observed daily. These worldwide data, collected over centuries, show that sunspot numbers enjoy a persistent 11-year periodicity (Figure 36.1), with maxima corresponding to times when the sun is "active" and minimum numbers occurring halfway between, when the sun is "quiet." The summer of 2013 corresponded, for example, to a time of maximum solar activity.

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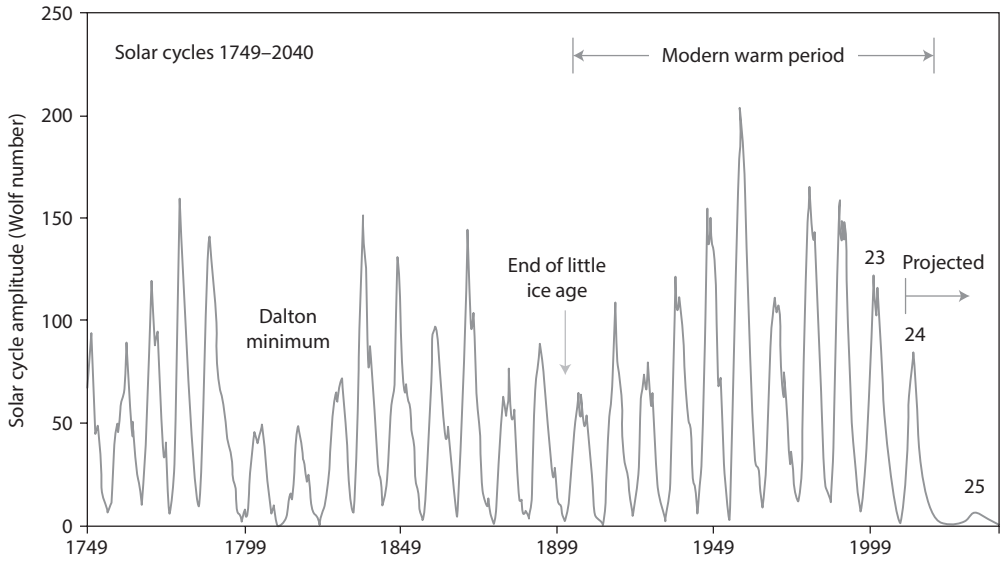

FIGURE 36.1 Record of solar sunspot numbers since 1749. Cycle 24 peaked in 2013.

The active sun emits ionized plasma (dense regions of highly energetic charged particles), some of which escapes solar gravity to stream into space (Figure 36.2), becoming what is referred to as the solar wind, traveling at about 400 km/s, even faster for extremely violent storms. Depending on where the earth is in its yearly orbit and the initial direction of this wind, the earth's magnetic field may be impacted by this wind, leading to measurable changes in the GMF at the surface of the earth. This lengthy journey from the sun, taking about 3 or 4 days to reach the earth, is the pathway that relates magnetic storms on the sun to human health problems.

How does one reckon short-time changes in the GMF? By international agreement, geomagnetic perturbations are studied using a variety of yardsticks as a measure of the change at the earth's surface due to the solar wind. Two such indices, A and K, are reported at various geomagnetic stations; when averaged globally, they are designated Ap and Kp (Table 36.1). Each index is determined by taking 3 h averages of the local magnetic field, which in turn is averaged over 13 locations around the globe. In practice, the daily average is mainly used, constructed from the eight values measured over each 24 h period.

BIOLOGICAL SENSITIVITY TO WEAK EXTREMELY LOW FREQUENCY MAGNETIC FIELDS

In principle, it is difficult to link solar storms to biological activity. Not only are the effects of these storms delayed in arriving at the earth's surface and extremely weak, but they are also short-lived and aperiodic in nature. The consequent

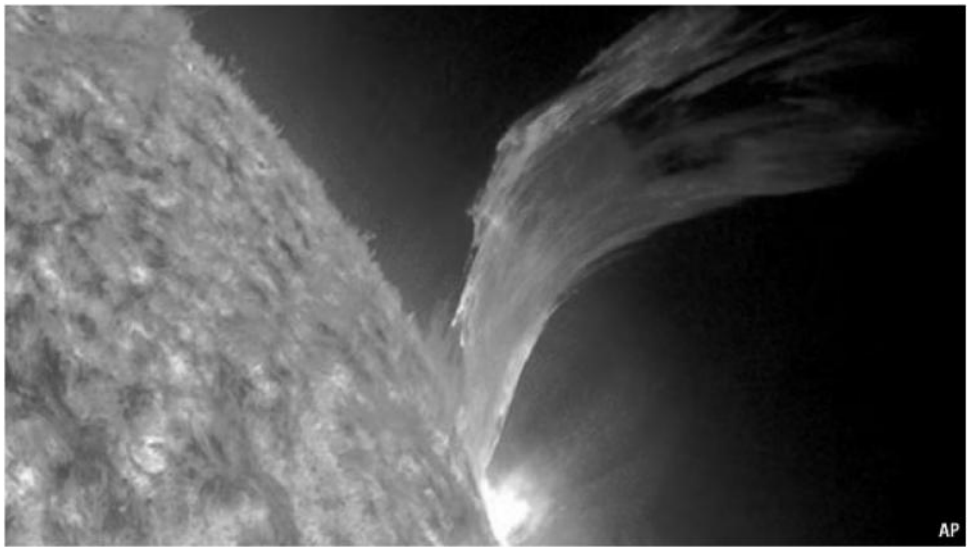

FIGURE 36.2 A solar flare photographed on the edge of the sun, showing what appears to be a total loss moving outward, presumably constituting a coronal mass ejection.

TABLE 36.1
Geomagnetic Indices Used to Categorize Different Levels of Geomagnetic Perturbation

Kp	Ap	Magnetic Change, nT	Description
0	0–2	0–5	Very quiet
1	3–5	5–10	Quiet
2	6–9	10–20	Quiet
3	12–18	20–40	Semi quiet
4	22–32	40–70	Unsettled
5	39–56	70–120	Minor storm
6	67–94	120–200	Major storm
7	111–154	200–330	Severe storm
8	179–236	330–500	Severe storm
9	300–400	>500	Extremely severe

changes measured at the earth are greatly reduced in intensity, and they only indirectly reflect the original magnetic events on the solar surface, several days earlier. The alterations in the geomagnetic field are the result of currents of electrons being formed in the vicinity of the earth following the emission of a solar flare from the sun. This causes the magnetic field at the earth's surface to change for a short period, until the currents above the earth are dissipated.

The net effect at the earth's surface is very small. Apart from local iron ore anomalies, the total geomagnetic field intensity ranges from 25 to 60 μT. One has to answer exactly how biological systems are affected by changes in this field of perhaps 0.2 μT over the course of several hours. Despite what seem so clear to those studying the decades-long correlations between illness and magnetic storms, claims suggesting that such fields can have physiological effects have evoked deep suspicion by the physics community.

Nevertheless, there is continuing evidence to lend support to the idea that solar activity does have biological significance. Despite the fact that a remarkable array of human illnesses correlates positively with solar storms, it is only now that one finds independent evidence to corroborate the notion that weak, low frequency magnetic fields are capable of impacting biological clock function in humans.

Even though there is considerable statistical evidence since the 1920s showing that humans are affected by solar activity, it was not until the groundbreaking work of Adey[3] some 50 years later that a reasonable physical explanation began to emerge. The subsequent hypothesis of ion cyclotron resonance (ICR), introduced by Liboff[4] in 1984, and later confirmed in dozens of experiments,[5] implicated low frequency magnetic fields, showing conclusively that they are biologically interactive, even to levels as weak as 10s of nT.[6]

This resonance concept holds that combined time-varying and static magnetic fields act in concert to stimulate biologically sensitive ions, thereby altering physiological response. This condition requires that the frequency of the time-varying magnetic component be related to the static field value through a constant of proportionality equal to the charge-to-mass ratio of the specific ion. Accordingly, many early ICR experiments focused on stimulating the calcium ion, an obvious choice considering its well-known second messenger capabilities.

Particularly noteworthy is that when the ICR hypothesis was introduced for the very first time, in 1984,[4] specific mention was made that this resonance process would lend itself to interactions involving the GMF. The ICR process provides a physical basis for explaining how weak low frequency magnetic fields of the sort associated with geomagnetic disturbances due to solar storms can affect living things. Most importantly, it strengthens the decades-long history of reports finding statistical connections between human wellbeing and solar activity.

The geomagnetic changes arising from solar storms range from 100s of nT to 1000s (0.1–1.0 μT), well below prior published predicted lower limits on biological sensitivity. Nevertheless, these latter constraints are clearly invalid considering the dozens of reports to the contrary. Furthermore, the relevance of the ICR response to geomagnetic effects on humans has in recent years been strengthened by Zhadin,[6] who found that the physical characteristics of amino acids are affected by vanishingly small magnetic fields, as little as 40 nT. This extension of ICR effects to very weak magnetic fields opens the door to the possibility that even the slightest changes in the geomagnetic field are capable of affecting life on earth.

CORRELATING STORMS WITH SICKNESS

There have been numerous reports indicating positive correlations between various medical problems and solar/geomagnetic storms. These have included a wide range of problems: behavioral difficulties,[7–9] effects on embryonic development,[10] sudden infant death syndrome,[11] influenza,[12–14] and, notably, heart disease.[15–25] As early as 1931, Alexander Chizhevsky[26] reported evidence linking sudden death from cardiac arrest to solar activity. Many of these claims have not been thoroughly reproduced, the one prominent exception being the extensive work focused on cardiovascular disease. Conversely, only a few observers have failed[27–29] to find connections to solar storms. Thus, it is now widely believed

that these effects, although still unexplained, are indeed real. Nonetheless, because different statistical approaches have been used, some seeking to correlate daily effects and others, monthly averages, the picture is less than perfect.

Because of our natural tendency to seek correlations, often at the expense of reasonable expectations, a variety of other periodic biophysical phenomena have also been explored for their possible connection to the human condition. Two such examples are Pc oscillations[30,31] and Schumann resonances.[32] However, even if these correlations are indeed viable they probably bear little connection, if any, to the more generally accepted outcomes for human health derived from solar wind interactions.

In the one case, although it is true that geomagnetic pulsations are indeed due to solar activity they are less dependent on solar storms. They occur within low frequency bands, the most intense being the Pc 1 band covering the range 0.1–5 Hz. Their approximate 1 nT intensity is far less than the bulk of the signals resulting from magnetic storms, which are usually measured in the 100s of nT, and separately known from laboratory studies to be biologically interactive. One speculative physiological argument is that Pc 1 signals make the heart particularly susceptible because their frequencies overlap those associated with the heart rate. However, it is difficult to describe a physically reasonable coupling process in this regard.

Schumann resonances represent another geophysical phenomenon widely studied for their potential impact on humans. It may very well be the case that there are biological effects connected to Schumann resonances, but such effects, if real, would be completely independent of those related to solar activity. Simply stated, Schumann resonances are not geomagnetic phenomena, and are completely unrelated to solar activity. They result from electric discharges due to lightning that is launched into the well-defined spatial gap between the two conducting sheets defined by the ground and the ionosphere.

In general, the approach to studying the effects of solar activity on biological system has consistently employed correlation analysis, an approach often found scientifically wanting without further evidence either in the laboratory or theoretically. Most often this type of analysis uses clinical endpoints such as the records of rate of suicides, heart attacks, or hospital admissions that are also registered regularly by government agencies. Because such registers can provide enormous numbers of cohorts, sometimes in the hundreds of thousands, the statistics often appear to be quite reasonable. However, until recently scientists were slow to accept standalone correlative studies, such as these, as reasonable evidence, regardless of the statistics. In our opinion, the supportive evidence has reached levels where credibility is no longer in question. Further, as has already been pointed out, the data obtained this way is consistent with parallel independent research implicating weak low frequency magnetic fields in a wide range of biological effects.[5]

COSMIC RADIATION

Our understanding of how solar activity affects humans is confounded by the fact that there are likely biological effects due to cosmic rays, the ubiquitous high energy particles originating not only in the sun but also in galactic and extragalactic regions. Some reports claim that solar-related health problems appear to be greater at higher geomagnetic latitude, an association that might perhaps follow from a similar effect observed in cosmic rays, where the intensity is greater at the poles than at the equator.[33] The problem is that increased

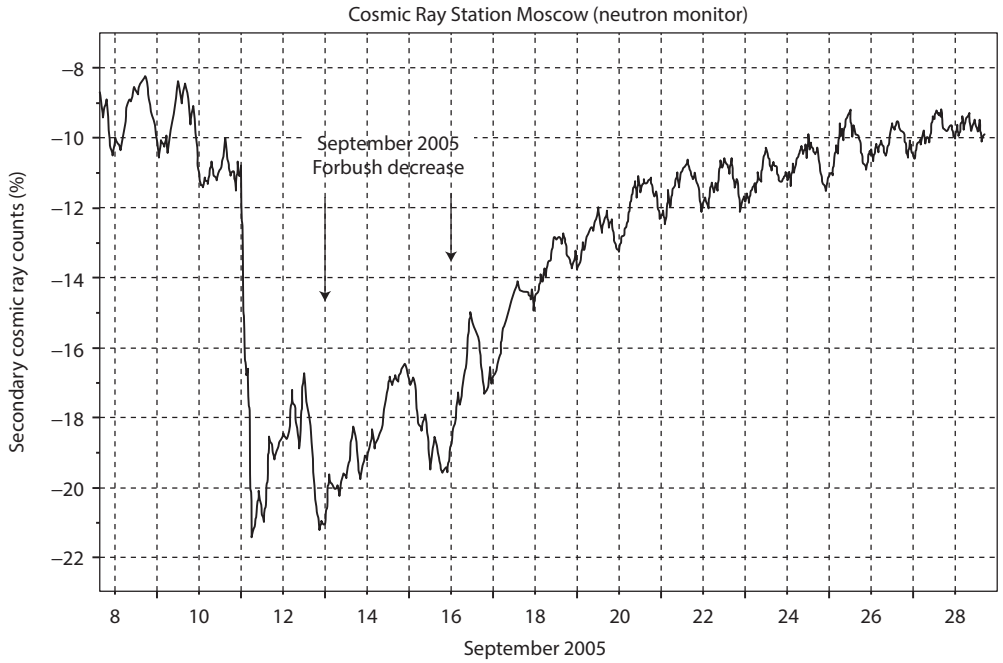

FIGURE 36.3 A typical Forbush decrease in sea-level cosmic ray intensity accompanying a solar storm.

cosmic radiation always accompanies *reduced* GMF levels. This well-established inverse relationship occurs because the GMF dipole acts to deflect cosmic rays away from the earth. When the earth's magnetic field is reduced, the cosmic ray intensity increases. Although no direct evidence exists specifically showing that enhanced cosmic radiation has biologic consequences, it is reasonable to make this assumption, given the fact that cosmic radiation is known to be highly ionizing.

A direct illustration of the inverse connection between cosmic ray intensity and geomagnetic field is the phenomenon of the Forbush decrease (Figure 36.3), where the cosmic ray flux falls precipitously when the solar wind arrives to sharply increase the geomagnetic field. Note that correlations have been reported between myocardial infarcts and Forbush decreases.[25] It is reasonably certain that the prime causative factor in such associations must be the change in magnetic field, not the change in cosmic ray intensity.

One common error in reporting possible cosmic ray effects is to give special significance to the specific monitoring technique employed. Statements[34] such as "…neutrons, produced by cosmic rays…can play a significant role [in the] timing of cardiovascular diseases…" are made without realizing that neutron monitoring is but one experimental method of many, chosen because of its simplicity, with which cosmic rays are studied. Whatever the biological effects of cosmic radiation, it is far more likely to result from ionization events than to the method of measurement itself.

In one instance[35] it was reported that adverse health effects appear to correlate with both lower as well as higher geomagnetic activity. This might conceivably be tied to the concomitant cosmic ray increase at reduced GMF levels. However, other data based on medical admissions at lower latitudes in Mexico City[19] and Havana[20] found similar rates for solar-related myocardial infarcts as had been reported at higher latitudes. Although it is very clear that weak magnetic fields can have physiological consequences, it is seems unreasonable to think that the absence of such fields would have similar effects.

CARDIAC PROBLEMS

The effects of solar disturbances on blood, specifically on the erythrocyte sedimentation rate (ESR), have been studied for some time.[36,37] These earlier *in vitro* reports inevitably led to a large number of related observations on humans. More than any other medical condition, morbid effects relating to the cardiovascular system have been repeatedly correlated with geomagnetic activity. These are detailed in a number of excellent reviews.[18,34]

Ghione[16] found higher systolic and diastolic blood pressures related to solar storm activity in 447 outpatients tested over a 5-year period. Gurfinkel[24] investigated the effect of enhanced geomagnetic indices on 80 heart patients, using perivascular edema, red blood cell aggregation, and blood flow rate as observables. Fully 70% of these individuals were significantly affected. A positive correlation between GMF and heart attacks was found for 1192 patients in Sofia[22] between 1995 and 2004. Another, separate, very large data set, based on ambulance calls in Moscow[34] during the period 1979–1981 found a 13% increase in heart attacks and a 7% increase in strokes. Additionally, examination of the daily incidence of 2290 myocardial infarcts in Mexico City from 1992 to 1996 revealed a 13% increase on geomagnetically active (GMA) days.[19] One study in Havana[20] conducted between 1992 and 1999 supported the connection between heart attacks and increased GMA, and went so far as to suggest the effect had a threshold in the 50–100 nT range. Positive correlations between 7798 myocardial infarctions in one Greek hospital and geomagnetic indices were observed[23] for the 10-year period beginning in 1997.

Using medical data originating in Lithuania this question has been examined in some detail by Stoupel.[38] A study of more than 850,000 deaths, grouped by monthly rates, was made, covering 20 years. Although this study lacked the specificity of the daily correlations used elsewhere, the approach was noteworthy in that care was taken to separate out the individual correlations associated with key variables: solar activity, GMA, and cosmic ray activity. In so doing, one can distinguish between effects related to direct observation of solar activity, by counting sunspots, and by the geomagnetic perturbations on the earth's surface, thereby taking account of the time lag introduced by the solar wind. One can readily correct for this lag, but cosmic ray effects are more difficult to disentangle. According to Stoupel, monthly averages of deaths from heart disease strongly correlate with cosmic ray activity and solar activity, but less so with geomagnetic activity. However, by restricting the analysis to individual monthly averages of GMA, this approach becomes insensitive to the few days per month when the effect may be more vivid.

A total of 15,543 myocardial infarcts occurring in 1989 and 1990 in St Petersburg[25] were compared to solar storms using the returning phase of Forbush decreases as a measure of geomagnetic perturbations. This work stands out because a credible attempt was made to establish a precise measure for the percentage increase in morbidity, reported as 10.5% ± 1.2%.

Novikova and Ryvkin[39] compiled lists of those who had heart attacks in the city of Sverdlovsk (presently Yekaterinburg) during the years 1961–1966. Both the total daily number of myocardial infarctions, or morbidity, as well as related deaths or mortality, was categorized as either occurring on a quiet solar day or active solar day. These results, covering a total of approximately 3600 cases, are shown in Table 36.2. The increase in heart attacks due to solar storms, according to these data, is roughly 8%–9%. A 5% increase in cardiac-related deaths was recorded in another study in Minnesota[40] that compared years of maximal solar activity to years of minimal solar activity.

Such abundant evidence makes it is difficult to avoid the conclusion that solar/geomagnetic activity can increase the rate of heart attacks by approximately 10%, compared to periods when the sun is quiet. The influence of geomagnetic activity on heart disease is further revealed in separate studies showing that the occurrences of stroke, as well as known

TABLE 36.2
Percentages of Cases of Myocardial Infarction in One Russian City Separated According to Whether These Occurred During Solar Active or Solar Quiet Periods

Year	Active	Morbidity Quiet	% Increase	Active	Mortality Quiet	% Increase
1961	78.8	70.4	8.4	24.5	18.8	5.7
1962	73.5	65.3	8.2	35.0	25.7	9.3
1963	77.6	73.2	4.2	24.9	20.6	4.3
1964	62.0	57.0	5.0	36.4	21.7	14.7
1965	79.1	75.0	4.1	27.9	25.3	2.6
1966	90.8	75.4	15.4	59.5	40.9	18.6
Mean %			7.5			9.2

Note: Thus, in 1964 heart attacks occurred 57% of the time on quiet days but 62% on active days, suggesting that there was a 5% greater chance of having a heart attack that year because of solar activity. Note that the year 1966 was marked by a large increase in solar storms, as the sun began to move into its more active mode consistent with its 11-year cycle. (From Novikova and Ryfkin.[39])

risk factors such as high blood pressure, pulse rate, and coagulation rate, also correlate with GMA.[34] Stoupel,[18] in reviewing these data, suggested that when geomagnetic activity is sufficiently great, this can overcome a hypothesized homeostatic response to a changing magnetic field, resulting in "heart rhythm disturbances and related sudden death, cardiovascular accidents, cardiovascular insufficiency, and vascular thrombosis, including myocardial infarction." It must be emphasized that the approach taken in all these cases, where the studies focused on hospital admissions or individuals that already had cardiovascular problems, implies that the correlational associations were established solely for high-risk individuals. In other words, there is nothing to indicate that the larger population exhibits the same response to geomagnetic disturbances.

Perhaps the strongest evidence yet found linking cardiovascular problems to solar activity was reported by Feigin et al.[41] Data collected on nearly 11,500 patients in five countries during the period 1981–2004 indicated a 19% increase in strokes for Ap values equal to or greater than 60, corresponding roughly to a 100 nT increase at the earth's surface. Even more striking is that when this data set is parsed, one finds that the risk of geomagnetically induced stroke is markedly increased as the Ap value increases.

SUICIDES

As suicide data are carefully maintained by most countries, the effects of solar activity on this particular observable have been widely investigated. One of the earliest attempts to establish such a correlation was made by Düll and Düll[42] in 1935 when they examined suicide records covering 5 years in comparison to solar activity over the same period. They reported that more suicides occur during periods of heightened solar activity. Although the work was initially criticized as statistically flawed, subsequent approaches to this question served to reinforce this early observation. A study of all suicides[9] in Australia from 1968 through 2002 involving nearly 70,000 individuals compared the dates of each death to solar-induced changes in the GMF. Looking only at events resulting in changes 100 nT and greater, sufficient correlation was found to conclude that "perturbations in ambient electromagnetic field activity impact behavior in a clinically meaningful manner." The identical conclusion was reached following a similar search[43] using suicide records in South Africa covering the years 1980–1992. One alternate view to these reports on GMF-related suicides suggests that it may be more correct to correlate the suicides with changes in solar radiance, but this possibility is not widely shared.

NEUROLOGICAL EFFECTS

Geomagnetic perturbations have been linked to a variety of neurological problems ranging from migraine headaches[44] to altered electroencephalography responses.[45,46] Persinger[47] found these effects so striking as to describe them as "geopsychopathology." Various studies have reported a connection between the rate of psychiatric hospital admissions and solar storm indices. Admissions at two hospitals totaling 28, 642 individuals were studied[48] for the years 1957 through 1961. The correlation ratios for both hospitals were not only statistically significant, but also very close, 0.26 and 0.27, with similar correlation levels were found by other observers. More recently, Kay[7] found a 26% increase in male hospital admissions due to bipolar disorder, which he attributed to disturbances in pineal circadian rhythms. A connection between solar activity and schizophrenia was noted by Kay,[49] as were apparent changes in psychiatric ward patients.[50]

DISCUSSION

It is clear that certain medical problems are exacerbated by solar activity. Many of the underlying factors are still murky, in part because different investigators often employ different approaches. Some use monthly averages of the geomagnetic indices, some use daily levels, and others probe times immediately before or immediately after the geomagnetic perturbation.

The simplest explanation as to how these problems are related to solar activity is that the biological interactions are enabled by the solar wind transporting charged particles ejected as plasma by the sun. If this wind reaches the earth's magnetosphere the geomagnetic field is temporarily disturbed resulting in changes ranging from 100s to 1000s of nT. A most important fact generally missing from discussions regarding this phenomenon is that this same range of short-term changes in magnetic field corresponds to those that have been independently determined to be biologically interactive in laboratory settings.

Although the empirical evidence for these geomagnetic effects has been well established, this research has suffered because it seems physically unreasonable to some that small transient changes in the background magnetic field could possibly have any effect on human health. A solution to this long-standing puzzling connection between solar activity and exacerbated human illness was suggested by Liboff[51] in 2013. This involves the fixed daily variation of ~50 nT in the GMF, more noticeable during periods when the sun is quiet (Figure 36.4).

This phenomenon is initiated in the upper levels of the atmosphere where the side of the earth illuminated by the sun undergoes a daily movement of electrons that in turn affects the magnetic field at the surface of the earth. Because this daily variation is always exactly in phase with the solar cycle, there is likely considerable evolutionary advantage in using this swing as a surrogate for the solar diurnal change. In effect, this magnetic swing enables living systems to utilize the 24 h biological clock even more completely than it does with its dependence on sunlight. Consider, for example, that this daily change in magnetic field occurs even on cloudy days. In other words, it is hypothesized that this small daily variation is an adjunct to the larger solar diurnal phasing of the biological clock.

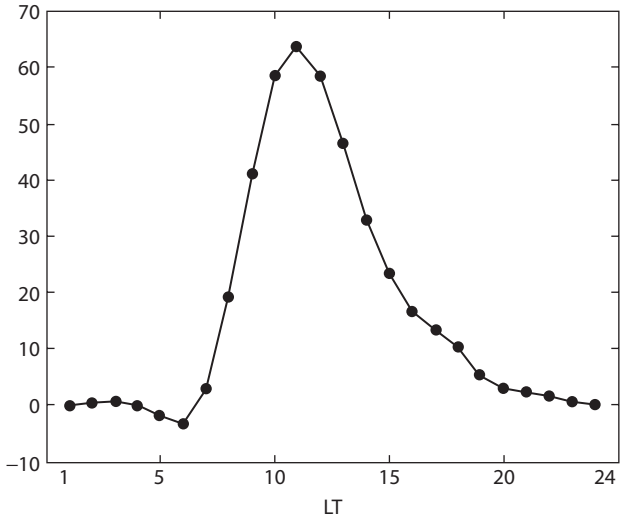

FIGURE 36.4 Change in the horizontal component of the geomagnetic field (GMF) measured in nT plotted against local time in hours (LT) clearly showing the 24 h variation.

In this scenario, chronodisruption is facilitated by the arrival of solar winds that generate magnetic fields that are not only greatly in excess of 50 nT, but are also out of phase with the solar-adjusted biological clock. In effect, the various physiological responses to geomagnetic activity are relegated to similar chronodisruptive problems[52–54] that are closely associated with jet-lag, night shift work, etc. Note that this does not actually explain the actual magnetic detection mechanism, only that we are somehow sensitive to very weak time-varying magnetic perturbations, a sensitivity that has its provenance in an ancient evolutionary adaptation.

Additional support for explaining solar-related changes in biological clock function is seen in reports[15] connecting coronary disease to changes in melatonin during geomagnetic disturbances. Close[55] also argues that the biological clock is the prime suspect in trying to understand why solar storms tend to exacerbate illness. He points to the very specific photosensitive protein cryptochrome that is widely believed to be the magnetic receptor utilized in animal navigation. He suggests that solar storm changes in magnetic field "lead to disorientation of hormonal systems…thus explaining the effects… on human health." However cryptochrome pigments are not only restricted to the retina but also appear to transmit information concerning the level of the magnetostatic field, not its time-varying characteristics.

One wonders about the reports claiming an association between cosmic radiation and the increased levels of illness that are associated with solar storms. It is certainly true that the inverse relation between cosmic ray intensity and the magnitude of the geomagnetic field can confound the already confusing connection between solar activity and illness. It is possible that some prefer to advance cosmic rays to changing magnetic fields as an explanation because of their reluctance to admit the likelihood of magnetic field responses at intensities well below 1 μT. This may also be the case because there is a convenient alternative, namely, knowing that cosmic rays can exhibit ionizing interactions with biological tissues. However, we note that this reluctance to link weak magnetic fields to biological response is mirrored in the similar resistance within the scientific community to acknowledge the great many laboratory reports indicating that such fields are indeed interactive.

Further, one also must consider that the cosmic ray energy distribution at the earth is only partly due to radiation emitted by the sun. Cosmic rays arriving at the earth originate not only from the sun but also from other areas of our galaxy as well as from extragalactic regions. The energies attached to the latter particles are fully ten orders of magnitude greater than those with a solar origin. The events attached to these very high energy cosmic rays are independent of solar storms, often worldwide, causing ionization cascades with still unknown biological consequences over an entire hemisphere. Whatever the relation between cosmic radiation and human wellbeing, it is simplistic to consider that it can be folded into the basic data package regarding solar-derived magnetic changes. Where necessary, cosmic ray dependences should only be treated as corrections to the human response to solar activity, not as alternative causes.

Saher[56] argues that "…epidemiological and genetic evidence indicates that the [solar] disruption of circadian rhythms might be directly linked to disease." However, there is reason to look beyond this simple linkage. Perturbations to the biological clock may be far more important to our wellbeing than previously believed, perhaps even extending to the question of electromagnetic hypersensitivity. Consider that the methods employed to find the connection between solar activity and illness focused solely on those at risk. In addition, the correlations, in order to relate the medical problems to a single day, made practical use of cohorts who presented their illnesses in sudden fashion. Thus, the associations that were established were only tested for illnesses that could be related to a single day or, at most, a few days of exposure. Myocardial infarctions are ideally suited for this approach, as are hospital admissions for sudden onsets.

However, other medical problems do not manifest themselves in such discrete fashion. Consider how difficult it would be to determine whether the onset of cancer or its sudden worsening is connected to solar activity. In the course of such a disease, which day could be chosen to see if it correlates with one that may be geomagnetically active? We can think of no reason to suggest that geomagnetic perturbations affect the enhancement of different diseases in different ways. We therefore conclude that solar-activated geomagnetic perturbations have the potential to increase the severity of all diseases, not merely those that have been successfully correlated. It may very well be the case that chronodisruption due to solar storms has a far greater effect on the expression of illness than currently believed.

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37 The Global Coherence Initiative
Investigating the Dynamic Relationship between People and Earth's Energetic Systems

Rollin McCraty and Annette Deyhle*

CONTENTS

INTRODUCTION

The convergence of several independent lines of evidence provides strong support for the existence of a global information field that connects all living systems and contributes to a type of global consciousness. Every cell in our body is bathed in an external and internal environment of fluctuating invisible magnetic forces that can affect virtually every cell and circuit in biological systems. Therefore, it should not be surprising that numerous physiological rhythms in humans and global collective behaviors are not only synchronized with solar and geomagnetic activity, but disruptions in these fields can create adverse effects on human health and behavior. The most likely mechanism for explaining how solar and geomagnetic influences affect human health and behavior are a coupling between the human nervous system and resonating geomagnetic frequencies called Schumann resonances, Alfven waves, and other very low frequency resonances that occur in the earth-ionosphere resonant cavity. It is well established that these resonant frequencies directly overlap with those of the human brain, and the cardiovascular and autonomic nervous systems. Evidence supporting the hypothesis that all living systems are interconnected via the earth's magnetic field, which can act as a carrier wave of biologically relevant and pattered information, is presented. In order to conduct this research, a global network of 12–14 ultrasensitive magnetic field detectors, specifically designed to measure the earth's magnetic resonances, are being installed strategically around the planet. An important goal of the project is to motivate as many people as possible to work together in a more coherent and collaborative manor to lift the collective human consciousness. If we are persuaded that not only external fields of solar and cosmic origins, but also human consciousness and emotion can affect the mental and emotional states of others (consciousness), it broadens our view of what interconnectedness means and how it can be intentionally utilized to shape the future of the world we live in. It implies that our attitudes, emotions, and intentions matter and that coherent, cooperative intent can have an important impact on global events and the quality of life on Earth.

THE GLOBAL COHERENCE INITIATIVE

The Global Coherence Initiative (GCI) was launched by the Institute of HeartMath, a nonprofit research and education organization, in 2008. It is a science-based, co-creative

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initiative that has the goal to unite millions of people globally in heart focused care and intention. Many people perceive that humanity has reached a critical juncture in the twenty-first century.[1] Worldwide, people are experiencing mounting concerns about climate change, natural disasters, extreme weather, terrorism, energy and water shortages, food and product safety, and economic instability. Also, there has been an increase in social unrest, revolutions, insurrections, and uprisings. The most prominent example of current times is the Arab Spring that started in December 2010. By December 2013, rulers have been forced from power in Tunisia, Egypt, Libya, and Yemen. Civil uprisings have erupted in Bahrain and Syria. In addition, Algeria, Iraq, Jordan, Kuwait, Morocco and Sudan have experienced major protests.[2] The path of transition to more stability globally is not certain, and, yet, there seems to be urgency for the old structures that do not serve humanity, all living beings and the environment to change. Hence, we are on the threshold of a new stage of social, spiritual, and cultural evolution.[3] We have the chance to evolve into a more interconnected, information-based social, economic, and cultural system that spans the entire planet.[1]

GCI employs several strategies to help increase personal, social, and global coherence. An internet-based network connects people globally, who want to participate in creating a shift in global consciousness. Currently, participants of 154 countries and over 100,000 people are involved in the initiative (www.glcoherence.org). Members of GCI receive regular updates that inform the participants where to direct their energetic contributions of heart-focused care and intention. GCI also helps to educate the global community by providing tools and technologies for increasing individual, social and global coherence. Furthermore, scientific data is gathered that allows monitoring of earth's electromagnetic fields with six state of the art magnetometers that are placed globally in suitable locations (www.glcoherence.org/gci-sensor-site-map.html). A total of 12–14 magnetometers is planned to complete the global network. Additionally, to further investigate the interactions between solar activity and the earth's geomagnetic field environment and human health and behaviors, scientific studies such as the Interconnectedness Study[4] and studies on heart rate variability (HRV) are being conducted.[5]

GCI Hypotheses

The following GCI Hypotheses guide the ongoing collaborative research:

1. Human and animal health, cognitive functions, emotions, and behavior are affected by planetary magnetic and energetic fields.
2. The earth's magnetic fields are carriers of biologically relevant information that connect all living systems.
3. Thus, we each affect the global information field.
4. Large numbers of people creating heart-centered states of care, love, and compassion will generate a more coherent field environment that can benefit others and help offset the current planetary wide discord and incoherence.

Embedded within the above hypotheses is a related hypothesis that human emotions and consciousness interact with and encode information in the geomagnetic field. Thereby, information is communicated nonlocally between people at a subconscious level, which in effect, links all living systems and influences collective consciousness. Thus, a feedback loop exists between all human beings and the earth's energetic systems. It is further proposed that when coherently aligned individuals are intentionally creating physiologically coherent waves, they more effectively resonate with and encode information in the planetary magnetic fields. These magnetic fields act as a carrier wave, thereby positively impacting all living systems contained within the field environment and the collective consciousness.[1]

Coherence

Coherence is a term that can be used in many different contexts and we will focus on the definitions relevant for this chapter. The Institute of HeartMath (IHM) has identified a psychophysiological state that is the underpinning of optimal function, termed heart coherence.[3,6–8] Practical techniques, tools, and technologies were developed by IHM that help the practitioner learn to get into and maintain a state of heart coherence. These tools and technologies help empower people to better manage stress, increase performance, and connect with a deeper self-awareness and intuitive intelligence.[6,9,10] Also, improvements in cognitive performance, focus and effectiveness, self-responsibility, and social cohesion were demonstrated.[3,6,11–14] At the individual level, a person's level of heart coherence can be assessed by monitoring the rhythmic patterns that are reflected in their HRV, the beat-to-beat changes in heart rate. Positive emotions, such as love, appreciation, and compassion, generate a heart rhythm pattern that is more ordered and coherent, whereas negative emotions, such as anxiety, anger, and fear, generate a disordered, incoherent heart rhythm pattern.[6] Ongoing feelings of impatience, frustration, irritation, worry or blame throw our inner rhythms out of sync and have a negative carryover effect on our hormonal and nervous systems.

Studies have found that the combination of emotional self-regulation techniques with heart rhythm coherence monitoring technology (emWave or Inner Balance) has proven to be highly successful for reducing stress, anxiety, anger, chronic pain, fatigue, and burnout, as well as many other stress-related conditions.[3,6,11–14] While there are many ways one can achieve a state of heart coherence, for example, deeper and slower rhythmic breathing and heart-focused meditation, studies have shown that emotional self-regulation and generating positive emotions, such as compassion, love, and appreciation, is an effective approach for a broad range of people.[7]

Global Coherence Monitoring System

GCI uses the Global Coherence Monitoring System to measure and explore fluctuations and resonances in the earth's magnetic field and in the earth-ionosphere resonant cavity

in order to conduct research on the mechanisms of how the earth's fields affect human mental and emotional processes, health, and collective behavior. In addition, we hope to investigate if changes in the earth's magnetic fields occur prior to natural catastrophes such as earthquakes, volcanic eruptions and human events, such as social unrest and terrorist attacks (see Figure 37.1).

This system is the first global network of GPS time stamped detectors designed to continuously measure magnetic signals that occur in the same range as human physiological frequencies, such as the brain and cardiovascular systems. Each site includes ultrasensitive magnetic field detectors specifically designed to measure the magnetic resonances in the earth–ionosphere cavity, resonances that are generated by the vibrations of the earth's geomagnetic field lines and ultralow frequencies that occur in the earth's magnetic field, all of which have been shown to impact human health, mental and emotional processes and behaviors. Each monitoring site detects the local alternating magnetic field strengths in three dimensions over a relatively wide frequency range (0.01–300 Hz), while maintaining a flat frequency response. There are several networks of ground based fluxgate magnetometers around the world, which measure the strength of the earth's magnetic field and geomagnetic disturbances (Kp), as well as several space weather satellites. The GCI monitoring system adds a missing component required to better understand how people and animals are affected by the rhythms and resonant frequencies in earth's magnetic fields as well as enabling us and other researchers to better understand the interconnections between solar and other external forces on the planetary magnetic field environment. Figure 37.2 show a photo of the monitoring site located in Boulder Creek, CA, USA. At of the beginning of 2014, five sites—one at the HeartMath Research Center in northern California, USA, one in the eastern province of Saudi Arabia, one in southern England, one in Canada, and one in New Zealand—are operational.

The data acquisition infrastructure captures, stamps with time and global positioning data, and transmits the data to a common server. In addition, each site has a random number generator (RNG) that is part of the Global Consciousness Project (GCP) network (described below). The monitoring system tracks changes in geomagnetic activity due to solar storms, changes in solar wind speed, disruption of Schumann resonances (SR) and, potentially, the signatures of major global events that have a strong emotional component. A growing body of data also suggests that changes occur in ionospheric activity prior to earthquake activity.[15,16] We make our data freely available to other research groups who may wish to explore how it may be utilized to predict earthquakes and other events. Thus, the network will provide a significant research tool to further understand how solar and geomagnetic disturbances and rhythms affect human health, emotions, behaviors and consciousness, and vice versa.

EARTH'S ENERGETIC SYSTEMS AND HUMAN HEALTH AND BEHAVIOR

Health Effects

Every cell in our bodies is bathed in an external and internal environment of fluctuating invisible magnetic forces.[17] Because fluctuations in magnetic fields can affect virtually every circuit in biological systems,[6,17,18] human physiological rhythms and global behaviors are not only synchronized with

FIGURE 37.1 Proposed locations for the global network of monitoring sites. These sites are specifically designed to measure the magnetic resonances in the earth–ionosphere cavity, resonances that are generated by the vibrations of the earth's geomagnetic field lines, and ultralow frequencies that occur in the earth's magnetic field.

FIGURE 37.2 The monitoring site at the HeartMath Research Center, located in Boulder Creek, CA, USA.

solar and geomagnetic activity, but disruptions in these fields can create adverse effects on human health and behavior.[19–21] The human body is designed to adapt to daily and seasonal climatic and geomagnetic variations. Environmental factors alter the hormone balance of the body, specifically the melatonin/serotonin balance, which affect many physiological functions, for example, blood pressure, breathing, immune system, reproductive, cardiac, and neurological processes.[22–28] Research by Burch et al.[24] and Rapoport et al.[29] provides evidence that the melatonin levels are reduced during increased solar and geomagnetic activity. Diseases such as cancer, neurological disease, acute heart disease and heart attacks are all related to melatonin levels that are too low, as is accelerated aging. In the daily cycle, the blood pressure, heart rate, neurological, cardiopulmonary, and reproductive functions are affected.[19,22,23,25,27,30–35] In addition, clinical measurements have identified significant changes in blood pressure, blood flow, aggregation and coagulation, cardiac arrhythmia, and heart rate variability during increased geomagnetic activity events, all of which are influenced by melatonin levels.[19,36] Electroencephalography (EEG) patterns, heart rate, blood pressure, and reaction times were measured in a group of people by Doronin et al.[19] The authors noted that the oscillations in the Kp index had identical periods in the monitored EEG alpha rhythm. This confirms that whole body changes occur in conjunction with geomagnetic activity by changing heart and brain patterns. Another study by Pobachenko et al.[37] monitored the Schumann resonances (SR) of the environment and the EEG in a frequency range between 6 and 16 Hz simultaneously. During a daily cycle, individuals studied showed variations in the EEG similar to changes in the SR. Hence, the biological EEG rhythm is characteristic of the daily rhythm of the SR.[37] The lowest frequency SR is approximately 7.83 hertz (Hz), with a daily variation of about ±0.5 Hz. The other frequencies are ~14, 20, 26, 33, 39, and 45 Hz. Figure 37.3 shows the frequencies of the SR, which are closely overlapping with alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–100 Hz) brain waves. Because the brain is a very sensitive electromagnetic organ, changes in geomagnetic activity and SR intensities appear to alter brain wave and neuro-hormone responses. Geomagnetic storms are also related to human health effects and death.[38,39] Altered EEG rhythms have been observed by Belov et al.;[30] while low frequency magnetic oscillations (around 3 Hz) had a sedative effect, stronger oscillations, around 10 Hz, stressed and stimulated people.[30]

Increased solar activity can disturb the biological rhythm of humans and exacerbate existing diseases. However, deviations are observed for some individuals, which can be due to the individual's adaptive ability. Increased solar activity and geomagnetic activity is also correlated to a significant increase in heart attacks and incidence of death, myocardial infarction incidence,[40] a 30%–80% increase in hospital admissions for cardiovascular disease, cardiovascular death, depression, mental disorders, psychiatric admission and suicide, homicides, and traffic accidents. [20,34,35,41–43] Birth rates were observed to drop and mortality to increase during increased solar and geomagnetic activity (GMA), and migraine attacks can be triggered.[44] Persinger and Halberg have independently shown that war and crimes were correlated to GMA.[45]

Scientific research has also reported that an increase in magnetic Pc frequencies (pulsations continuous) can affect the human cardiovascular system because Pc-1 frequencies are in a comparable range with those of the human cardiovascular system and rhythms.[46] A study carried out in India on animals and humans demonstrated that humans and animals can be affected by Pc frequencies.[47] The experiments showed changes in the electrophysiological, neurochemical,

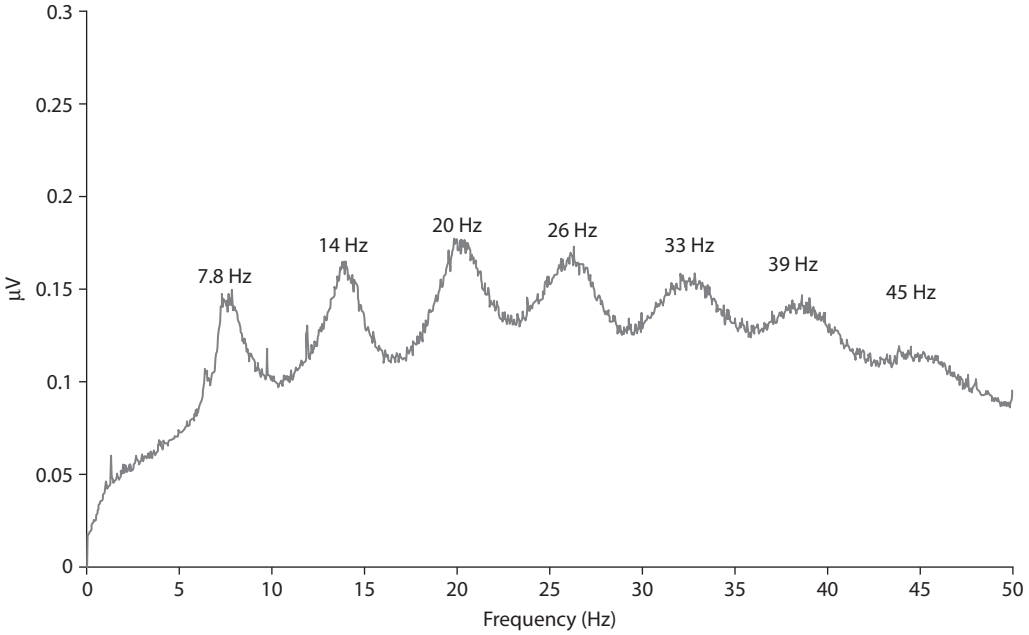


FIGURE 37.3 Schuman resonance data recorded from the GCI sensor site in Boulder Creek, CA, USA.

and biochemical parameters. The subjects experienced uneasiness, confusion, and restlessness and a lack of sense of wellbeing when subjected to the pulsating fields. Some complained of headaches.[47]

It is important to note that, of all the bodily systems studied thus far, changes in geomagnetic conditions appear to most strongly affect the rhythms of the heart and the brain.[17,28,35,37,38,48–52]

Historically, many cultures believed that their collective behavior could be influenced by the sun and other external cycles and influences. This belief has proven to be true. On a larger societal scale, increased violence, crime rate, social unrest, revolutions, and frequency of terrorist attacks have been linked to the solar cycle and the resulting disturbances in the geomagnetic field.[21,45,53–56] The first scientific evidence of this belief was provided by Alexander Tchijevsky, a Russian scientist who noticed that more severe battles during World War I occurred during peak sunspot periods.[56] He then conducted a thorough study of global human history dating back to 1749, which he then compared to the solar cycles over the same time period until 1926. Figure 37.4, reconstructed from Tchijevsky's original data, plots the number of significant human events compared to the solar cycle from 1749 to 1926.[56]

Energetic Influxes and Human Flourishing

Solar activity has not only has been associated with social unrest, it has also been related to the periods of greatest human flourishing with clear spurts in architecture, arts and science, and positive social change.[57] We can learn from past mistakes and consciously choose new ways of navigating energy influxes to create periods of human flourishing and humanitarian advances. When outdated structures that do not serve humanity collapse, an opportunity opens for them to be replaced with more suitable and sustainable models. Such positive change can affect the political, economic, medical, and educational systems, as well as relationships of individuals at work and home and in communities. At times of such pertinent energy influx, we have the greatest opportunity to instate positive change in our world. We can learn from past mistakes and consciously choose new ways of navigating energy influxes to create periods of human flourishing and advances.

It is well established that the earth and ionosphere generate a symphony of resonant frequencies that directly overlap with those of the human brain and cardiovascular system. The central hypothesis is that changes in these resonances can in turn influence the function of the human autonomic nervous system brain, and cardiovascular system. So, the question is, can we influence how those changes in solar and geomagnetic activity affect us positively or negatively? Until recently, it has not been possible to test this central hypothesis scientifically due to reliable, continuous measures of ionospheric and field line resonances being unavailable, in combination with the ability to monitor peoples' HRV as a measure of nervous system activity along with health and social indicators.

Interconnectedness Study

Previously, data and results from the Global Coherence Initiative Interconnectedness Study were presented in McCraty et al.[1] In 2010, 1643 GCI members from 51 countries completed a biweekly survey at random times 6 days each week over a 6-month period. The survey contained six valid scales: positive affect, wellbeing, anxiety, confusion, fatigue, and physical symptoms. The survey data were subjected to correlation analysis with a number of planetary and solar activity variables such as solar wind speed, magnetic

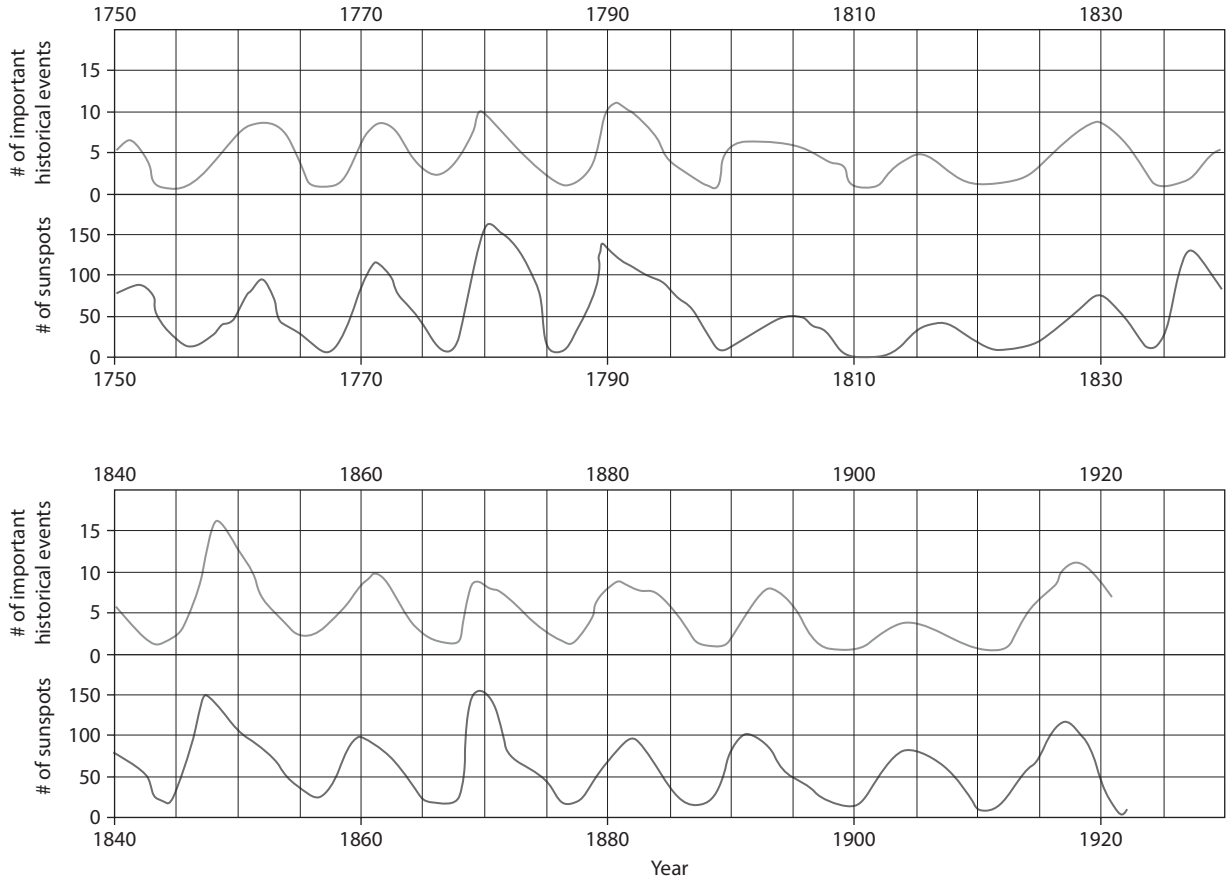


FIGURE 37.4 Tchijevsky's original data. The top line plots the yearly number of important political and social events, such as the start of a war, social revolutions, etc., while the bottom line plots the solar activity as indicated by the number of sunspots from 1749 to 1922. The histories of 72 countries were compiled, and it was found that 80% of the most significant events occurred during the solar maximum, which correlates with highest periods of geomagnetic activity.

field and plasma data, measures of energetic protons, solar flux, and geomagnetic activity indices. When solar wind speed, Kp, Ap (Kp and Ap magnetic indices were designed to describe variations in the geomagnetic field), and polar cap activity increased, positive affect among the participants decreased. Wellbeing scores were negatively correlated with solar wind speed, Kp-index, Ap-index, and polar cap magnetic activity. Thus, when solar wind speed increased and the geomagnetic field was disturbed, the levels of fatigue, anxiety, and mental confusion increased. The study also uncovered some unexpected findings. For example, the solar radio flux index was positively correlated with reduced fatigue and improved positive affect, indicating that there are mechanisms that improve human wellbeing that are not yet fully understood. Clearly additional research needs to be conducted in order to understand the effects of the various variables and the time sequence of their effects.[1]

Examples of Magnetometer Data

Data collected by our magnetometers in different locations is providing some new insights in to globally correlated activity and significant local differences. Figure 37.5 shows an example of Pc-3 activity simultaneously recorded at the monitoring sites in Boulder Creek, CA, USA, Alberta, Canada, and New Zealand. The data from the North American sites closely overlaps, while the data from New Zealand has a different rhythm.

Another example is shown in Figure 37.6 where Pc-1 activity detected at the California and Canada sites is displayed. While the Pc-1 data in Canada displays a greater amplitude, and while most of the rhythm is synchronized, there are periods where it is ~180° out of phase. Further data processing is currently underway which is examining other parameters in more depth, such as longitudinal, latitudinal parameters, time of the day, and other solar and geomagnetic parameters and their implications on human health indicators.

HRV Studies

Among physical environmental variables affecting biological processes and human health, the natural variation in the geomagnetic field in and around the earth has been reportedly involved in relation to several human cardiovascular variables. These include blood pressure,[58] heart rate (HR), and HRV.[59,60] Although there is mounting evidence for such

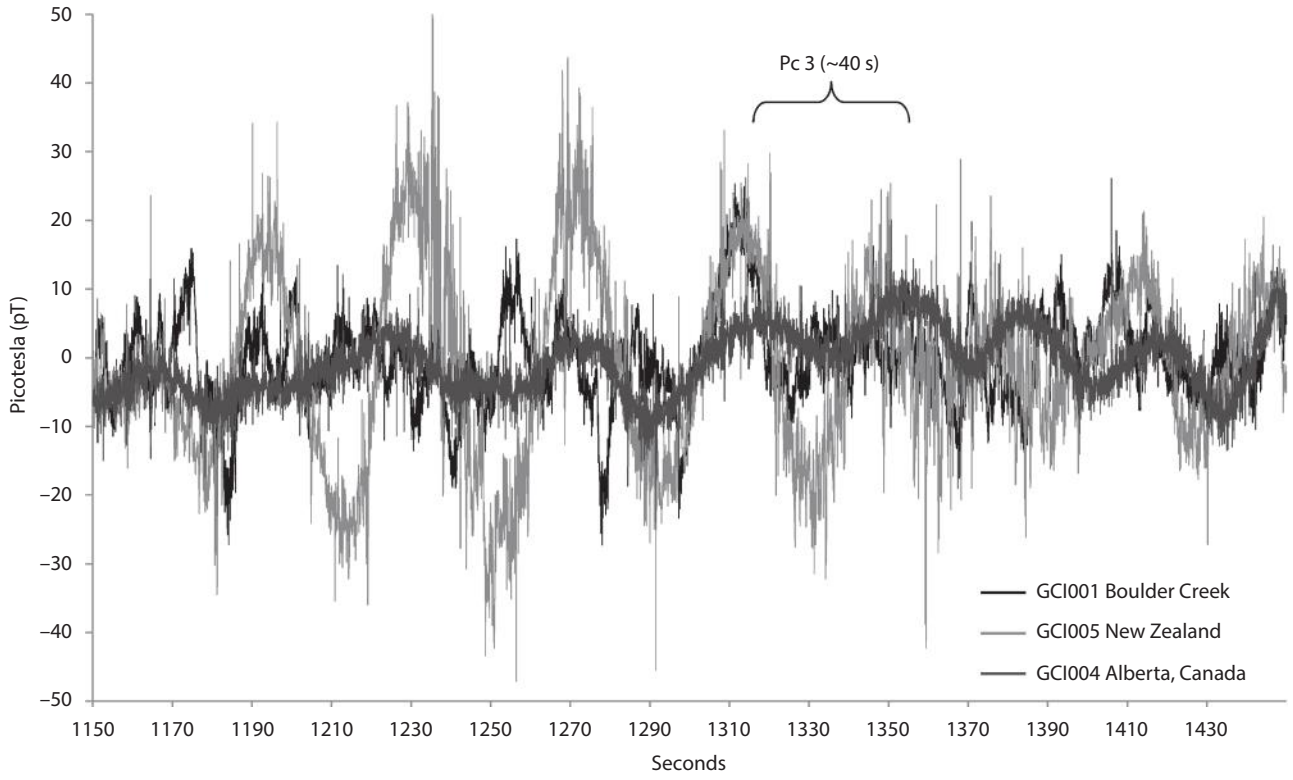


FIGURE 37.5 Simultaneously recorded data from Boulder Creek, CA, USA, Alberta, Canada, and New Zealand sites. This figure shows an example of the time varying magnetic field in the Pc3 frequency (~40 s rhythm) range that is in the same range of the very low frequency band of heart rate variability. The lower amplitude data (black) is the site in Canada, and the high amplitude data (gray) is from the New Zealand site. The data from the California site (dark gray) is harder to see, as it is mostly the same frequency and amplitude as the data from the Canadian site. While the data from the North America sites closely overlaps, the data from New Zealand has a much higher amplitude and moves in and out of phase with data from the other locations.

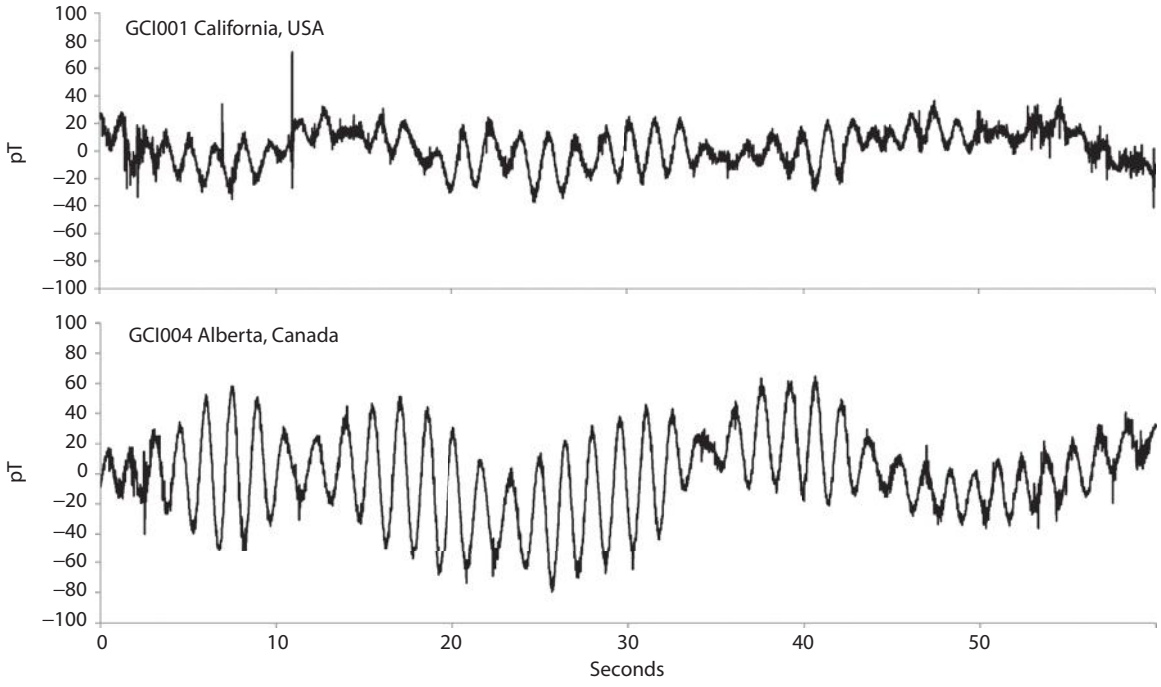


FIGURE 37.6 Example of Pc-1 data recorded from the Californian and Canadian sites. The Pc-1 activity (~1.25 s rhythm) recorded at the site in Canada has a greater amplitude, and, while most of the data is synchronized, there are periods where it is ~180° out of phase.

effects, they are far from being fully understood. Several studies have found significant associations between magnetic storms and decreased HRV, indicating a possible mechanism linking geomagnetic activity with increased incidents of coronary disease and myocardial infarction.[34,39,40] One study that analyzed week long recordings found a 25% reduction in the very low frequency (VLF) rhythm during magnetically disturbed days as compared to quite days. The low frequency (LF) rhythm was also significantly reduced but the high frequency (HF) rhythms were not.[61,62]

In order to further investigate the potential correlations between solar and magnetic factors and HRV, we undertook a collaborative study with Dr. Abdullah Alabdulgader, director of Prince Sultan Cardiac Center in Al Ahsa, Saudi Arabia, spanning a 5-month period. A total of 960 24 h HRV recordings were obtained from a group of 16 women (mean age 31, 24–49). HRV data was collected for 24 h a day, 3 consecutive days each week over a 5-month period with Bodyguard HRV recorders between March and August of 2012. The HRV measures assessed were the inter-beat-interval (IBI), SDNN, RMSSD, total power, VLF, LF, and HF power, and the LF/HF ratio. The solar activity and magnetic variables were solar wind speed, Kp and Ap index, PC(N), sunspot number, solar radio flux (f10.7), cosmic rays, Schumann resonance integral (area under the curve around 7.8 Hz), and the mean and standard deviation (SD) of the time varying magnetic field data collected at the GCI sites located in Boulder Creek, CA, USA (GCI 1) and Saudi Arabia (GCI 2). The mean and SD were computed hourly. The mean field variation reflects ultra-low frequency changes and SD which is highly correlated with total spectral power, reflects overall variance in the field. Figure 37.7 shows an example of the mean and SD of the magnetic field variation. Note the large increase in the SD that occurred on July 14 that resulted from a coronal mass ejection that hit the earth's magnetic field at approximately 1800 UT that day.

Circadian effects were removed from both environmental and HRV variables. For each of the 16 study participants, a correlation matrix was calculated between each environmental and HRV variable. Figure 37.8 shows the results of the correlation analysis. Overall, the study strongly confirms that autonomic nervous system activity, as reflected by HRV measures, is affected by solar and geomagnetic influences. All of the HRV measures, with the exception of IBIs, were negatively correlated with solar wind speed, and the LF and HF power was also negatively correlated with the magnetic field mean data from the local site in Saudi Arabia, but not the site in California, suggesting that local measurements are important. Surprisingly, there were a number of positive correlations. The f10.7 was correlated with increased HRV in all measures with the exception of the SD of the HRV and IBIs. The SD of the magnetic field variation from both the Saudi Arabian and Californian sites was positively correlated with RMSSD and HF power, both of which reflect parasympathetic activity, and Schumann resonance power was positively correlated with the IBIs.

Although there were a number of global correlations, at the individual level, the HRV responses varied and in some cases different individuals showed different responses to the same environmental variable.

When looking at the data from both the Interconnectedness Study and the HRV data, it is clear that when the earth's magnetic field was calmer or the solar radio flux was increased that the study participants felt better, were more mentally and emotionally stable and had higher levels of HRV. Conversely, when the magnetic field was disturbed, HRV was lower and participants' emotional well-being and mental clarity were adversely affected.

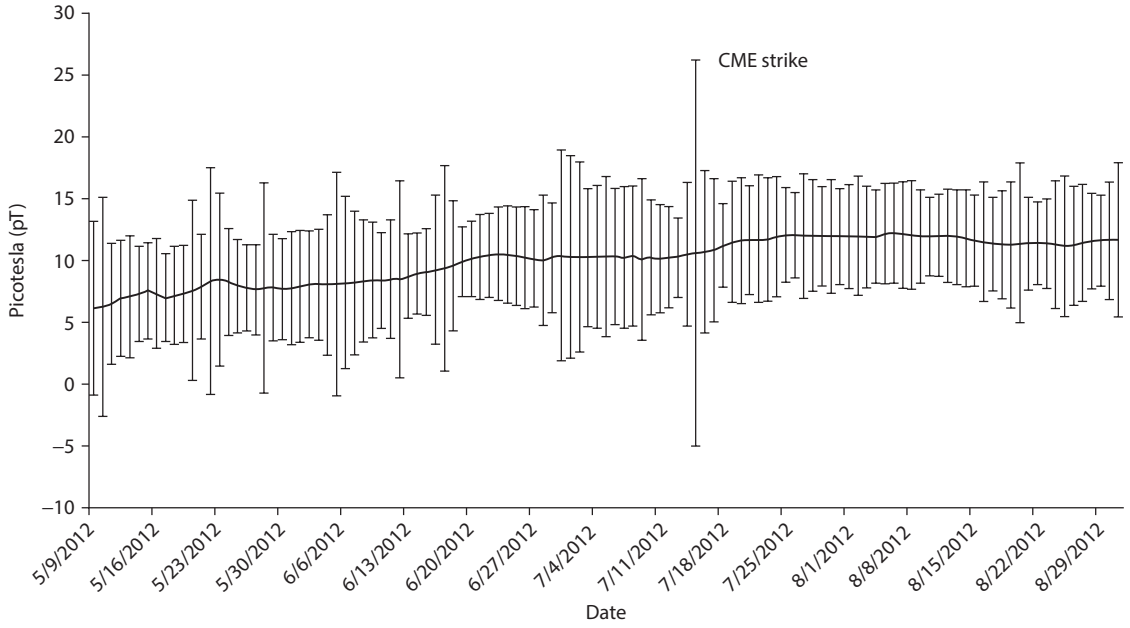
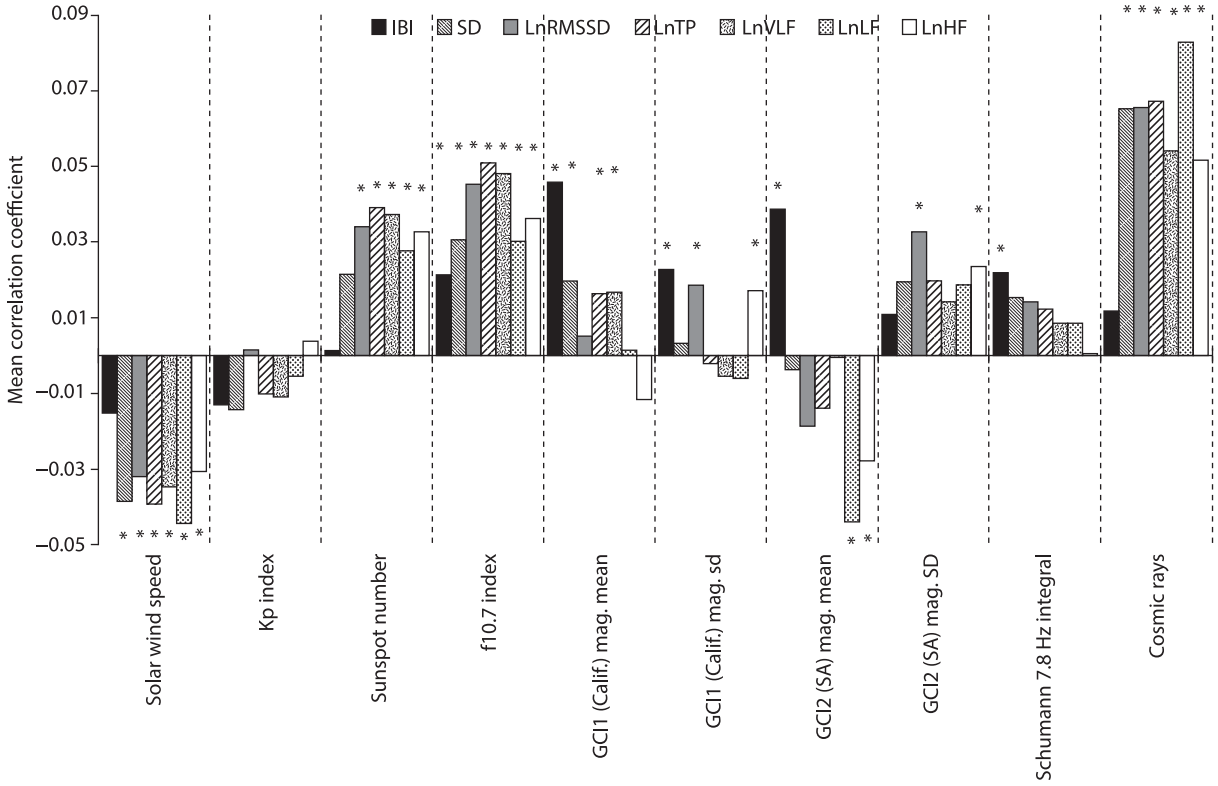


FIGURE 37.7 An example of the mean and standard deviation of the magnetic field data recorded from the monitoring site in Saudi Arabia.



*$p < 0.05$ (corrected for multiple comparisons)

FIGURE 37.8 The correlations between the heart rate variability data (inter-beat-interval, standard deviation [SD] very low frequency, low frequency, and high frequency power) and environmental data (solar wind speed, Kp index, sunspot numbers, f10.7 index, magnetometer means and SD) from the monitoring sites in California (GCI 1) and Saudi Arabia (GCI 2), Schumann resonance power at 7.8 Hz, and cosmic rays).

Figure 37.9 shows an example of healthy participants' HRV-HF power plotted along with the total magnetic power spectrum from the magnetometer site in Boulder Creek, CA, USA, over a 30-day period. This data is from a study of ten participants located in northern California whose HRV was continuously monitored over a 30-day period. The magnetic field data in the plot, which is inversely correlated, has been inverted in the plot to help illustrate the visual correlation, which can be clearly seen in the graph.

INTERCONNECTIVITY OF ALL LIVING SYSTEMS THROUGH THE EARTH'S MAGNETIC FIELD

Magnetic Fields Carry Biologically Relevant Information

The evidence that human health and behavior are globally influenced by solar and geomagnetic activity is relatively strong and convincing. We have also shown in our laboratory that the heart's electromagnetic field can be detected by nearby animals or the nervous systems of other people[63] (see also Energetic Heart chapter in this book).

One of the GCI hypotheses is that the earth's magnetic fields are carriers of biologically relevant information that connects all living systems. Thus, we each affect the global information field.

There is experimental evidence that human bioemotional energy can have a subtle but significant (scientifically measurable) nonlocal effect on people, events, and organic matter.[1] It is becoming clear that a bioelectromagnetic field such as the ones radiated by each human heart and brain can affect other individuals and the "global information field environment." For example, research conducted in our laboratory has confirmed the hypothesis that when an individual is in a state of heart coherence, the heart radiates a more coherent electromagnetic signal into the environment and that, when one is in a coherent state, that we are more sensitive to detecting the information in the fields radiated by others.[63] Of all the organs, the heart generates the largest rhythmic electromagnetic field, one that is approximately 100 times stronger than that produced by the brain. This field can be detected several feet from the body with sensitive magnetometers.[64] This magnetic field provides a plausible mechanism for how we can "feel" or sense another person's presence and emotional state independent of body language or other factors. We have also found that there is a direct relationship between the heart rhythm patterns and the spectral information encoded in the frequency spectra of the magnetic field radiated by the

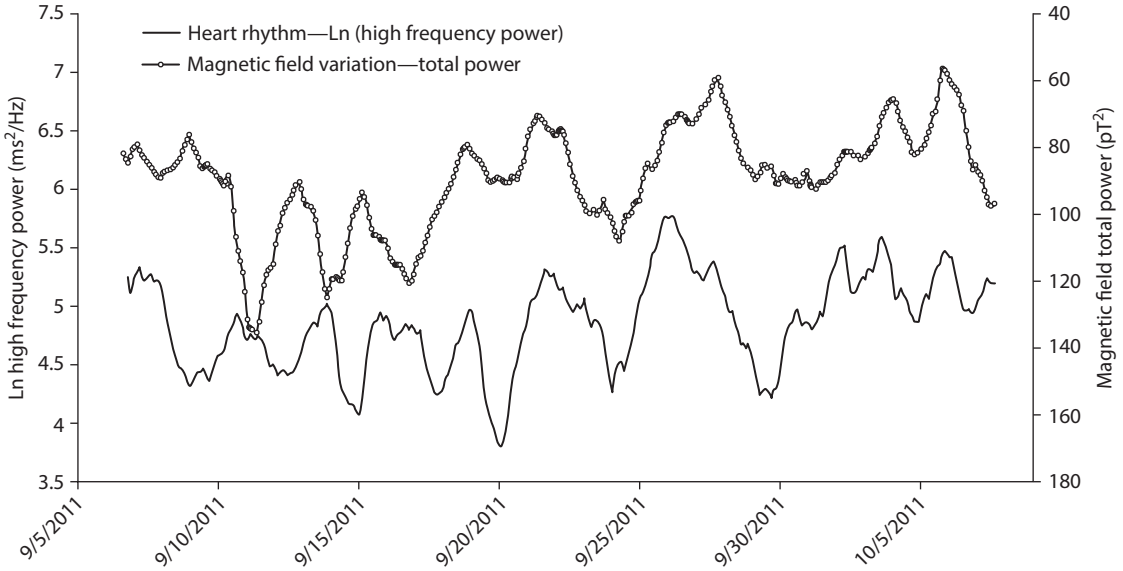


FIGURE 37.9 Example of one participant's high frequency power derived from their heart rate variability and the total power of the time varying magnetic field at the site California over a 30-day period.

heart. Thus, information about a person's emotional state is encoded in the heart's magnetic field, which is communicated throughout the body and into the external environment.[1]

In a study on interpersonal effects of nonverbal compassionate communication, measuring psychophysiologic effects, Kemper and Shaltout found significant changes in the receiver's autonomic nervous system.[65] A growing body of evidence suggests that an energetic field is formed among individuals in groups through which communication among all the group members occurs simultaneously. In other words, there is a literal "group field" that connects all the members.[3]

Morris[66] studied the effect of heart coherence in a group setting where people trained in maintaining states of heart coherence for several minutes could facilitate coherence in untrained participants. The results showed that the coherence of untrained participants was indeed facilitated by other participants who were in a coherent state. Support for the hypothesis that magnetic fields are carriers of biologically relevant information has been provided by a recent study conducted by Montagnier et al.[67] They discovered that epigenetic information related to DNA could be detected as electromagnetic signals in a highly diluted solution and that this information can be transferred to and imprinted in pure water that has never been exposed to DNA. Furthermore, this information can instruct the recreation of DNA when the appropriate basic constituents of DNA are present and extremely low electromagnetic frequency fields of 7.8 Hz are present. They also showed that the presence of the magnetic field was needed for the information transfer to occur.[67] The authors also state that such a very low electromagnetic frequency field that stimulates DNA information transfer could come from natural sources, such as Schuman resonances, which start at 7.83 Hz.[67] Also, Michael Persinger, a well-known neuroscientist, has conducted numerous studies examining the effects of magnetic fields with the same magnitude as the geomagnetic field on brain functions and information transfer.[38,50] Not only has he shown that applying external fields similar to the SRs can induce altered states of consciousness, he has also suggested in a detailed theory that the space occupied by the geomagnetic field can store information related to brain activity and that this information can be accessed by the human brain.[68] Persinger also suggests that the earth's magnetic field can act as a carrier of information between individuals and that information, rather than the signal intensity, is important for interaction with neural networks.[69] The above findings clearly support part of our hypothesis that the earth's magnetic fields are carriers of biologically relevant information.

We are further suggesting that as humans have brain and heart frequencies overlapping the earth's magnetic field resonances, they are not only receivers of biologically relevant information, but they can also couple with the earth's magnetic fields and thus feed information into the global field environment.

Interconnection between the Human Energy Field, Collective Human Emotions and the Planetary Energy Field

Our fourth hypothesis states*:*

> Large numbers of people creating heart-centered states of care, love, and compassion will generate a more coherent field environment that can benefit others and help offset the current planetary-wide discord and incoherence.

There is also a substantial body of evidence indicating interactions between human emotions and a global field when large numbers of people have similar emotional responses to events or organized global peace meditations.[70–72] For

example, quantum physicist John Hagelin has conducted research on the "Power of the Collective" and concluded that "since meditation provides an effective, scientifically proven way to dissolve individual stress and if society is composed of individuals, then it seems like common sense to use meditation to similarly diffuse societal stress."[71] A study conducted in 1993 in Washington, DC, USA showed a 25% drop in crime rate with 2500 meditators mediated over specific periods of time,[72] which means that a relatively small group of a few thousand was able to influence a much larger group—a million and a half. The question was then posed that if crime rates could be decreased, could a group of meditators also influence social conflicts and wars? A similar experiment was done during the peak of the Israel–Lebanon war in the 1980s. Drs. Charles Alexander and John Davies at Harvard University organized groups of experienced meditators in Jerusalem, Yugoslavia, and the United States to mediate and focus attention on the area at various intervals over a 27-month period. After controlling statistically for weather changes, Lebanese, Muslim, Christian, and Jewish holidays, police activity, fluctuation in group sizes and other variant influences during the course of the study, the levels of violence in Lebanon decreased between 40% and 80% each time a meditating group was in place, with the largest reductions occurring when the numbers of meditators were largest. During these periods, the average number of people killed during the war per day dropped from 12 to three, a decrease of more than 70%. War-related injuries fell by 68% and the intensity level of conflict decreased by 48%.[70,73]

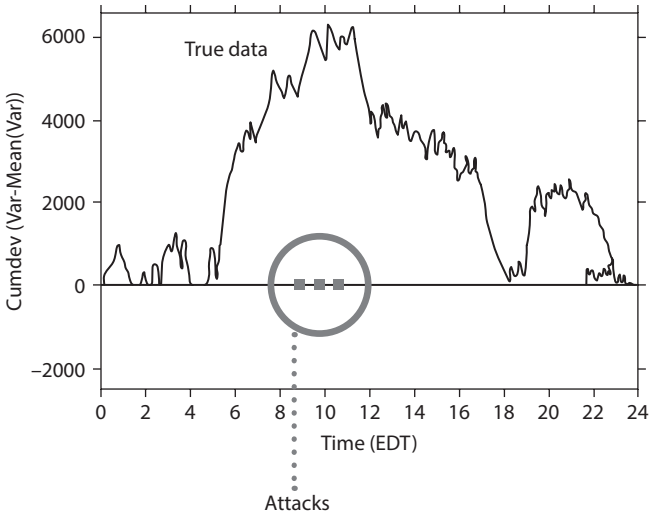


FIGURE 37.10 Evidence of collective intuition: correlated random number generator data from the Global Consciousness Project network before, during and after the September 11, 2001, terrorist attacks on the World Trade Center.

Interconnection between Collective Human Emotions, Random Number Generators and the Geomagnetic Field

Further evidence that there is an interconnection between collective human emotionality and global events has been provided by Professor Roger Nelson and chief scientist of the GCP. GCP maintains a worldwide network of random number generators (RNGs) and results suggest that human emotionality affects the randomness of these electronic devices in a globally correlated manner. Nelson, states:

> The GCP is a long-term experiment that asks fundamental questions about human consciousness. It provides evidence for effects of synchronized collective attention—operationally defined global consciousness—on a world-spanning network of physical devices. There are multiple indicators of anomalous data structure which are correlated specifically with moments of importance to humans. The findings suggest that some aspect of consciousness may directly create effects in the material world. This is a provocative notion, but it is the most viable of several alternative explanations.[74]

Nelson also found clear evidence that larger events defined by the number of people engaged and their level of "importance" produces larger effects on the global network. An interesting finding is a significant correlation between global events that elicit a high level of emotionality from a large part of the world's population and periods of nonrandom order generated by the RNGs.[75] For example, multiple independent analyses of the network during the terrorist attacks that took place in the United States on the morning of September 11, 2001 (Figure 37.10), correlate with a large and significant shift in the output of the global network of RNGs.[76]

Another potential indicator of human emotional energy interacting with earth's magnetic field was provided from measures of the earth's geomagnetic field during the September 11, 2001, terrorist attacks.

Figure 37.11 shows data recorded from two separate space weather satellites in geosynchronous orbit in the days before and after the attacks. The data from the magnetometers on these two satellites, which are positioned over the east and west coasts of the United States, reveal that a large shift occurred in the earth's geomagnetic field at the same time as the attacks. Note the difference in the fields in the days before and after the attacks. The incoherence and discord in the fields during the days after the attacks may reflect the mass emotional turmoil that occurred as news of the attacks spread around the globe. The same patterns were also observed in ground based magnetometers. Although the data shown in Figure 37.11 does not prove that human emotion modulated the earth's geomagnetic field, combined with the GCP and other data, they support the overarching hypothesis that the earth's energetic systems are coupled with and exchange information in a bidirectional manor with the collective emotional energy of humanity.

Although the mechanisms for how human emotions create more coherence in the randomness of this global network are not yet understood, the data, however, clearly show that they do have such affects and data now have an odds against chance ratio of over a billion to one.[76]

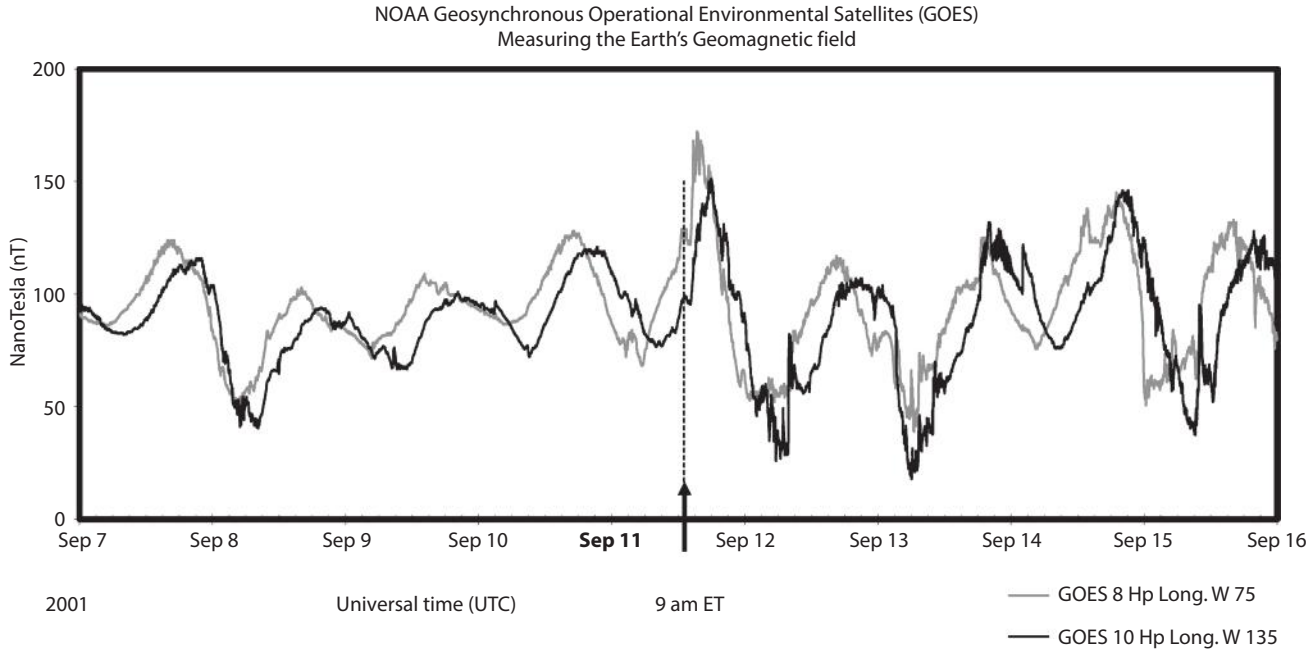


FIGURE 37.11 The data recorded from the Geostationary Operational Environmental Satellites 8 and 10, which are in geosynchronous orbit over the east and west coasts of the United States in the days before, during, and after the September 11, 2001, terrorist attacks.

When an event is characterized by deep and widespread compassion, the GCP effects are stronger,[74] which could be explained because compassion is related to interconnection and positive emotional engagement. When we experience true feelings of compassion, we tend to shift into a more coherent physiological state[6] and are thus radiating more coherent magnetic waves into the environment.[63] Compassion is an emotional state that brings us together and makes us coherent; we invest a small part of our individual being to connect with others and, as the GCP data indicate, with the global field environment. A study that examined GCP data between 1998 and 2008, matched satellite-based interplanetary magnetic field (IMF) polarity with GCP defined world events such as meditations, celebrations, natural catastrophes, or violence. Results suggested that RNG deviations may depend on a positive IMF polarity coinciding with emotionally significant conditions and/or entropy changes.[77]

The GCP group has investigated a number of theoretical models that could potentially explain the global effect they are detecting with the network. As summary, an excerpt of their analysis:

> Finally, a non-linear dynamic field model proposes that individual minds are mutually interactive, and that the interactions are responsible for an emergent field which depends on individual consciousness but is not reducible to it. The model implies that the dynamic and interactive qualities of consciousness also involve subtle interactions with the physical world and that these are responsible for certain anomalous phenomena such as are found in the GCP experiment.[74] (p. 12)

One of our goals is to test the hypothesis that large numbers of people in a heart-coherent state and holding a shared intention can encode information on the earth's energetic and geomagnetic fields that act as carrier waves of this physiologically patterned and relevant information. If living systems are indeed interconnected and communicate with each other via such biological and electromagnetic fields, it stands to reason that humans can work together in a cocreative relationship to consciously increase the coherence in the global field environment which in turn distributes this information to all living systems within the field. Of course, the idea is not new that shared intentions can influence others at a distance. Such ideas have been the subject of numerous studies that have looked at the effects of prayer, meditations, and groups sending intentions in various experimental contexts.[78–80] How can we have such an influence on each other at a distance? There are no clear answers yet, however, we hypothesize that there is a unified field that interacts with and affects consciousness. We also suggest that individually generated coherent waves are more likely to be coupled to the larger collective field environment than when in states of incoherence. The GCI theory of change states that as enough individuals increase their personal coherence, it can lead to increased social coherence (family, teams, organizations), and as increasing numbers of social units (families, schools, communities, etc.) become more coherently aligned, it can in turn lead to increased global coherence, all of which is facilitated through self-reinforcing feedback loops between humanity and the global field environment (Figure 37.12).

As more and more people increase their personal coherence, it strengthens and stabilizes the standing waves and coherent information transferred to the planetary magnetic field. Once a coherent standing wave is established, reinforced, and amplified through collective coherent intention,

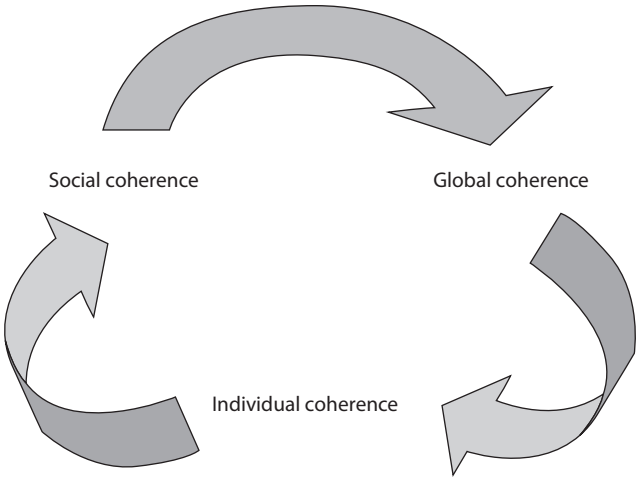


FIGURE 37.12 Global Coherence Initiative theory of change.

it in turn facilitates the amplification of the collective heart, mind and consciousness, making it easier for more and more people to increase their coherence and lift their consciousness. Every individual contributes to the global field environment and each person's attitudes, intentions and emotional experiences count. This is empowering for many individuals who often feel overwhelmed by the current negative predictions and conflicts on the planet. They come to realize that their actions can make a difference and that by increasing their own coherence, they can become "Coherence Builders" and make a contribution that can help facilitate the shift that many now perceive to be occurring. The personal benefits of better emotional self-regulation, enhanced wellbeing, more self-responsibility, better health, and improved relationships people experience are powerful motivators that reinforce the process for the individual. As more and more individuals become increasingly self-regulated and grow in conscious awareness, the increased individual coherence in turn increases social coherence, which is reflected in increased cooperation and effective cocreative initiatives for the benefit of society and the planet. It is our perspective that a shift in consciousness is necessary in order for a significant shift to occur that enables new levels of cooperation and collaboration in innovative problem solving and intuitive discernment for addressing our social, environmental and economic problems. In time, global coherence will be indicated by more communities, states, and countries adopting a more coherent planetary view.[1]

CONCLUSIONS

An ongoing goal of GCI is to further the study of interconnectedness between humanity and the earth's energetic systems. In order to conduct research on the mechanisms of how the earth's fields affect human mental and emotional processes, health outcomes, and collective human behavior and explore how collective human emotions and intentions may be reflected in the earth's electromagnetic and energetic fields, a global network of ultrasensitive magnetic field detectors, specifically designed to measure the magnetic resonances in the earth/ionosphere cavity and resonances and earth's geomagnetic field lines resonances, are being installed at strategic locations around the earth. We are hopeful that our efforts will facilitate a deeper understanding of the mechanisms by which human health and behaviors are modulated by the earth's geomagnetic fields and further clarify what aspects of the field environment mediate the varied and specific effects.

Data from the Interconnectedness Study and the HRV studies are yielding promising results and add to the body of evidence that humans are affected by planetary energetic fields. GCI hypothesizes that human emotions and consciousness interact with and encode information in planetary energetic fields, including the geomagnetic field, thereby communicating information nonlocally between people at a subconscious level, which, in effect, links all living systems and gives rise to a form of collective consciousness. Thus, a feedback loop exists among all human beings and the earth's energetic systems. Our basic hypothesis is that when enough individuals and social groups increase their coherence and utilize that increased coherence to intentionally create a more coherent standing reference wave in the global field, it will help lift the global consciousness. This can be achieved when an increasing ratio of people move towards more balanced and self-regulated emotions and responses. This, in turn, can help facilitate cooperation and collaboration in innovative problem solving and intuitive discernment for addressing society's significant social, environmental, and economic problems. In time, as more individuals stabilize the global field and families, workplaces, and communities move to increased social coherence, it will lead to increased global coherence. This will be indicated by countries adopting a more coherent planetary view so that social and economic oppression, warfare, cultural intolerance, crime, and disregard for the environment can be addressed meaningfully and successfully.

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38 Biophysics of Earthing (Grounding) the Human Body

James L. Oschman, Gaétan Chevalier, and A. Clinton Ober*

CONTENTS

INTRODUCTION

In medicine, the path to new discovery is often difficult and challenging. When a valuable discovery is made, it can be even more difficult to get it to the people who need it. This is true even for discoveries that could resolve costly and debilitating disorders that affect many people and ruin many national economies, and that, therefore, deserve the highest priority. A discovery of this kind is the topic of this chapter.

In a classic letter to *Science* entitled *Dionysians and Apolionians*, Albert Szent-Györgyi stated it this way:

> Wilhelm Ostwald[1] divided scientists into the classical and the romantic. One could call them also systematic and intuitive. John R. Platt calls them Apollonian and Dionysian. These classifications reflect extremes of two different attitudes of the mind that can be found equally in art, painting, sculpture, music, or dance. One could probably discover them in other alleys of life. In science the Apollonian tends to develop established lines to perfection, while the Dionysian rather relies on intuition and is more likely to open new, unexpected paths for research. Nobody knows what "intuition" really is. My guess is that it is a sort of subconscious reasoning, only the end result of which becomes conscious.
>
> These are not merely academic problems. They have most important corollaries and consequences. The future of mankind depends on the progress of science, and the progress of science depends on the support it can find. Support mostly takes the form of grants, and the present methods of distributing grants unduly favor the Apollonian. Applying for a grant begins with writing a project. The Apollonian clearly sees the future lines of his research and has no difficulty writing a clear project. Not so the Dionysian, who knows only the direction in which he wants to go out into the unknown; he has no idea what he is going to find there and how he is going to find it.[2]

The book you are holding in your hands can be extremely valuable to any scientist or therapist entering unknown territory. Here you will find scientific concepts that are mostly outside of the mainstream, therefore, they can act as fertile new ground for contemplation, synthesis, and new discovery. The human body is always unknown territory, for when we think we understand one aspect, several other mysteries pop up.

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INFLAMMATION

We now know that many, if not all, of the most common, debilitating, and costly health disorders and diseases are partly or entirely energetic in nature, and are therefore, difficult to prevent, treat, or even comprehend when energy is left out of the discussion. Moreover, cures for the most serious health problems will remain elusive until medical researchers consider energetics. This does not mean textbook biochemical or molecular energetics, it means the energetics as described by the steadily maturing sciences of physics, biophysics, and quantum physics. This fact is documented by one of the most significant advances in biomedicine that has taken place in recent times. Specifically, the study of inflammation has become one of the most active areas of biomedical research, with over 400,000 peer reviewed studies completed during the period 1967–2013 (see Figure 38.1).[3] Inflammation is incomprehensible without an energetic perspective.

Chronic disease is the number one cause of death and disability worldwide. Treating patients with chronic diseases accounts for 75% of U.S. health care spending, which surpassed $2.3 trillion in 2008. The most common and costly chronic diseases are heart disease, cancer, stroke, chronic obstructive pulmonary disease, osteoporosis, and diabetes.[4] Other significant inflammatory conditions include Alzheimer disease, asthma, bowel disorders, cirrhosis of the liver, cystic fibrosis, lupus, meningitis, multiple sclerosis, psoriasis, and arthritis. Tragically, many patients suffer from several of these problems simultaneously.

The public has been informed about the inflammation connection in articles published in major news sources (e.g., The Secret Killer, *Time* Magazine, 2004).[5] While abundant research has documented a relationship between chronic inflammation and virtually all chronic diseases, including all of the diseases of aging, profoundly important questions are unanswered. In fact, they are rarely discussed:

- What causes chronic inflammation?
- Precisely why is inflammation associated with so many different chronic diseases, just exactly what is the connection?
- Why have these chronic diseases reached epidemic proportions in recent times?
- What can an individual do about it?
- When an energetic approach is effective for a chronic issue, what is this telling us about human biology that could help us stay healthy and recover from disease should it arise?

This chapter relates to all of these questions. It concerns a natural approach to inflammation and chronic disease that is "of the earth" and that has been recognized since ancient times. Unfortunately, modern biomedicine rarely looks at

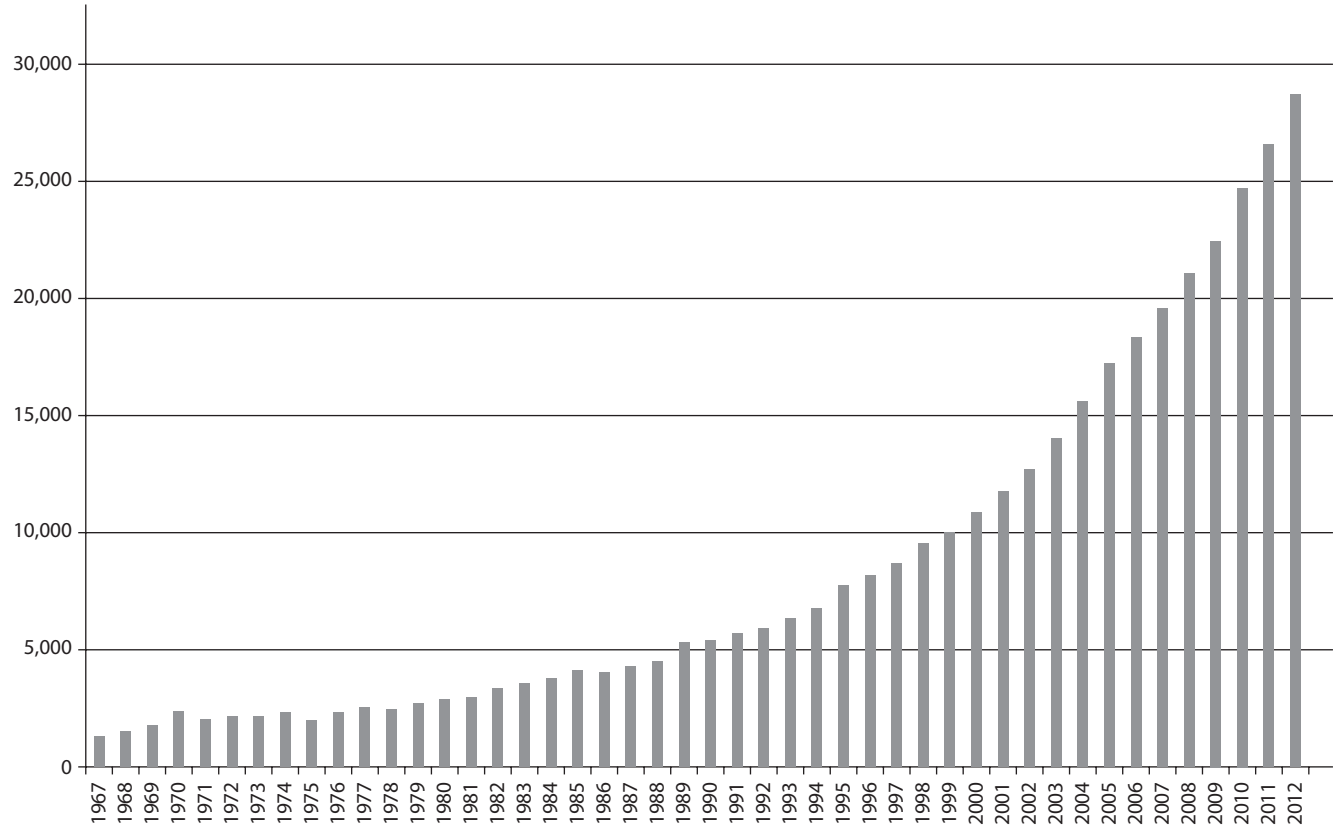

FIGURE 38.1 Growth in number of peer reviewed studies of inflammation, 1967–2012, data from the National Library of Medicine database, PubMed (as of January 20, 2013).

traditional wisdom, focusing instead on the latest pharmacology and high-tech devices. We begin with the benefits of direct physical contact with the surface of the earth, as with bare feet or hands. This is termed "grounding" or "Earthing." In the process of studying why Earthing is so beneficial, scientists have uncovered some of the missing pieces of the inflammatory response, developed new information on how the immune system works, and described natural methods anyone can use to support their immune system.

BAREFOOT

People who work barefoot in the garden or walk barefoot along the beach often experience a special sense of well-being, just from being in direct physical contact with the earth. Some teachers of ancient practices such as Yoga and *Qigong* recommend that all exercises be done while barefoot on the earth. There is no comparison between walking, running, or practicing any form of movement therapy or martial arts indoors and doing the same activities with bare feet in direct contact with the earth. Why should this be the case?

The significance of barefoot contact with the earth has been known since ancient times. Native American elders have discussed this in their traditional story telling:

> It was good for the skin to touch the bare earth, and the old people liked to remove their moccasins and walk with their bare feet on the sacred Earth…they sat on the ground with the feeling of being close to a mothering power…the soil was soothing, strengthening, cleansing and healing.
>
> **~Luther Standing Bear (1868–1939)**
> *Sioux Tribal Leader*[6]

In the late nineteenth century, a back-to-nature movement in Germany claimed many health benefits from being barefoot outdoors, even in cold weather.[7] In the 1920s, George Starr White, MD, investigated the practice of sleeping grounded after being informed by some individuals that they could not sleep properly, "unless they were on the ground or connected to the ground in some way," such as with copper wires attached to grounded-to-Earth water, gas, or radiator pipes. White reported that sleep improved with these techniques.[8] However, these ideas never caught on in mainstream society.

A modern Yoga teacher says that the benefits of walking barefoot on the earth include:

- A better balance in our nervous systems
- Improved circulation
- Reduction in inflammation in our bodies
- It is the ultimate antioxidant!

~Samantha Fox Olson[9]

Recent research confirms each of these points.

Throughout history, humans mostly walked barefoot or with footwear made of animal skins (moccasins). They slept on the ground or on animal hides. We shall see that recent research confirms the health advantages they achieved by this lifestyle and explains why this happens. Through direct contact or through perspiration-dampened and electrically conductive animal skins used as footwear or sleeping pads, the ground's abundant free electrons were able to enter their bodies, which are electrically conductive. Through this mechanism, every part of the body can equilibrate with the electrical potential of the earth, thereby stabilizing the electrical environment of all organs, tissues, cells and molecules, and providing a key ingredient needed for the operation of the immune system.

MODERN LIFESTYLE AND DIABETES

Modern lifestyle has increasingly separated humans from contact with earth's electrical field and free electrons. For example, since the 1960s, we have increasingly worn shoes with insulating rubber or plastic or composite soles, instead of the traditional leather soles fashioned from animal hides. Some have lamented that the use of insulating materials in post-World War II shoes has separated us from the Earth's energy field.[10] Obviously, we no longer sleep and walk directly on the ground as we did in times past. Moreover, our houses have floors made of wood or acrylic that are also insulating. Even carpets are made from synthetic materials that are nonconductive, and that can cause build-up of harmful static electrical charges on our bodies.

During recent decades, stress related chronic illness, immune disorders, and inflammatory diseases have increased dramatically, and some researchers have suggested that environmental factors are the likely cause. However, the possibility of modern disconnection with the earth's surface as a cause of chronic disease has not been considered by modern biomedicine. The research summarized in this chapter points in that direction.

For example, we are experiencing a global epidemic of diabetes, and there are compelling reasons to look at the possibility that this may in part be related to our loss of contact with the surface of the earth. Figure 38.2 graphs the escalating incidence of diabetes along with the growth of sales of athletic shoes, virtually all of which have insulating rubber or plastic soles. In the early 1950s, some 95% of shoes had leather soles. Leather is a material that will conduct electrons if it is moist, as from the inevitable perspiration from sweat glands on the bottoms of the feet. Fifty years later, 95% of shoes had insulating soles, mostly made of synthetic or composite materials, electrical insulators that completely disconnect the wearer from the earth. Other lifestyle changes over the same time period included the introduction of fast-food, computers, and cellular telephones. People moved indoors to watch television. Skin contact with the surface of the earth became rare.

Diabetes accounts for 10% of all health care dollars spent.[11]

> The world is losing the battle against diabetes as the number of people estimated to be living with the disease soars to a new record of 382 million this year, medical experts said on Thursday. The vast majority have type 2 diabetes - the

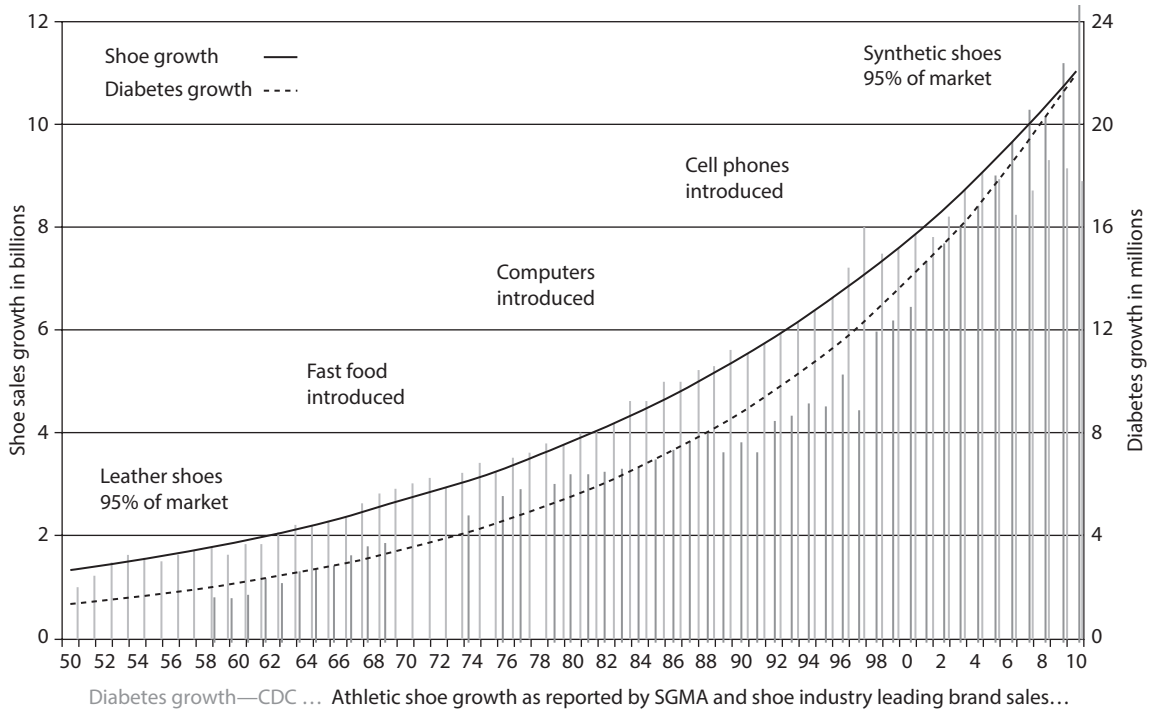

FIGURE 38.2 Sixty years of synthetic soled shoe sales growth correlates with last sixty years of diabetes growth.

kind linked to obesity and lack of exercise - and the epidemic is spreading as more people in the developing world adopt Western, urban lifestyles. The latest estimate from the International Diabetes Federation is equivalent to a global prevalence rate of 8.4% of the adult population and compares to 371 million cases in 2012.[12]

A recent news headline:

Diabetes Ailing 114 Million Chinese Risks Ravaging Budget: Diabetes may consume $22 billion, or more than half of China's annual health budget, if all those afflicted with the condition get routine, state-funded care. The disease is putting an "overwhelming burden" on the country, according to the International Diabetes Federation, which says China spent $17 billion, or about $194 a patient, on diabetes last year. A study released last week found China has 114 million diabetics or 21.6 million more than the Brussels-based federation estimated in November. Extending average care to the enlarged population of diabetes sufferers would wipe out all of China's additional investment in health. The government budgeted spending 260.25 billion yuan ($42.5 billion) this year, a 27% increase, on basic medical services and subsidies for a state-run health insurance program. China's diabetes costs will balloon, with almost 500 million Chinese at risk of developing the disease. "It's very scary," said T.H. Lam, a professor of public health at the University of Hong Kong. "This only represents the beginning of the diabetic epidemic. The worst is yet to come."

Diabetes costs an average of $1270 per patient globally and $8478 in the U.S., according to the International Diabetes Federation. Treatment for the metabolic condition and its associated ailments is expensive because patients with poor blood-sugar control can develop complications ranging from heart disease and stroke to gangrenous foot ulcers, blindness and kidney failure.

–Bloomberg News, September 12, 2013

At the end of the last century, experiments initiated independently by Ober in the USA,[13] and cardiologist and neurosurgeon father and son on the medical staff of a military clinic in Poland, Karol and Pawel Sokal,[14] revealed distinct physiological and health benefits with the use of conductive bed pads, mats, EKG- and TENS-type electrode patches, and plates connected the earth outside. These physiological changes included effects on blood glucose regulation.

REDUCTION OF PRIMARY INDICATORS OF OSTEOPOROSIS, IMPROVEMENT OF GLUCOSE REGULATION, AND IMMUNE RESPONSE

The Sokals were seeking regulating factors that are universal in nature and that might be disturbed in the modern environment. Their hypothesis was that interactions between living organisms and the electrical properties of the earth, either by direct contact with the earth's electrically charged surface and/or by field interactions with the earth's electrical field, could be involved in physiological regulatory processes. They mentioned theories about the origin of life involving electrical phenomena that triggered the combining of the elements in the primordial aqueous environment to form stable biomolecules that could reproduce themselves. Perhaps in modern times such electrical phenomena continue to be important for stabilizing various essential regulatory processes.

Their study was designed to answer the question: Does the contact with the earth affect calcium–phosphate homeostasis, concentration of electrolytes, glucose metabolism, proteins, and thyroid function? They conducted a series of experiments to determine whether contact with the earth via a copper conductor can affect physiological processes. The results related to diabetes, osteoporosis, and thyroid function.

> Earthing had a direct, statistically significant and beneficial effect on the regulation of blood glucose in patients with noninsulin-dependent diabetes mellitus. This was demonstrated by the decrease in fasting glucose concentrations (means ± standard error of the mean) from 10.6 ± 1.2 to 7.4 ± 0.8 mmol/L, $p < 0.05$.

Double-blind experiments were conducted on groups ranging from 12 to 84 subjects who followed similar physical activity, diet, and fluid intake during the trial periods. Grounding was achieved with copper plates (30 × 80 mm) placed on the lower part of the leg, attached with a strip so that it would not come off during the night. The plates were connected by a conductive wire to a larger plate (60 × 250 mm) placed in contact with the earth outside.

Earthing continually during rest and physical activity over a 72 h period decreased fasting glucose among patients with noninsulin-dependent diabetes mellitus (NIDDM). Patients had been well controlled with glibenclamide,* an antidiabetic drug, for about 6 months, but at the time of study had unsatisfactory glycemic control despite dietary and exercise advice and glibenclamide doses of 10 mg/day.

In another experiment with nonmedicated subjects, grounding during a single night of sleep resulted in statistically significant changes in concentrations of minerals and electrolytes in the blood serum: iron, ionized calcium, inorganic phosphorus, sodium, potassium, and magnesium. Renal excretion of both calcium and phosphorus was reduced significantly. These reductions in blood and urinary calcium and phosphorus directly relate to osteoporosis. The results suggest that earthing for only a single night reduces the primary indicators of osteoporosis. This is a remarkable finding that needs a follow-up study by those interested in public health and the high costs of medical care.

The Sokals drew blood samples from six male and six female adults with no history of thyroid disease. A single night of grounding produced a significant decrease of free tri-iodothyronine and an increase of free thyroxin and thyroid-stimulating hormone. The significance of these results is unclear, but the logical explanation is that earthing influences hepatic, hypothalamic, and pituitary relationships via adjusting thyroid function.

Many individuals on thyroid medication reported symptoms of hyperthyroid, such as heart palpitations, after starting grounding.[15] Such symptoms typically vanish after medication is adjusted downward under medical supervision. Through a series of feedback regulations, thyroid hormones affect almost every physiological process in the body, including growth and development, metabolism, body temperature, and heart rate. Further study of Earthing effects on thyroid function will obviously be valuable.

> The Sokals concluded that earthing the human body influences human physiological processes, including increasing the activity of catabolic processes and may be "the primary factor regulating endocrine and nervous systems." They also concluded that grounding the human body represents a "universal regulating factor in Nature" that strongly influences bioelectrical, bioenergetic, and biochemical processes and appears to offer a significant modulating effect on the chronic illnesses they encounter daily in their clinical practices.

In another experiment done by the Sokals, the effect of grounding on the classic immune response following vaccination was examined. Earthing accelerated the immune response, as demonstrated by increases in gamma globulin concentration. This result confirms an association between earthing and the immune response, as was suggested in a study of delayed onset muscular soreness (DOMS) to be discussed below.[16] The reason for this association will also be discussed below.

The Sokals also found that earthing patients with NIDDM continuously during rest and physical activity over a 72 h period decreased their fasting glucose levels. This is another profoundly important result. It supports the idea that disconnecting from the earth affects blood glucose and this could be a significant factor in diabetes. Could it be that the simple change in lifestyle from leather soled shoes to electrically insulating plastics and rubber was a major contributor to our epidemics of diabetes and other chronic diseases? Given the scope of the suffering and the financial significance of the global diabetes problem, this idea deserves serious attention from the biomedical research and public health communities, especially in the regions where diabetes is epidemic.

EARTHING, SLEEP AND CORTISOL PROFILES

A modern understanding of the value of contact with the earth began with the discovery that a simple grounding system placed on a mattress enabled a person to sleep better.[12,17,18,] The grounded sleep system (Figure 38.3) consists of a bed sheet with conductive carbon or silver threads woven

* Glibenclamide, also known as glyburide is an anti-diabetic drug in a class of medications known as sulfonylureas, closely related to sulfa drugs. It is sold under the trade names Diabeta, Glynase and Micronase in the United States and Daonil, Semi-Daonil and Euglucon in the UK, and Delmide in India. It is also sold in combination with metformin under the trade names Glucovance, Benimet and Glibomet. The drug works by binding to and activating the sulfonylurea receptor 1, the regulatory subunit of the ATP-sensitive potassium channels in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening the voltage-dependent calcium channel. This results in an increase in intracellular calcium in the beta cell and subsequent stimulation of insulin release.

FIGURE 38.3 The grounded sleep system consists of a cotton sheet with conductive carbon or silver threads woven into it. The threads connect to a wire that goes out the bedroom window or through the wall to a metal rod inserted into the earth near a healthy plant. Sleeping on this system connects the body to the earth. A repeated report from people using this system is that sleeping grounded improves the quality of sleep.

into it. The threads connect to a wire that goes out the bedroom window or through the wall to a metal rod inserted into the earth, preferably near a healthy plant. Sleeping on this system connects the body to the earth's electrons and to its electrical field (Figure 38.3). It is an extremely simple change in life-style that can have a huge impact on one's health, as we shall see below.

The grounding or "earthing" story is summarized by the cartoon in Figure 38.4. There is a continuous flow of electrons from the sun to the ionosphere via the solar wind, and thence to the earth's surface via lightning strikes. Lightening keeps the conductive surface of the earth electrically charged.[19] At any given time there are probably about 2000 thunderstorms around the world producing about 44 flashes of lightning each second. About 78% of those flashes occur in the tropics, between 30N and 30S latitude.[20]

Electrostatics is the branch of physics that teaches that when two conductive objects with different electrical potential touch each other, there is a virtually instantaneous transfer of charge so that the two objects equilibrate to the same electrical potential.[21] The human body is a conductor of electricity and so is the earth. "Grounded" or "earthed" means that our bodies are conductively coupled or electrically coupled with the surface of the earth and its abundant supply of electrons. This is a natural condition in which earth's free or mobile electrons spread over and into our bodies, stabilizing our internal electrical environment. At the same time, it appears that an earth connection allows rhythms in the earth's electric field to entrain the body's biological clocks. This is the most likely explanation for the fact that a brief (e.g., 15 min) period of standing barefoot on the earth eliminates the effects of jet-lag, most likely by shifting a person's biological clocks to the rhythms present at their new location.

A repeated report from people using this system is that sleeping while grounded to the earth improves the quality of sleep. Insomnia is a serious problem for approximately half of the people in the USA. The problem is so severe that news

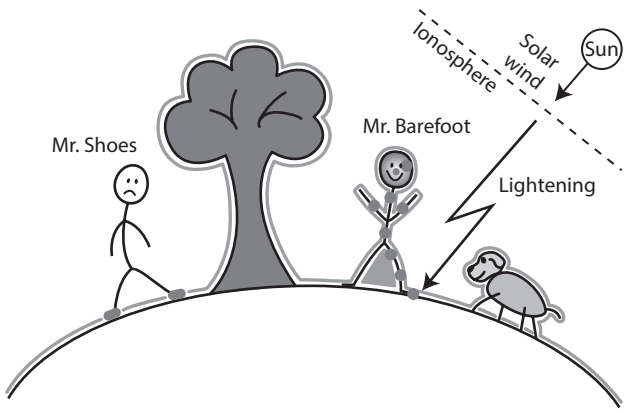

FIGURE 38.4 A continuous flow of electrons from the sun to the ionosphere and to the earth via lightning strikes keeps the surface of the earth electrically charged. Electrostatics teaches that when two conductive objects with different electrical potential touch each other, there is a virtually instantaneous transfer of charge so that the two objects equilibrate to the same electrical potential. The human body is a conductor of electricity and so is the earth. "Grounded" or "earthed" means that our bodies are connected to the surface of the earth and its abundant supply of electrons. This is a natural condition in which earth's electrons spread over and into our bodies, stabilizing our internal electrical environment.

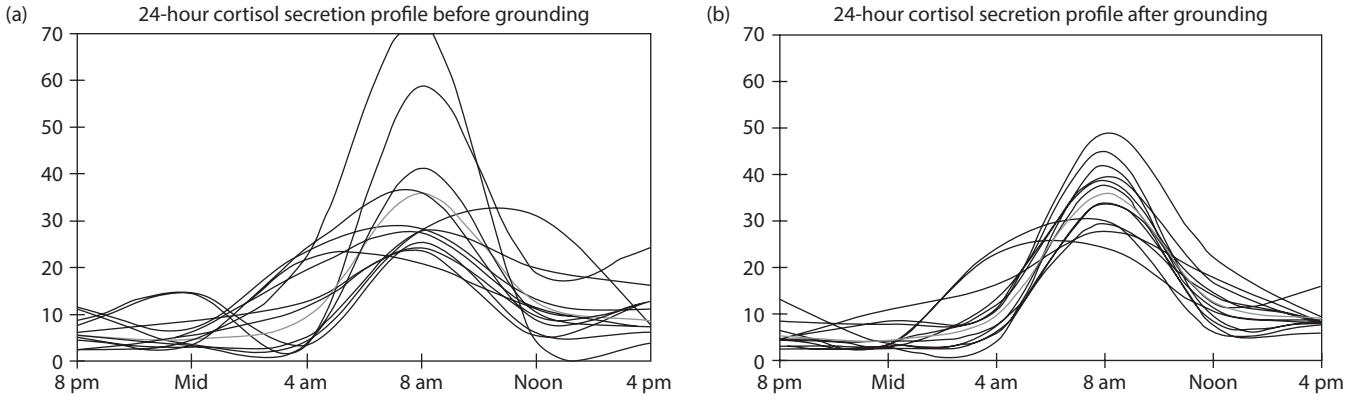

FIGURE 38.5 (**See color insert.**) Cortisol levels before and after grounding. In unstressed individuals, the normal 24 h cortisol secretion profile follows a predictable pattern: lowest around midnight and highest around 8 a.m. Graph (a) illustrates the wide variation of patterns among study participants prior to grounding, while (b) shows a realignment and normalization trend of patterns after six weeks of sleeping grounded. (From Ghaly M, Teplitz D. *J Alternat ComplMed* 2004;10:767–76.)

and business media take notice.[22,23] Poor sleep is thought to lead to many automobile, industrial, and other types of accidents, and costs U.S. businesses nearly $150 billion annually in absenteeism and lost productivity.[24] Therefore, further investigations of grounded sleep seem worthwhile.

A pilot study showed that improved sleep was associated with normalization of the day-night rhythm of the "stress hormone," cortisol (Figure 38.5).[25] Cortisol is a stress hormone that is associated with both psychological and physical stress, inflammation, and sleep dysfunction in humans. Chronic elevation of cortisol can result in disruption of circadian rhythms, which, in turn, contributes to a multitude of adverse health conditions, including sleep disorders, hypertension and cardiovascular disease, stroke, decreased bone density, decreased immune response, mood disturbances, autoimmune diseases, and abnormal glucose levels.[26]

Cortisol rhythms have broad impact on most if not all systems in the body. Cortisol is both a mediator and a marker of the stress response. The finding that grounding or earthing the body during sleep normalizes the day-night cortisol rhythm, while improving subjective reports of sleep, pain and stress[24] is indicative of a deep significance to natural contact with the surface of the earth. The convergence of endocrine measures with subjective behavioral data make a strong case for the conclusions reached.

Neurologic effects of chronic elevated cortisol secretion include chronic activation of the sympathetic nervous system (flight-or-fight response) leading to hypertension and cardiovascular disease. The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system have been utilized as objective markers of stress reactions.[27] Previous research has established relationships between cortisol levels and sleep dysfunction, stress, pain, anxiety, depression, irritability, inflammation, circadian rhythms, the immune response, and various chronic diseases. These relationships are real; they have been the topic of literally thousands of scientific studies. For example, a search of the National Library of Medicine database, PubMed, lists nearly 13,000 studies with key words "cortisol" and "stress" and 1900 studies with key words "cortisol" and "sleep." A scholarly summary of this science can be found in *Measuring Stress*.[28] See, in particular, Chapter 8, on measuring stress hormones.[29] Cortisol is widely studied because it is a central, readily measured and an easy-to-interpret factor.

Cortisol-releasing mechanisms seem to be involved in the regulation of sleep.[30] Twenty-four-hour hyper-secretion of cortisol has been linked to chronic insomnia.[31] Evening and nocturnal cortisol levels were significantly increased in patients with severe chronic primary insomnia.[32] Power frequency 50–60 Hz extra-low frequency electromagnetic fields and pulsed radiofrequency fields are reported to affect sleep. Sleep disruption has been reported in human populations with nighttime exposure to elevated 50–60 Hz electromagnetic fields.[33,34] Weak, pulsed radiofrequency radiation at 20 μW/crn2 has been reported to alter the HPA axis with a slight elevation in cortisol serum level.[35] Significantly suppressed sleep electroencephalographic (EEG) and disruption of rapid eye movement (REM) sleep are reported after exposure to pulsed radiofrequencies.[33,36–38] Pulsed radiofrequency exposure is reported to alter cerebral blood flow, and sleep and waking EEGs.[35] Mann and colleagues reported significant sleep differences after exposure to weak pulsed radiofrequency radiation, with a predominance of the parasympathetic over sympathetic tone in the autonomic nervous system.[33] Together, these studies indicated that weak exposures to electromagnetic fields can disrupt normal sleep patterns as measured by various parameters, including direct measurement of hormones, sleep quality, duration of sleep, sleep EEG, REM sleep patterns, parasympathetic/sympathetic autonomic nervous system balance, and disruption of normal sleep spectral-power density ranges. Disregulation of circadian cortisol profiles is also associated with pain.[39]

A book on earthing presents two decades of accumulated anecdotal cases of people with many types of health challenges whose conditions have improved because of earthing.[15] For example, from the evidence presented here, it is not surprising that there are reports that a vast number of autoimmune disorders are partly, or completely, ameliorated by earthing.

Pain and Stress

Many who had improved sleep with earthing also reported reduction in pain from new or old injuries or from conditions such as arthritis. As more feedback was gathered, it appeared that many other uncomfortable or debilitating conditions were partly, or completely, mitigated by grounding the body during sleep.

When any method seems to have a broad spectrum of benefits, as often happens with sleeping grounded, one can look for a common underlying mechanism. One mechanism is obvious: extensive scientific research from around the world has already shown that lack of sleep stresses the body and has many detrimental health consequences. The cortisol study (Figure 38.5) strengthened the argument that grounding the body reduces stress so that people can sleep better. A procedure that improves sleep could therefore provide relief from a host of disorders related to adrenal exhaustion, stress and the resulting anxiety.

Melatonin is the most important of the pineal hormones. In a previously unpublished study, it was found that melatonin increased in 66% of subject after sleeping grounded for 6 weeks (Figure 38.6). Increases ranged between 2% and 16%. Melatonin decreased by 6% in only one of the subjects. The other three remained the same. Melatonin increases are important because melatonin is a hormone that supports the immune system, promotes deep and restful sleep, slows cell damage and aging, improves energy, and may even inhibit the growth of cancer cells.[40]

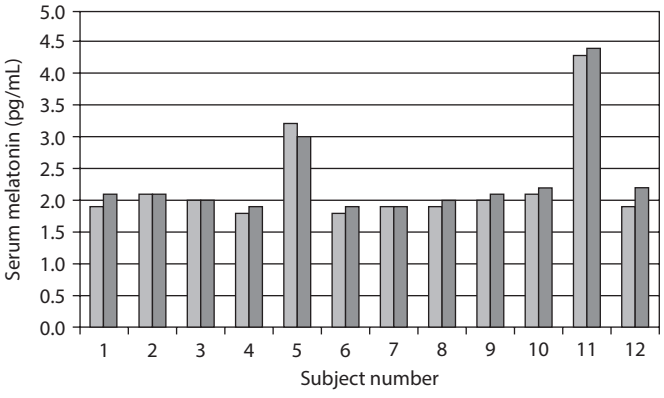

FIGURE 38.6 Melatonin increased in 66% of subjects after sleeping grounded for 6 weeks. Increases ranged between 2% and 16%. Melatonin decreased by 6% in only one of the subjects. The other three remained the same. Melatonin is the most important of the pineal hormones. Melatonin increases are important because melatonin is a hormone that supports the immune system, promotes deep and restful sleep, slows cell damage and aging, improves energy and may even inhibit the growth of cancer cells. (From Jardim-Perassi BV et al. *PLoS One* 2014;9(1):1–11.)

> Sleeping grounded is the first intervention ever discovered that speeds recovery from the pain of delayed onset muscle soreness.

Looking further, we know that lack of sleep is often the result of pain—people simply cannot sleep well when they are in pain. Hence, reduction of pain might lead to improved sleep, reduction in stress to the body, and relief from a wide variety of unpleasant and debilitating conditions. Many who started sleeping on a grounding pad reported less pain and discomfort, not only during the night, but on the following day.

Pain reduction from sleeping grounded has been well documented in a controlled study of delayed onset muscle soreness (DOMS). This is a well-known result of excessive, unfamiliar, or intensive exercise. Muscle cell breakdown and inflammation occur along the muscle Z-lines (the regions where tension developed within the muscle cell is conducted to the myofascial system and bones, to produce movements[41]) and muscle cell membranes become leaky. Muscle soreness begins 24–48 h after the exercise and can last well over 96 h. DOMS is an excellent experimental model for the study of acute inflammation. The excessive exercise can be standardized and it does not produce any permanent injury to the subject. In all measurements after the initiation of the trauma, ungrounded subjects expressed the perception of greater pain. Related to the pain finding was evidence of a muted white blood cell response indicating that a grounded body experiences less inflammation (Figure 38.7). Subjects were also tested with a blood pressure cuff on the calf of the injured leg. Subjects that had slept grounded consistently, at every measurement taken, could withstand greater pressure than controls. Sleeping grounded is the first intervention ever discovered that speeds recovery from the pain of DOMS.[16]

Induced Electrical Fields

One of the documented causes of sleep disturbance is the environmental electric field from home wiring and appliances. The wires to a lamp or clock radio on a table next to the bed induce measurable voltages on the body, as do wires concealed behind walls. The electric field is present even when the lamp is turned off. These induced voltages were measured by an electrical engineer, Roger Applewhite, who is expert in the design of electrostatic discharge grounding systems for the electronics industry.[42] Measurements were taken while ungrounded and then grounded using a conductive patch or conductive bed pad. Applewhite measured the induced fields at three positions: left breast, abdomen, and left thigh. Each method (patch and sheet) immediately reduced the common alternating current (AC) 60 Hz ambient voltage induced on the body by a highly significant factor of about 70 on average. Figure 38.8 shows this dramatic effect.

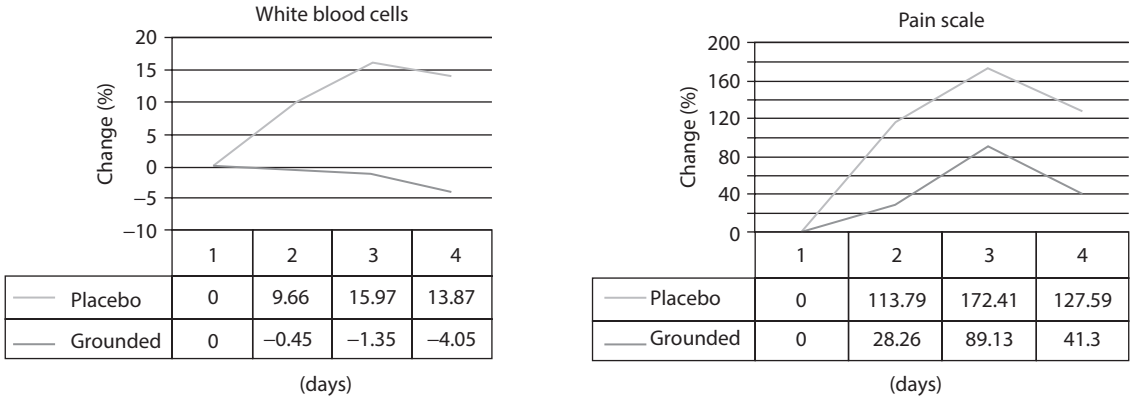

FIGURE 38.7 Delayed onset muscle soreness and grounding. In all measurements, ungrounded subjects expressed the perception of greater pain. Related to the pain finding was evidence of a muted white blood cell response indicating that a grounded body experiences less inflammation. (From Brown R, Chevalier G, Hill M. *J Alternat Compl Med* 2010;16(3):265–73.)

The Applewhite study showed that when the body is grounded, its electrical potential becomes equalized with the Earth's electrical potential through a transfer of electrons from the earth to the body. This, in turn, prevents the 60 Hz field from producing an AC electric potential at the surface of the body and from producing perturbations or oscillations of charged molecules inside the body. The study confirms the "umbrella" effect of earthing the body explained by Nobel Prize winner Richard Feynman in his famous Berkeley lectures on physics.[43] Feynman said that when the body potential is the same as that of the earth (grounded), the body becomes an extension of the earth's gigantic electric system. The earth's potential thus becomes the "working agent that cancels, reduces, or pushes away electric fields from the body."

As pointed out above, the surface of the earth has an abundance of electrons that give it a negative electrical charge. If you are standing outside on a clear day, wearing shoes or standing on an insulating surface (like a wood or vinyl floor), there is an electrical charge of some 200 volts between the earth and the top of your head (Figure 38.9).

Applewhite documented changes in the voltages induced on the body by monitoring the voltage drop across a resistor. The results confirmed the "umbrella effect" described above.

FIGURE 38.8 Effect of grounding with bed pad on 60 Hz induced body voltage. (From Applewhite R *Euro Biol Bioelectromagn* 2005;1:23–40.)

The electrons in the body of the grounded person are not perturbed by environmental electrical systems.

You might ask, "If there really is a voltage difference of 200 volts from head to toe why don't I get a shock when I go outside?"

The answer is that to experience a shock there has to be a current flow through your body. The air is a relatively poor conductor, and therefore, allows virtually no electrical current flow from the atmosphere, through your head, through your body, and to the surface of the earth. If you are standing outside in your bare feet (the right side of Figure 38.9), you are earthed: your whole body is in electrical contact with the earth's surface. Your body is a relatively good conductor. Your skin, respiratory and digestive tracts, and the earth's surface make a continuous charged surface with the same electrical potential. In a later section, we will see that earth's surface charge reaches the surfaces the red blood cells, where it has important effects by reducing blood viscosity.

Stated simply, one of the best things a person can do to lessen the likelihood of developing a chronic disease is to spend at least part of their day connected to the earth. Going outside barefoot is one way to do this. Another is to place a grounding sheet on one's bed (Figure 38.3) and a third way is to have a grounding mat under one's feet if they are sitting at a desk. These are exceedingly simple, virtually trivial alterations in one's lifestyle that can have profound health implications.

Also notice to the right in Figure 38.9 that the charged area is pushed up and away from your head if you are grounded. Any object that is in direct contact with the earth—a person, a dog, a tree—creates this shielding effect (see also Figure 38.4). The object is essentially residing within the protective "umbrella" of earth's natural electric field. This protective phenomenon also occurs inside your home or office, if you are connected to the earth with an earthing system such as a bed or foot pad.

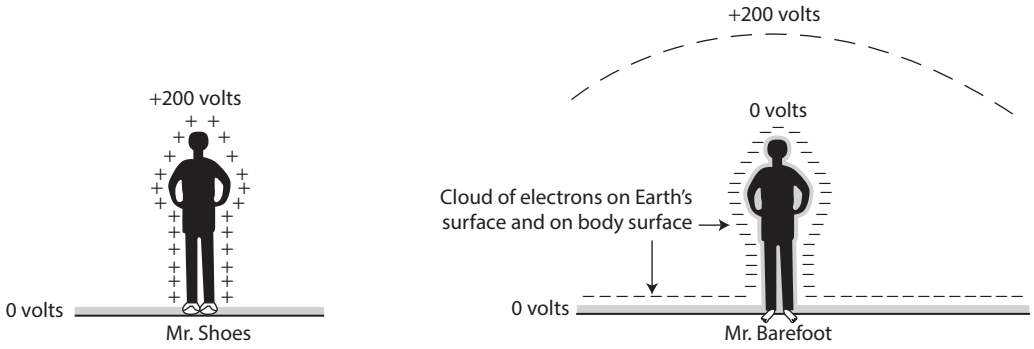

FIGURE 38.9 The surface of the earth has an abundance of electrons that give it a negative electrical charge. Left, if you are standing outside on a clear day, wearing shoes or standing on an insulating surface like a wood or vinyl floor or asphalt, there is an electrical charge of some 200 volts between the Earth and the top of your head. Right, if you are standing outside in your bare feet, your whole body is in electrical contact with the Earth's surface. Your body is a relatively good conductor. Your skin and the Earth's surface make a continuous charged surface with the same electrical potential. Also, notice in the diagram on the right that the charged area is pushed up and away from your head if you are grounded. Any object in direct contact with the earth—a person, a dog, a tree—creates this shielding effect (see also Figure 38.4). The object is essentially residing within the protective "umbrella" of earth's natural electric field. This protective phenomenon also occurs inside your house or office if you are connected to the earth with an earthing device, such as a grounding wrist pad or a foot pad. Adapted from Richard Feynman's famous Berkeley Lectures on Physics. (From Ober C, Sinatra ST, Zucker M. *Earthing: The Most Important Health Discovery Ever?* Laguna Beach, CA: Basic Health Publications; Second Edition, 2014, p. 76.)

HEALTH ON THE 10TH FLOOR

Chevalier has discussed evidence that living in high-rise buildings can have adverse health effects.[44] Specifically, in 2009, Wolinsky and colleagues, using data from a large, nationally representative sample of older people (>70 years) on Medicare, showed that significant stroke risks are associated with living in multi-story residential dwellings versus single-story residential homes. They also reported that in 2005 about 150,000 Americans died from their strokes, placing stroke as the third leading cause of death in the U.S.[45]

> Stated simply, one of the best things a person can do to lessen the likelihood of developing a chronic disease is to spend at least part of their day connected to the earth in one way or another. Going outside barefoot is one method that many find enjoyable. Another is to place a grounding sheet and/or pillow on one's bed (Figure 38.3). A third way is to have a grounding mat under bare feet while sitting at a desk. These are exceedingly simple, virtually trivial lifestyle changes that have profound implications for health and longevity.

In presenting this information, Chevalier suggested that being disconnected from the ground, that is, from the earth's surface, for prolonged periods of time, supports low key inflammatory processes that take years to develop into chronic diseases. These inflammatory processes are aggravated by the distance from the ground: the higher above the ground a person lives, and the longer they stay there, the more hazardous it is for their health. Grounding appears to eliminate one of the major contributors to these inflammatory processes and remediates many chronic diseases once they have begun. Stated simply, one of the best things a person can do to lessen the likelihood of developing a chronic disease is to spend at least part of their day connected to the earth. To repeat, going outside barefoot is one way to do this. Another is to place a grounding sheet on one's bed (Figure 38.3) and a third way is to have a grounding mat under their feet if they are sitting at a desk. These exceedingly simple, virtually trivial lifestyle changes can have profound health implications.

Wollinsky and co-workers suggested that the increased stroke risk in multi-story residential dwellings reflects the greater physical, social, and psychological burdens faced by older adults in those settings. Chevalier discussed this and other possible explanations for elevated stroke and chronic disease incidence. On balance, Chevalier's hypothesis seems the most logical explanation. He notes the sum total of the benefits from earthing summarized in this chapter: better sleep, less pain, normalization of daily cortisol levels and circadian rhythms, decrease in inflammation, reduction in stress, normalization of the function of the autonomic nervous system, decreased blood viscosity, faster recovery after injury or from disease, reduction of primary indicators of osteoporosis, improvement of glucose regulation, and more efficient immune responses to trauma. All of these factors are significant for the health of every person, and are especially important for the aging adult. Higher blood viscosity is often correlated with stroke and virtually all of the other cardiovascular issues that are often considered the consequences of aging. Hence, the reduction in blood viscosity found with earthing may have a significant cardiovascular protective effect on older people living in multi-story buildings. Earthing appears to be one of the simplest and yet most profound interventions for helping reduce cardiovascular risk and cardiovascular events.

Consider, for example, a 6 foot tall person standing on the second floor of a multi-story building. Assuming an average of 10 feet per floor and using the typical value of 150 V/m, this person's body will be about 732 V at the top of their head and 457 V at the bottom of their feet. Furthermore, this voltage will increase by 457 V for every floor above the second floor. It is understandable that such a large electric potential the higher one is from ground level could interfere with the functioning of the electrical aspects of the cardiovascular and immune systems.

Take as an example a 6-foot tall person standing on the second floor of a multi-story building. Assuming an average of 10 feet per floor and using the typical value of 150 V/m, this person's body will be at 732 V at the top of the head and 457 V at the bottom of the feet. Furthermore, this voltage will increase by 457 V for every floor above that floor. It is understandable that such a large electric potential the higher one is from ground level could interfere with the functioning of the electrical aspects of the immune system. The constant recharging of the body by positive charges in the atmosphere will neutralize many of the negative charges needed to neutralize reactive oxygen species (free radicals) generated by the oxidative burst—the body's response to injury (discussed in more detail below).

Jamieson and colleagues asked whether the failure to appropriately ground humans is a factor contributing to the potential consequences of electro-pollution in offices.[46] Considerable debate exists on whether electromagnetic fields in our environment pose a risk to health.[47] But there is no question that the body reacts to the presence of environmental electric fields. Applewhite's study unambiguously demonstrated that grounding essentially eliminates the ambient voltage induced on the body from common electricity power sources. We strongly suspect, from the evidence we have gathered, that this has beneficial health consequences.

What has a splinter in your finger or a wound on the foot to do with the risk of developing Alzheimer's disease, a heart attack, or contracting cancer of the colon? More than most people think! As we learn more and more about the causes of these and many other serious diseases, it becomes increasingly clear, that there is a link to our old defense mechanism; inflammation—the same biological process that causes tissue around a splinter to turn red and an injured foot to swell. The evidence is piling up and begins to radically change the perception of why we get chronic diseases.

–Dorthe Krogsgaard and Peter Lund Frandsen[48]

INFLAMMATION AND IMMUNE RESPONSE

Going one-step further, there is good evidence that painful conditions that prevent restful sleep are often the result of various kinds of acute or chronic inflammation—conditions caused in part by highly reactive molecules known as reactive oxygen species (sometimes referred to as free radicals). These molecules are generated by normal metabolism and by the immune system as part of the response to injury or trauma. They are thought to be the immediate cause of the characteristic features or "pillars" of inflammation that have been recognized since ancient times: pain, redness, heat, swelling, and loss of function.

Krogsgaard and Lund Frandsen from Denmark have stated (perhaps over-stated) an example of how a simple injury can lead to serious problems many years later (see box).[48] At this point, we do not really know enough to verify or refute this statement, but it does tell a story we suspect may be at least partly correct.

The way a small injury can lead to a chronic medical issue has been concisely summarized, again, by Krogsgaard and Lund Frandsen (see box).

Sometimes an inflammation process runs amok and continues much longer than is needed and spreads beyond the originally damaged area. There are several theories about how this happens. Perhaps something goes wrong in the communication between immune cells so that the signal to end the injury response does not arrive. Maybe there are too many free radicals and/or not enough antioxidants or not enough electrons to neutralize them. Degradation products from the inflammation process may bind to proteins in the connective tissue to form a barrier around the inflammation (the inflammatory barricade). When the process is encapsulated in this way, it is at high risk of becoming chronic, because immune cells and antioxidants don't have free access through the wall of the "inflammatory pouch." Various toxins may leak out from the area and create an irritation that generates further inflammation – and a vicious cycle is started, which, depending on the person's strong and weak sides, can develop into such seemingly diverse conditions as diabetes, bronchitis, asthma, chronic intestinal disorders, atherosclerosis, Alzheimer's, rheumatoid arthritis, multiple sclerosis, cancer.…

–Krogsgaard and Lund Frandsen[48]

Inflammation produces heat that can be measured with infrared medical imaging. A study using this approach revealed rapid reductions in inflammation at the same time as pain was reduced (Figure 38.10).

How does grounding the body reduce inflammation? One logical explanation is that grounding the body allows anti-oxidant electrons from the earth to enter the body and neutralize highly charged reactive oxygen species at sites of inflammation. If this hypothesis is correct, one would expect changes in the well-researched profiles in blood chemistry and

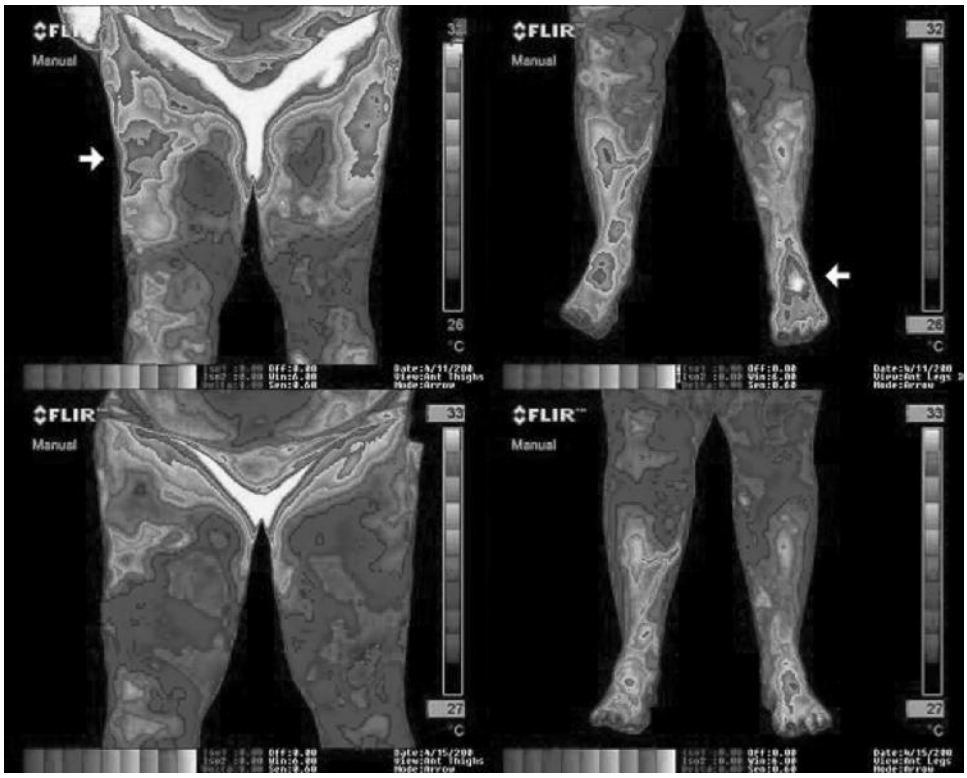

FIGURE 38.10 (**See color insert.**) Reduction in inflammation and pain after sleeping grounded for four nights. Medical infrared imaging shows warm and painful areas (arrows). Sleeping grounded for four nights resolved the pain and the hot areas cooled. (From Amalu W. Medical Thermography case studies. Clinical earthing application in 20 case studies. Available online from http://74.63.154.231/here/wp-content/uploads/2013/06/Amalu_thermographic_case_studies_2004.pdf.)

white blood cell counts associated with inflammation. Such changes have been documented by Brown and colleagues.[15]

PHYSIOLOGICAL EFFECTS OF EARTHING

To follow changes in physiology produced by earthing, the arrangement shown in Figure 38.11a was used. A ground wire was connected to a switch box so that the grounding could be turned on or off during experiments without the subject knowing about whether or not they were grounded. The ground was connected to the subject at the acupoints known as Kidney 1 (Figure 38.11b). Acupuncturists refer to this point as the primary entry point for *Qi*, known in Hawaii as "*mana*" and in Sanskrit as "*prana*." The point is located near the ball of the foot. Gaétan Chevalier and colleagues performed a series of studies using this arrangement that makes it possible to establish a precisely timed earth connection, and to record changes in various physiological parameters before and after the connection is made. Specifically, changes in pulse rate, respiratory rate, blood oxygenation, perfusion index, skin conductance, emotional stress, heart rate variability, and improved autonomic tone have been documented.

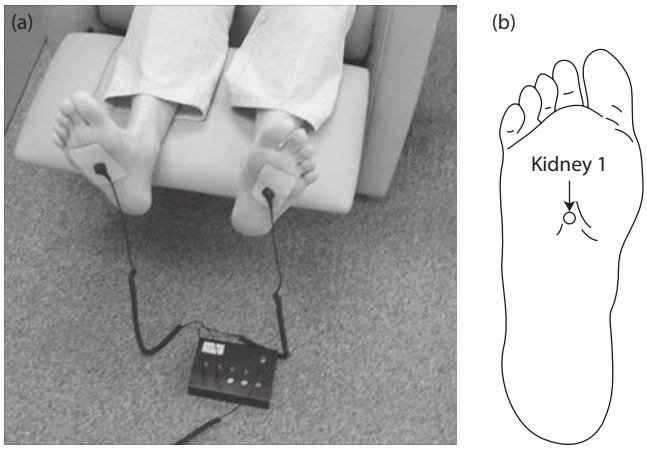

FIGURE 38.11 (a) Technique for studying the physiological effects of connecting the earth to the human body. Conductive patches are placed on the balls of the feet. Wires connect these patches to an earthing rod inserted into the soil outside, near a healthy plant to assure a good connection with the supply of free electrons from the earth's surface. (b) Proximity of the conductive patch to acupuncture meridian point known as Kidney 1. (From Chevalier G, Mori KD. The effect of earthing on human physiology. Part 2: Electrodermal measurements. *Subtle Energ Energ Med* 2007;18(3):11–34.)

Stress Reduction

The effects of earthing on day-night cortisol rhythms indicated changes in blood chemistry related to stress (Figure 38.5).

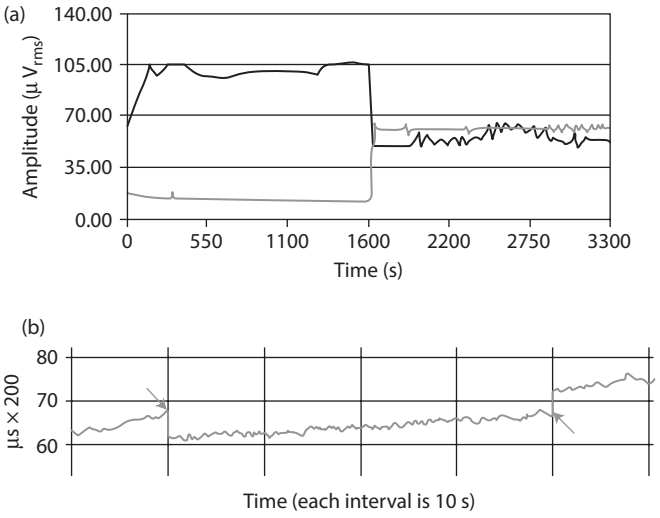

FIGURE 38.12 (a) Virtually instantaneous normalization of muscle tension at the moment of grounding (arrow) measured with electromyography of trapezius muscle. (b) Virtually instantaneous drop in skin resistance, a measure of sympathetic nervous system activity, at the moment of grounding (left arrow), and return at the moment of un-grounding (right arrow). (From Chevalier G, Mori K, Oschman JL. The effect of earthing (grounding) on human physiology. *Eur Biol Bioelectromagnet* 2006;2(1):600–21.)

Further study showed rapid shifts in the autonomic nervous system from sympathetic to parasympathetic dominance and normalization of muscle tension (Figure 38.12a), completing the documentation of the cascade of effects of grounding the body on sleep, inflammation, pain, and the debilitating consequences of stress and lack of proper sleep. Some of the effects are nearly instantaneous, as shown in Figure 38.12b, showing the rapid drop in skin resistance, a measure of sympathetic nervous system activity, at the moment of grounding (left arrow), and return at the moment of un-grounding (right arrow).

Cardiovascular Effects

> Erythrocytes have a strong net negative charge called the zeta potential produced by the scialoglycoprotein coat such that approximately 18 nm is the shortest span between two cells.
>
> **—Wintrobe's Clinical Hematology[49]**

The effects of earthing on the cardiovascular system are profound. A study examined effects of 2 h of grounding on the electrical charge (zeta potential) on red blood cells (RBCs) and the extent of RBC clumping. Ten subjects were grounded with conductive patches on the soles of their feet and palms of their hands. Wires connected the patches to a stainless-steel rod inserted in the earth outdoors. Small fingertip pinprick blood samples were placed on microscope slides and an electric field was applied to them. Zeta potentials were determined using the Smoluchowski equation. RBC aggregation was measured by counting the numbers of clustered cells in each sample (Figure 38.13a). Electrophoretic mobility of the RBCs was determined by measuring terminal velocities of the cells in video recordings taken through a microscope using the system shown in Figure 38.13b. The classic text on zeta potential is *Control of Colloid Stability Through Zeta Potential* (with a closing chapter on its relationship to cardiovascular disease)

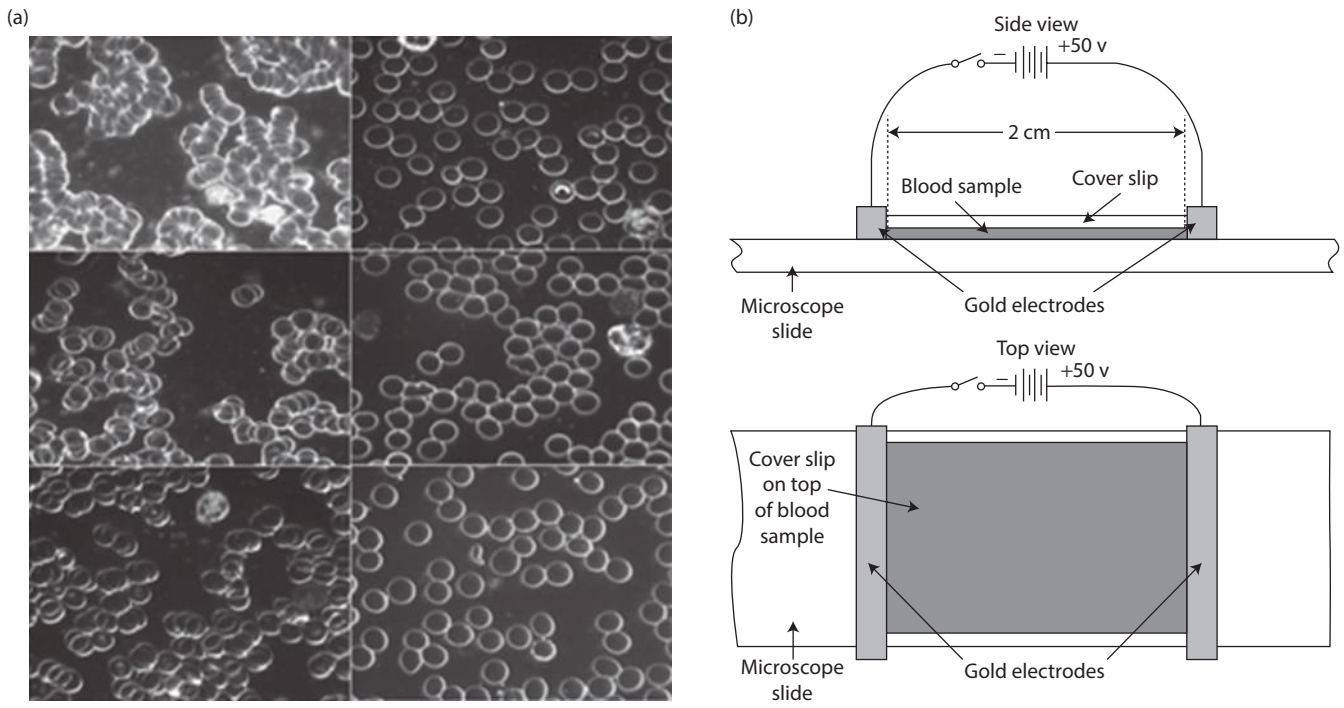

FIGURE 38.13 (a) Reduction in clumping of red cells in three subjects showing before (left) and after 40 min of earthing (right). (b) Apparatus used to measure the electrophoretic mobility (zeta-potential) of red cells before and after earthing.

by T.M. Riddick.[50] The perspectives Riddick developed on cardiovascular disease are important but have not been widely recognized, probably because rheology is a highly specialized and interdisciplinary subject. Moreover, blood is a very complex material, and many variables affect its ability to carry oxygen, nutrients, and metabolic waste products.

Earthing or grounding significantly reduced RBC aggregation and increased zeta potentials in all samples by an average factor of 2.70. It was concluded that grounding the body increases the surface charge on RBCs, thereby reducing blood viscosity and clumping.

Earthing appears to be one of the simplest and yet most profound interventions for helping reduce cardiovascular risk and cardiovascular events. Elevated blood viscosity has been implicated in virtually every aspect of cardiovascular disease, such as hypertension, left ventricular hypertrophy, peripheral artery disease, etc. Cardiovascular diseases are the number one cause of death worldwide.

Mechanism of Immune Response

We suggest that the mechanism by which earthing influences the immune response to injury is as follows:

- The polyelectrolyte ground substance (Figure 38.14) extends throughout the body. The charged groups on the glycosaminoglycans have enormous capacity to store electrons. In the ungrounded person, these charge "reservoirs" in the connective tissue ground substance are depleted of electrons (Figure 38.14a). It is thought that electrons in these reservoirs are continually utilized in all the cells and tissues in the body to neutralize reactive oxygen species produced during metabolism and other oxidative processes. Without grounding, the whole body becomes gradually "electron depleted." When the body connects with the earth, the charge reservoirs in the connective tissue ground substance become saturated with electrons (Figure 38.14b). This is referred to as a state of inflammatory preparedness. An injury to any part of the body will have immediate access to stored electrons in nearby ground substance reservoirs, and this will have a protective effect on healthy tissue.
- It is suggested that the way the ungrounded vs. grounded person reacts to an injury is as shown in Figure 38.15.

Neutrophils are the most abundant white blood cells in mammals. They are the first line of defense of the innate immune system. Neutrophils quickly aggregate at a site of injury, attracted by cytokines. These are small cell-signaling protein molecules produced by activated capillary endothelial cells, mast cells, and macrophages. Neutrophils also release cytokines, which in turn amplify the inflammatory reactions by several other cell types.[51] Electromagnetic interactions

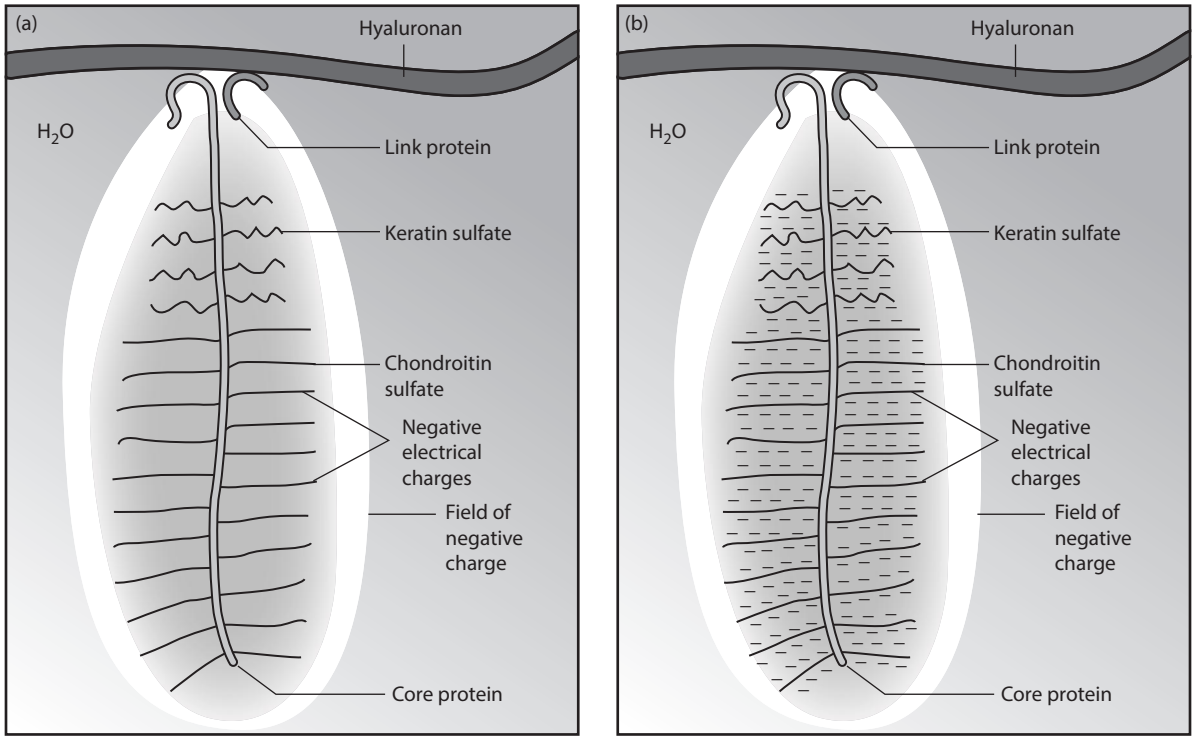

FIGURE 38.14 (a) Ungrounded person: charge reservoirs in the connective tissue ground substance are depleted of electrons. The whole body is "electron depleted." (b) Grounded person: charge reservoirs in the connective tissue ground substance are saturated with electrons. This is referred to as a state of inflammatory preparedness. (Redrawn from Lee RP. Interface. In: *Mechanisms of Spirit in Osteopathy*. Portland, OR: Stillness Press; 2005. With permission.)

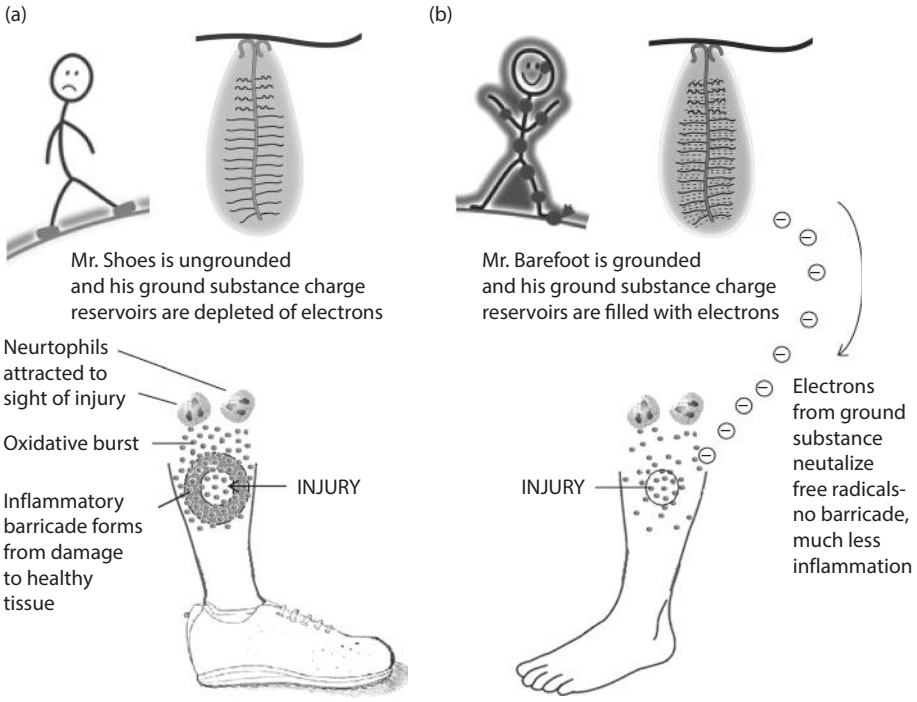

FIGURE 38.15 (a) The ungrounded person will form an inflammatory barricade around the injury site. (b) The grounded person will not form an inflammatory barricade because reactive oxygen species (free radicals) that could damage nearby healthy tissue are immediately neutralized by electrons from the living matrix and from the electron-saturated ground substance.

between the various cytokines may also be involved, as described in the chapter in this book by Oschman and Oschman.[52] These shifts in activity by white blood cells were documented in the DOMS study (e.g., Figure 38.7).

Neutrophils are phagocytes, capable of ingesting microorganisms or other foreign particles. They can internalize and kill many microbes, each phagocytic event resulting in the formation of a phagosome into which reactive oxygen species (ROS) and hydrolytic enzymes are secreted. The consumption of oxygen during the generation of ROS by various cells of the immune system has been termed the "respiratory burst" or "oxidative burst." The respiratory burst produces large quantities of two very potent oxidative agents: superoxide and hydrogen peroxide. Most researchers are convinced that superoxide and hydrogen peroxide are the primary active agents in the oxidative burst and the killing of pathogens.[53]

The inflammatory or Selye or granuloma pouch as described by Selye (Figure 38.16) has been widely used in studies of inflammation.[54–56] We suggest that the "inflammatory barricade" forming the wall of the pouch is created by damage to healthy tissue in the ungrounded person because of a lack of electrons that would otherwise serve a protective function. If the tissue is healthy and if the ground substance is saturated with electrons as in Figure 38.14b, the tissue matrix will be able to deliver electrons to the healthy tissue surrounding site of injury. In this situation, the inflammatory barricade will not form. This is important because the inflammatory barricade slows or prevents the entry of regenerative cells into the "repair field," a term introduced by W.D. Kessler.[57]

The mechanism for the movements of electrons in tissues has been described as semiconduction.[58] Albert Szent-Györgyi made a distinction between E, or energy stored in chemical bonds, and E*, excited energy that is mobile (Figure 38.17). The basic hypothesis is that the living tissue matrix is a semiconductor network extending throughout the body and is capable of rapidly delivering mobile anti-oxidant electrons, or E* to any point where a free radical appears. If the matrix is in a healthy state, it will be everywhere conductive to E* and the mobile electrons from the ground substance reservoirs will quickly migrate toward any reactive oxygen species that form. If the matrix conduction is blocked, or if electrons are not available (electron depletion; Figure 38.14a), the inflammatory barricade will form. When the matrix is healthy and conductive, and when the ground substance is saturated with electrons, healthy tissue will be protected and free radical damage will be minimized.

Selye and others have obtained evidence that necrotic tissue breakdown products from inflammatory pockets can leak into the blood and lymphatic circulation, producing slow but progressive toxicity or atrophy in various organs at a distance from the original site of trauma. For example, on page 161 of the first edition of *The Stress of Life*, Selye describes how he was able to inject inflammatory pouches in rats with irritants or microbes, producing a syndrome characterized by an inflammation of the heart valves (endocarditis) very similar to that which occurs in children suffering from rheumatic fever. Under some conditions, this was accompanied by inflammation of the kidney (nephritis) and excessive stimulation of the blood-forming organs. This inflammatory

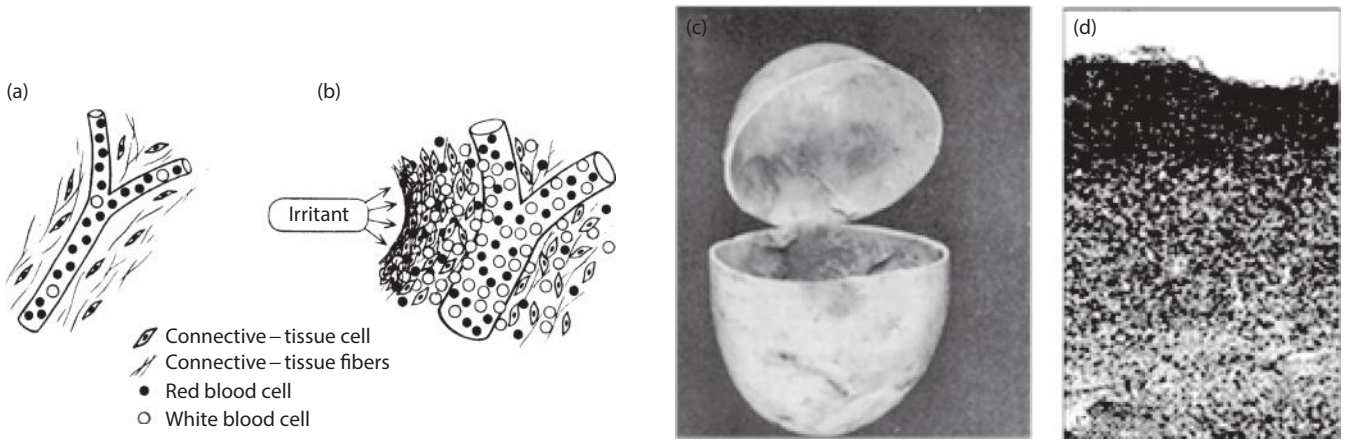

FIGURE 38.16 Formation of the inflammatory barricade, according to Selye.[55] (a) Normal connective tissue territory. (b) Same tissue exposed to irritant. Vessel dilates, blood cells migrate toward irritant, connective tissue cells and fibers form a thick impenetrable barricade that prevents the spread of the irritant into the blood, but that also prevents the entry of regenerative cells that could repair the tissue. The result can be a long-lasting pocket of incompletely resolved inflammation that can eventually leak toxins into the system and disturb functioning of an organ or tissue. (c) The inflammatory or Selye or granuloma pouch as described by Selye[55] widely used in studies of inflammation. (d) Histology of the inflammatory barricade: facing the chamber is a wall of connective tissue that is impenetrable to dissolved antioxidants and a barrier to cells that can regenerate damaged tissues (Ben Harrison, WFIRM). Electrons are the ultimate anti-oxidants. It is suggested that electrons can be semi-conducted into the inflammatory pouch where they can neutralize reactive oxygen species (free radicals). (From Selye H. *J Am Med Assoc* 1953;152(13):1207–13.)

pouch concept explains how local pockets of inflammation can trigger a diversity of chronic diseases and disturbances, many of which frustrate the physician because it is difficult to locate the cause. Selye's work tied inflammatory responses with stress, cortisol secretion, and adaptation.

"Silent inflammation" refers to a condition in which the inflamed site is not painful, and may go unnoticed, even though it may be causing problems elsewhere in the body. The phenomenon was described long ago in dentistry, beginning with 25 years of root canal research by Dr. Weston Price,[59] but currently receives little attention except by "biological" dentists.

The walled off areas as described by Selye may correspond to the dense tissue areas known to practitioners of bodywork, energy, and movement therapies. For example, Ida P. Rolf, in her book, Rolfing®[60] stated that: "In practically all bodies, in one muscle or another, small lumps or thickened nonresilient bands can be felt deep in the tissue. The lumps may be as small as small peas or as large as walnuts." Rolf reproduced Selye's picture of an inflammatory pouch produced by injecting air into fascial sheaths (Figure 38.16b). "Some similarly injurious process no doubt gives rise to the lumpy knottings we have noted." Some of the benefits of Rolfing® (Structural Integration) and other bodywork, energetic, and movement techniques may derive from their ability to reduce or eliminate these pockets of inflammation, and thereby prevent or relieve chronic illnesses. Likewise, a variety of therapeutic technologies introduce or induce electric currents that flow within tissues. Examples include Frequency Specific Microcurrent,[61] Pulsing Electromagnetic Field Therapies,[62] Ondamed®,[63] and perhaps other devices described in this book. It is worthwhile to explore the possibility that successes with these techniques may in part be due to induced semiconduction of mobile electrons across inflammatory barricades.

Implications for Aging

The leading theory for the cause of aging is the so-called free radical theory. Simply stated, it has been suggested that aging results from the cumulative damage done to cells and tissues by oxidative stress (reactive oxygen and reactive nitrogen species or "free radicals") produced during normal biochemical processes, such as oxidative metabolism, and during the body's natural responses to injury and pollutants. Because the free radical is a molecule with one or more unpaired electrons, it has charge and magnetic properties that make it highly reactive as well as attractive to free electrons. This is the physics that makes these molecules so destructive, they literally rip electrons from pathogens and damaged cells produced during an injury. Key work of Gershman and Gilbert revealed that elevated oxygen atmospheres in incubators were causing retrolental fibroplasia (now called retinopathy of prematurity).[64] This was one of several clues that led Denham Harman to propose his free radical theory of aging, the most widely studied model of aging.[65]

Today, oxidative stress is being implicated in virtually all of the diseases of aging and in the aging process itself. Recognition of the mobile electron as the ideal antioxidant has led to an explanation of how earthing, as well as a number of clinical devices, are so effective at reducing inflammation and treating chronic diseases. The ability of charges to migrate through the living matrix is relevant to anti-aging medicine because of the potential antioxidant nature of the mobile electrons. While a great deal of research is being

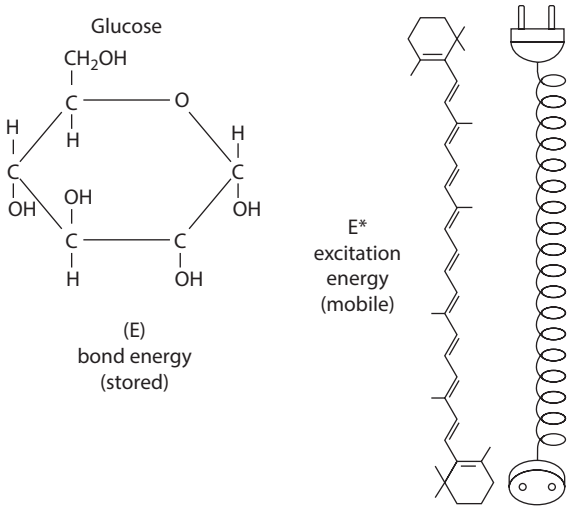

FIGURE 38.17 Albert Szent-Györgyi referred to the immobile electron energy stored in the bonds of the glucose molecule as (E) to distinguish it from mobile excited electrons E*. The carotene molecule on the right contains a series of double bonds, each of which has one electron that is not confined to the bond but is free to move. On the right, he compares the electronically conductive carotene molecule with the power cord for a toaster. The carotene molecule is a semiconductor, whereas the power cord is a conductor. (From Szent-Györgyi A. *Bioelectronics.* New York: Academic Press; 1968. p. 23, Figure 15.8.)

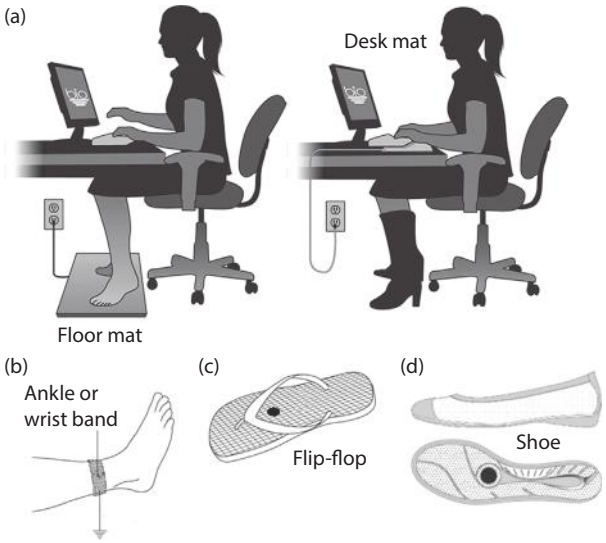

FIGURE 38.18 Methods for bringing earthing into the home or office. (a) Earthing pad for under the feet or wrist in an office. (b) Conductive strap for ankle or wrist. (c) Earthing flip flop with conductive plug at Kidney 1. (d) Women's ballet flat with earthing plug at Kidney 1.

done to correlate inflammation with disease states, there are few theories on the mechanisms involved. The research on earthing has provided a logical and testable theory based on a variety of kinds of evidence. The anti-inflammatory effects of connecting to the earth arise because the earth's surface is an abundant source of excited and mobile electrons.[66]

BRINGING THE EARTH TO YOU

Following on Ober's original discovery[13] a number of technologies were developed that could simply and conveniently bring the advantages of connecting with the earth into the home or other building (Figure 38.18). These include conductive grounding sheets for the bed, grounding pads for under the feet or wrists when working at a computer, and bracelets that can be worn around the wrist or ankles or chest. Grounding flip-flops and shoes connect people with the earth during the day as they are walking about (Figure 38.18). These shoes have a conductive plug positioned next to Kidney 1 to allow electrons to enter the body. Users of these products report a variety of benefits ranging from improved sleep to reduction or elimination of cardiac arrhythmias. These reports have been summarized in a book by Ober, Sinatra, and Zucker.[15]

WHEN IS A RAT A RAT?

The various physiological effects of earthing that have been summarized here bring up the question, "what is a normal organism." The people you see every day vary greatly in their degree of inflammatory preparedness versus electron depletion, depending on how long they have been isolated from the surface of the earth. For many, the only contact they have with electrons from the earth is when they take a shower, assuming that the water they are using comes to them through metal pipes buried in the earth. An electron-depleted person may look and feel perfectly normal, just like everyone else. The difference between a grounded and ungrounded person probably does not show up until the person has an injury or is recovering from a disease, or until they begin to age. From our observations, we suspect that the grounded person will heal faster and have a lower probability of developing the chronic diseases associated with aging, compared to the less grounded individual. We also predict that the grounded person will sleep better and show fewer of the well-documented effects of stress. These are hypotheses of sufficient importance for public health and medicine to warrant further study.

In 1906, the Wistar Institute in Philadelphia developed and bred the Wistar rat, the first standardized laboratory animal. The Wistar rat became one of the most popular animals for laboratory research. It is estimated that more than half of all laboratory rats in the USA today are descendants of the original Wistar ratline. The Sprague Dawley rat and Long-Evans strains were developed from Wistar rats. As of December 25, 2013, there are 253,226 peer reviewed studies of Sprague Dawley rats listed in PubMed, and 221,446 articles specifically mentioning the use of Wistar rats. This represents an enormous amount of research. Domestic laboratory rats differ from wild rats in many ways. They are calmer and less likely to bite, they can tolerate greater crowding, they breed earlier and produce more offspring, and their brains, livers, kidneys, adrenal glands, and hearts are smaller.

Much modern research on physiology, biochemistry, genetics, diseases, the effects of drugs, and other topics in health

and medicine has been done with rat models. Laboratory rats have also proved valuable in psychological studies of learning and memory. The historical importance of this species to scientific research is reflected by the amount of literature on it, roughly 50% more than that on laboratory mice.[67]

When research is done with an animal model, the investigators invariably describe the methods they use, including the strain of the animals. This is done so that others can repeat the studies if they wish. An assumption is that all Wistar rats will be genetically and physiologically similar. However, a 1972 study compared neoplasms in Sprague-Dawley rats from six different commercial suppliers. They found highly significant differences in the incidences of endocrine and mammary tumors. There were also significant variations in the incidences of adrenal medulla tumors among rats from the same source raised in different laboratories. The authors of the study "stressed the need for extreme caution in evaluation of carcinogenicity studies conducted at different laboratories and/or on rats from different sources."[68]

From our perspective, these findings of great variations in animals are not surprising. Among other things, the physiological status and behavior of animals will differ widely depending on the extent of grounding. Are their cages made of metal, and if they are, is that metal grounded? How close are their cages to wires or conduits carrying 60/50 Hz electricity? From the studies reported here, those factors can make a significant difference. In fact, they represent a "hidden variable" that may have affected the outcomes of countless studies, and could have affected the ability of other investigators to reproduce particular studies.

We know that most, if not all, physiological processes involve electrical activities of one sort or another. When nerves conduct, muscles contract, glands secrete, and sensory organs sense electrical processes are involved. These electrical activities are powered by adenosine triphosphate (ATP) generated by the electron transport chain in mitochondria, a system that requires a continuous supply of electrons.

The conventional view is that all electrical activities in a living system involve ionic currents, but there are good reasons, discussed in the chapter by Oschman and Oschman in this book (Recent Developments in Bioelectromagnetic and Subtle Energy Medicine), and also in reference 53, to consider electron movements as well. We view the acupuncture meridian system as the most likely candidate for distributing electrons from the earth to the system-wide ground substance material, via the point on the ball of the foot known as Kidney 1 (Figure 38.11b).

A consistent observation is that grounding the human body normalizes physiological balances by equilibrating every part of the body with the electrical potential of the earth, thereby stabilizing the electrical environment for all physiological and regulatory processes. The Sokals referred to the earth as a "universal regulating factor in Nature" that strongly influences bioelectrical, bioenergetic, and biochemical processes. Therefore, we are not surprised by the 1972 study comparing neoplasms in rats from different suppliers or animals raised in different laboratories[58].

Often researchers struggle to replicate the results of an important study reported by others. They often assume they are doing something wrong. They may not have considered the electrical environment of their experimental animals. A prediction is that some of the variability in outcomes from one laboratory to another would decrease if experimental animals were provided with a standardized electrical environment. For the animals to be fully healthy and "normal," their cages should be grounded and kept a distance from electrical wiring. This is especially crucial if the study involves measuring recovery from some sort of injury or trauma to the animal being studied. From our experience, the effects of injury or trauma will be very different in grounded versus ungrounded animals.

ELECTRONS VERSUS ANTI-OXIDANTS

Knowing of the potential health effects of reactive oxygen species, commonly called free radicals, and the need to reduce oxidative stress and inflammation to prevent the diseases of aging, it has been easy to convince the public that dietary supplements containing anti-oxidants should keep everyone healthy and prolong lives. An enormous and highly profitable dietary supplement and vitamin business has emerged to meet the resulting demand. Unfortunately, there are fundamental problems with dietary antioxidants.

Dr. David B. Agus is one of the world's leading cancer doctors and a pioneering biomedical researcher. His book, *The End of Illness*, was number one on the New York Times Bestseller List.[69] After reviewing the literature on anti-oxidants, he made the controversial statement shown in the box. As an expert on the body as a complex system, he speaks with some authority on the fact that we still do not know enough about the regulation of oxidative metabolism to be certain about what dietary antioxidants do to the body's normal balancing act between creating free radicals and neutralizing them.

A second issue arises from Agus' statement that "…once inside the human body, they seem strangely powerless." One reason for this is the impenetrable inflammatory barricade, a wall of connective tissue surrounding a site of injury (Figure 38.16). As collagen is a semiconductor,[70] this barrier is readily traversed by mobile electrons, but not by dissolved anti-oxidants.

> Since the early 1990s scientists have been putting these compounds through their paces, using double-blind randomized controlled trials – the gold standard for medical intervention studies. Time and again, however, the supplements failed to pass the test. True, they knock the wind out of free radicals in a test tube. But once inside the human body, they seem strangely powerless. Not only are they bad at preventing oxidative damage, they can even make things worse. Many scientists are now concluding that, at best, they are a waste of time and money. At worst they could be harmful.

Recent discoveries on the ways water associates with the surfaces of proteins and cell membranes reveals a fundamental and little recognized aspect of how anti-oxidants and other substances move within the body. The usual view is that they are absorbed across the intestinal wall, enter the circulatory system, then diffuse from capillaries into the extracellular spaces, and thence to the cells. Gerald Pollack and his colleagues have determined that the water adjacent to surfaces is in a so-called "fourth phase" that makes it distinctly different from the familiar phases: solid, liquid, or gas.[71] The water adjacent to hydrophilic surfaces, such as cell membranes, proteins, and many other molecules is highly ordered into a liquid crystalline arrangement that excludes solutes. Pollack refers to this as the "exclusion zone" and to this aqueous phase as exclusion zone or EZ water (Figure 38.19).

There has been a long debate about the nature of water inside of cells (reviewed, for example, by Luby-Phelps)[72] and it now appears that cells contain little water in which molecules can dissolve and diffuse from place to place. The cell is so filled with highly ordered liquid crystalline proteins/water complexes and exclusion zones that there is little room for the diffusion of solutes. On the basis of Pollack's work, it now appears that the same may be true of the extracellular spaces in the body, as they are virtually filled with polyelectrolyte gel or ground substance. Hence, much of the water inside the body is trapped in a gel state.

This raises a new question. Precisely how do antioxidant molecules get from the circulatory system to the places where they are needed to combat inflammation? Exclusion zones may be found throughout the extracellular spaces that were previously viewed as containing "bulk water" through which molecules can diffuse from place to place. Pollack's work shows that the exclusion zone excludes the protein albumin as well as various dyes with molecular weights as low as 100 daltons, only a little larger than common salt molecules. The inflammatory barricade acts as a further barrier to the diffusion of antioxidants into the "repair field" left behind after an injury.

The free or mobile electron does not have this problem. We view the entire healthy fabric of the body as a semiconductor network. Electrons from the earth can enter this network via the point on the ball of the foot known as Kidney 1, and can be rapidly semi-conducted to any point in the body where they are needed to refill charge reservoirs or to neutralize free radicals.

A final difficulty with the dietary antioxidant story is the manner by which the scientist/entrepreneur demonstrates the value of antioxidant substances. A typical story:

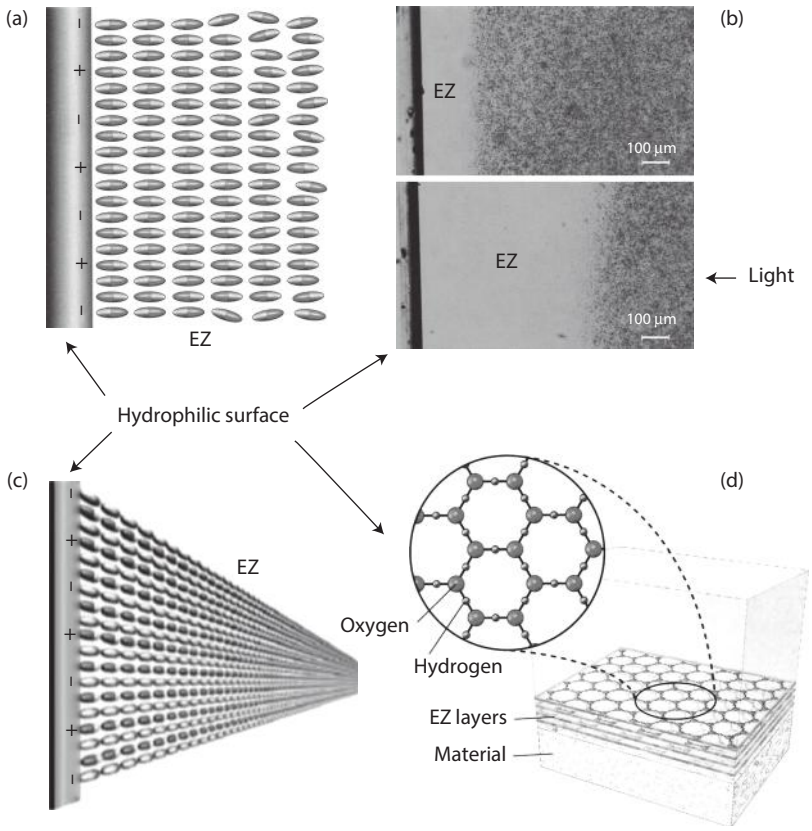

FIGURE 38.19 (**See color insert.**) (a) Dipolar water molecules (electronegative region shown in red) line up adjacent to a hydrophilic (water-loving) surface. (b) The region close to the surface excludes solutes, demonstrated here with the use of microspheres. The lower picture shows how the exclusion zone is expanded in the presence of light. (c) The exclusion zone is extends far from the hydrophilic surface. (d) The water molecules form honeycomb sheets. (From Pollack G. *The Fourth Phase of Water: Beyond Solid, Liquid and Vapor.* Seattle, WA; Ebner & Sons; 2013.)

> Someone picks a perfectly innocent plant, like the blueberry. They chemically extract a molecule from blueberries. Then they put cultured cells in a Petri dish or test tube. These poor cells are under severe oxidative stress, as they are being exposed to an oxygen concentration that is 5–10 times higher than they would ever experience *in vivo*. Under these stressful conditions, the cells secrete measurable amounts of reactive oxygen species (free radicals) in an effort to survive. To this nonbiological preparation our investigator/entrepreneur adds a bit of their blueberry extract. The levels of reactive oxygen species (free radicals) drop significantly. Voilà! We have something we can sell. With a combination of this awful science and good advertising, a billion or so dollars' worth of the antioxidant supplement are sold. A lot of perfectly good blueberries are used up in the process, and many unsuspecting people have less money but no less inflammation.

We can make a distinction between physical anti-inflammatory methods (earthing) and chemical anti-inflammatory methods (blueberries, cranberry capsules, Green tea extract, effervescent vitamin C, pomegranate concentrate, beta carotene, selenium, grape seed extract, high-dose vitamin E, pine bark extract, bee spit, and the like). The case for this is put forward succinctly in *The Antioxidant Myth: A Medical Fairy Tale*.[73]

The flow of electrons from the earth into the body via Kidney 1, located on the ball of the foot (Figure 38.11), and then throughout the meridian system, can explain how the mobile electron can serve as a natural antioxidant. A working hypothesis is that the body is composed of semiconducting materials that form a network (called the living matrix) that extends throughout the body. It can thereby saturate all of the polyelectrolyte polymers or ground substance matrix with electrons that are then available to participate in any inflammatory process, large or small, taking place in any tissue in the body.

This is not to say that earthing does not affect the chemistry of the body. Most, if not all, biochemical reactions are redox reactions involving transfers of electrons. Paul H. Scudder has published a book on organic chemistry in which all of the organic reactions are described in terms of electron transfers.[74] Scudder breaks down common organic processes into their basic units to explain the electron flow pathways that underlie these processes. The glycosaminoglycan ground substance stores electrons so they will be available where and when needed. This point was confirmed by one of the leading experts on ground substance, Professor Hartmut Heine.[75] It appears that the ground substance can become depleted of electrons when a person has not contacted the earth for a long time.

CONCLUSIONS

The earthing or grounding studies can be summarized with the statement that connecting with the earth is easy and can have many benefits. It is something anyone can do without cost by simply removing their shoes and socks and walking barefoot on the earth. Various methods have been developed to bring an earth connection into the home or office. It has been suggested that this is especially important for those living or working in high-rise buildings.

The research on earthing has revealed a new picture of the nature of inflammation and the reason it can lead to chronic diseases. We can see the inflammatory barricade, which was recognized in ancient times and is still accepted by Western medical science as a common response to injury, does not have to form. Prevention of chronic inflammation is accomplished by having the body's ground substance reservoirs saturated with electrons that can prevent "collateral damage" in healthy tissues, provided that the person is grounded and the living matrix is functioning properly.

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Section VIII

Mechanisms of Action and Hypotheses

39 Recent Developments in Bioelectromagnetic and Subtle Energy Medicine

James L. Oschman and Nora H. Oschman*

CONTENTS

> Intuition makes us look at unrelated facts and then think about them until they can all be brought under one law.
>
> **–Albert Einstein (from Hermanns 1983)[1]**

INTRODUCTION

From the edges of science, the places conventional scientists shy away from, several completely new ways of looking at bioelectromagnetic and subtle energy interactions are emerging. Individually, many of these insights are either controversial or simply ignored by the mainstream. However, when they are fitted together, these seemingly unrelated issues, and the technical details about them, point toward concepts of profound significance for public health and medicine. "Profound significance" is emphasized, as we are discussing serious attempts to understand and develop treatments for our most costly, debilitating, and deadly diseases that will continue to ruin the lives of people and the economies of nations until medicine comes to grips with them.

Some scientists and physicians have recognized that our inability to treat cancer, cardiovascular disorders, and other chronic diseases, the most frequent causes of disability and death worldwide, is probably due to the fact that we are just not looking at these issues in the right way. For example, from a world-famous cancer doctor and medical researcher:

> I'm infuriated by the statistics, disappointed in the progress that the medical profession has made, and exasperated by the backward thinking that science continues to espouse, which no doubt cripples our hunt for the magic bullet. Medical science has made extraordinary progress over the past century, but in my field (oncology), the progress stalled out decades ago.
>
> **–David B. Agus MD[2]**

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This chapter will point out what we regard as some of the "backward thinking" Agus mentioned, and will present and discuss concepts that add up to a new perspective on regulatory biology with direct relevance to cancer and other chronic diseases. Recognition of each of these perspectives has been hampered by a set of flawed textbook explanations and over-simplified images of how the human body works. Each of these concepts will be the topic of a section in the presentation. They are

- It is instructive to view the mammalian cell as a microorganism
- Exciting biology takes place one or two levels below molecules
- Biomedicine has been stuck with the millennia-old legacy of Lucretian or "billiard ball" biochemistry
- Our over-simplified view of hormone-receptor and substrate-enzyme interactions
- Lucretian biochemistry and olfaction

It is instructive to view the mammalian cell as a microorganism

> A single-celled paramecium swims gracefully, avoids predators, finds food, mates, and has sex, all without a single synapse. "Of nerve there is no trace. But the cell framework, the cytoskeleton might serve."
>
> **–Sherrington, 1951[3]**

The quotation reminds us of the existence of evolutionarily ancient systems for sensation, information processing, and movement that are present in single celled organisms. These minute creatures are entirely lacking in nerves or synapses. How does a "primitive" creature, such as a paramecium,

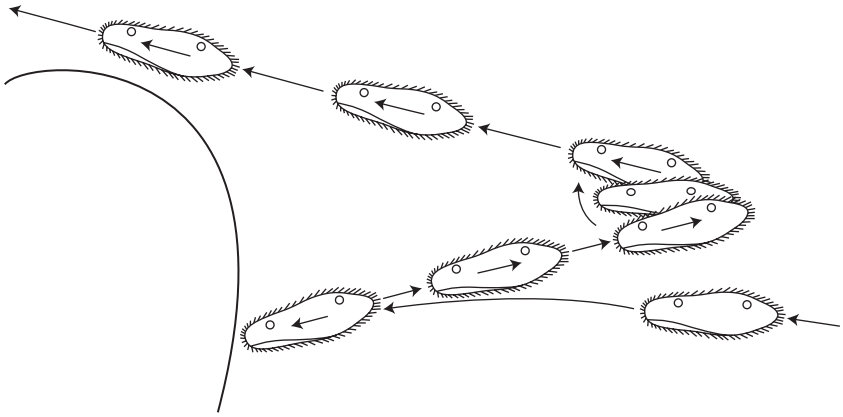

FIGURE 39.1 A single-celled paramecium swims gracefully, avoids predators, finds food, mates, and has sex, all without a single synapse. "Of nerve there is no trace. But the cell framework, the cytoskeleton might serve." ~Sherrington, 1951. (Based on Jennings HS. 1906. *Behavior of the Lower Organisms*. New York, NY: The Columbia University Press. Figure 36, page 48.)

lead such a sophisticated life? How does it hunt living prey, respond to lights, sounds and smells, mate, and display other complex sequences of movements, all without the benefit of a nervous system (Figure 39.1)?

In 1972, a distinguished American geneticist, Theodore T. Puck, published *The Mammalian Cell as a Microorganism*.[4] While it never reached the New York Times Bestseller List, Puck's book put forward a concept, based on careful study of the behavior of mammalian cells in culture, which provides a useful perspective. While a mammalian cell may be 500–1000 times larger than a bacterium, they share similar survival mechanisms. Hence, every one of the trillions of cells in our bodies is a sophisticated system capable of listening and responding to its environment in ways comparable to those present in the lowly paramecium.

In *Wetware: A Computer in Every Cell*, Dennis Bray explains how all cells are built of molecular biochemical circuits that process information from the environment and how they perform logical operations, comparable in sophistication to those taking place in electronic devices.[5] Bray defines *Wetware* as the sum of all of the information-rich biochemical processes and "computations" taking place inside a cell – the interactions of dissolved molecules or arrays of molecules forming complex webs or circuits. For example, the bacterium *Escherichia coli* has a cluster of trans-membrane receptors and associated molecules that detect chemical attractants and repellents. The cluster amplifies the signal about 35-fold.[6] Once a stimulus has been detected, information can propagate through protein complexes within the cell via conformational waves. This could be a universal mechanism for functional integration within living cells, as described by Bai et al.[7]

Mammalian cells contain miniature "musculoskeletal systems" composed of microtubules (the "bones" of the cell), microfilaments (the "muscles" of the cell), and fibrous protein networks that can act as a sort of microscopic "connective tissue/nervous system." These components enable cells to "listen" to their environment and then change shape, divide, and migrate from place to place as needed to maintain themselves and the integrity of the whole organism. Like any other microorganism, the mammalian cell can sense when its environment is unfavorable, and respond appropriately in an attempt to survive and continue the processes for which it was designed.

Microorganisms have two responses to environmental stress: they can wall themselves off from their environment by forming relatively impenetrable cysts or spores that protect them until conditions improve or they can migrate away in search of a more favorable milieu. We can reasonably ask, do these two primitive cellular responses correspond respectively to the formation of tumors and metastasis in multicellular organisms?

In recent years, it has been discovered that bacteria also contain a number of cytoskeletal structures that are homologs of the three major types of eukaryotic cytoskeletal proteins, actin, tubulin, and intermediate filament proteins.[8] The behavior of the paramecium supports our assertion that mammalian cells are capable of utilizing primordial sensory, communication, and movement systems that are far older in terms of evolution than the nervous system. The extracellular coats of the "primitive" microorganisms evolved into the mammalian extracellular matrix. Specifically, the extracellular sugar polymer coatings of individual bacteria, viruses, and protozoa extended the "reach" of these ancient organisms into their environments and formed the oldest and most pervasive information and defense system in nature (Figure 39.2). The connective tissue and fascia are modern expressions of these early cell coats. Hence, primordial systems for sensation, information processing, and movement persist throughout the modern mammalian organism. Contemporary biologists and neuroscientists are so captivated by nerves and nerve nets that they rarely think about the possibility that there may be other intracellular and extracellular communication systems that could explain phenomena that are difficult to account for by neural mechanisms.

A search for communication systems that are faster than the nervous system was initiated because of an interest in biophysical mechanisms involved in unconscious mental processing. That inquiry began, in part, because of a mutual

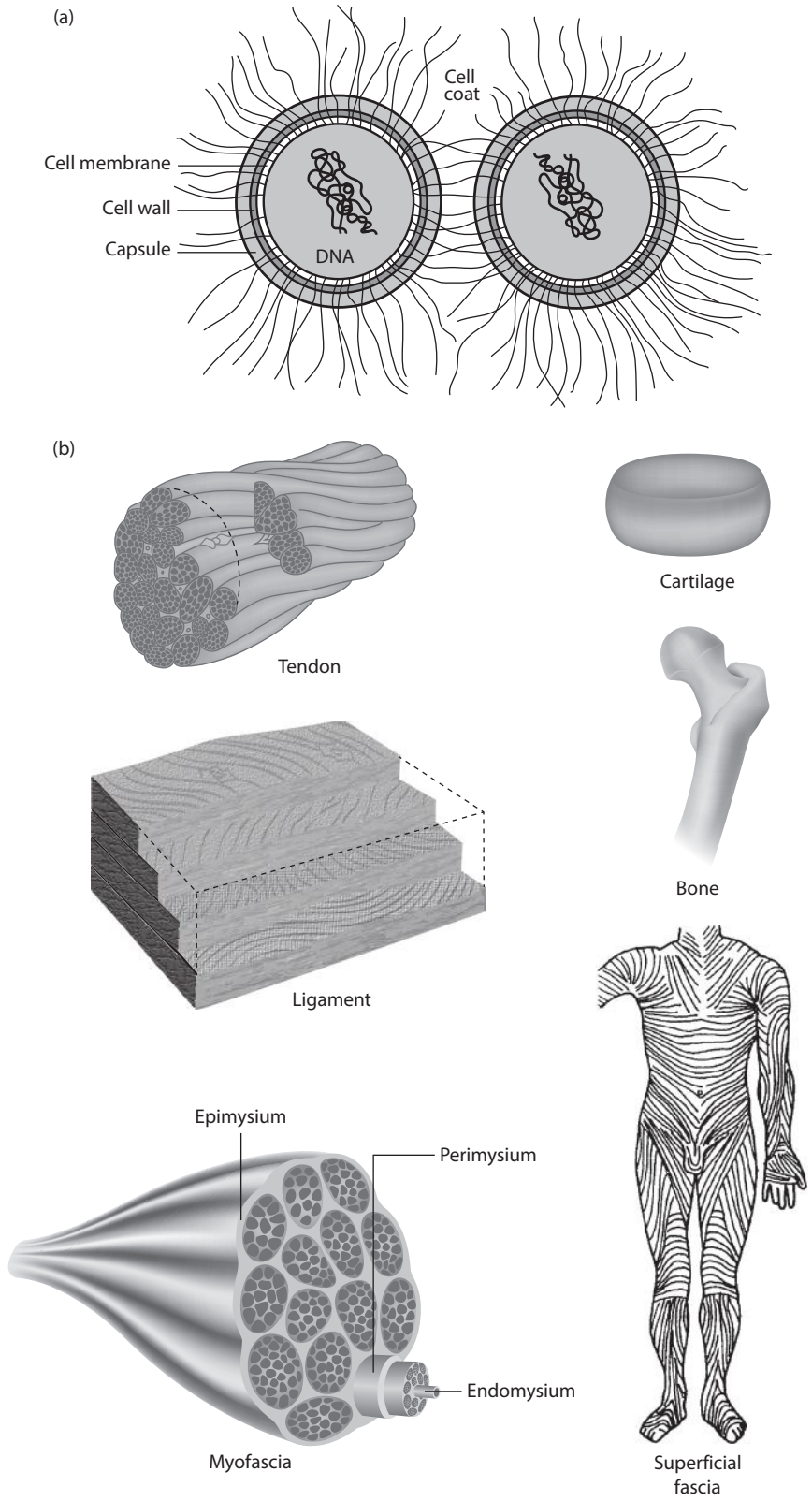

FIGURE 39.2 (a) The extracellular sugar polymer coatings of individual bacteria, viruses, and protozoa extended the "reach" of these ancient organisms into their environments and formed the oldest and most pervasive information and defense system in nature. (b) The connective tissue and fascia are modern expressions of these early cell coats; (b) is based on Figure 2.5.1 in Oschman JL Fascia as a body-wide communication system, Chapter 2.5 in Fascia: The tensional network of the human body. (Reprinted from Schleip R, Findley TW, Chaitow, L, Huijing PA, Eds, *Fascia: The Tensional Network of the Human Body: The Science and Clinical Applications in Manual and Movement Therapy*, 1st Edition. p. 106, Copyright 2012, with permission from Elsevier.)

interest, shared with Maurie D Pressman, MD, in the nature of the "altered state" often referred to as "the zone" that is experienced by elite athletes and other performers.[9] This state is characterized by heightened perception of the environment and extremely rapid actions or movements that seem far too fast and sophisticated to be explained by neural processing. It was proposed that "the zone" is a manifestation of an aspect of the unconscious mind: its capacity to absorb and utilize vast amounts of sensory information by means of rapid signal processing. The idea is that these phenomena result from a combination of ultra-fast biological processes that are present in all cells and tissues, including but not limited to neurons. Semi-conduction, wetware, electromagnetic-photonic communications, and quantum coherence are examples of such processes. A conclusion was that there are a number of biophysical processes that are good candidates for the global system that both accounts for remarkable or peak athletic or artistic performances, that regulates cellular activities throughout the body, and that creates chaos for cells and tissues (that is, disease) when it is not functioning properly. Hence, an exploration of these processes is a very worthy endeavor that could potentially lead to major advances. Fortunately, we now have the means to study these processes.[9]

EXCITING BIOLOGY TAKES PLACE ONE OR TWO LEVELS BELOW MOLECULES

Albert Szent-Györgyi, considered by some to be the "Father" of modern biochemistry, lost a daughter and a wife to cancer. This inspired him to dedicate his brilliant and insightful mind to solving the riddle of cancer.

> Most human suffering, at present, is caused by the so-called "degenerative diseases" – the name standing for "diseases we don't understand and, consequently, can do nothing about." The existence of such a closed group of diseases also points towards some major gap in our basic knowledge. Possibly, all these gaps, may they relate to normal function or to disease, have one common denominator, some process which, hitherto, eluded detection. Some fundamental fact, if not a whole dimension, is missing from our biological thinking.[10]

He quickly realized the reason for the continuing failure of medical researchers to make progress against the most deadly ailments of our times. He was convinced that the problem was that modern medicine, distracted by the rapid advances in biochemistry, molecular biology, and pharmacology (he had made fundamental discoveries in each of these areas), had dropped energetics from serious study and consideration. In the process, energetic interactions were neglected, except for the study of the metabolism of high energy phosphate bonds. A search for the missing facts or dimensions has been a major motivation for our studies of energy medicine, leading up to this article. Szent-Györgyi had no time for searching for "a magic bullet."

> We can't understand cancer until we understand life, because cancer is just distorted life. I can control only what I understand. The whole cancer field, for as long as I can remember, has been centered on coming up with a quick cure for the disease. This is plain nonsense. First you must understand how the cell is put together – how it works.[11]
>
> He sought to understand not why cancer cells grow, but what stops normal cells from proliferating except when required. You cannot regulate traffic with only a green light. You must have a green and a red light. He suggested that the regulatory mechanism had originated very early in the evolution of the earth, in early living systems.[12]

Szent-Györgyi concluded that life is too rapid and subtle to be explained by clumsy macromolecules, slow moving chemical reactions, and nerve impulses. In other words, living systems must have a primordial regulatory system that can move energy and information extremely rapidly throughout the body. He was convinced that this ancient regulatory system depended on small, highly mobile, and responsive entities: delocalized electrons and very mobile protons. So he looked at electron transfers between the molecules that join together to form cells and tissues. He suggested that anything that disrupts charge-transfer processes in and between proteins might drive cells into the cancerous state. Cancer and other chronic diseases occur when that system is not working properly, when cells lose touch with neighboring cells and tissues. He began a search for this system, publishing his pioneering studies in the early issues of the *International Journal of Quantum Chemistry* and in books entitled *Bioenergetics*,[10] *Introduction to a Submolecular Biology*,[13] *Electronic Biology and Cancer: A New Theory of Cancer*,[14] and *The Living State and Cancer*.[15]

Szent-Györgyi felt he had to go below the molecular level, to the sub-molecular level, which could only be studied with quantum physics. Though he was an obvious candidate for some of the federal government's "war on cancer" money, Szent-Györgyi refused to write the kind of grant applications that such funding required. Investigators were expected to explain in detail the work they planned to do, the results they expected to achieve, and how long it would take. Szent-Györgyi, still doing basic research, maintained that if he already knew what he would do and what he would find, he would not need funding! He knew only the direction in which he wanted to go out into the unknown; he had no idea what he was going to find there and how he was going to find it. His frustration with the granting process was expressed in a letter to *Science*[16] and in an article entitled *Looking Back*[17] and led to some critical discussion about how grants are awarded.[18]

Szent-Györgyi's ideas about cancer—which incorporated quantum physics—seemed bizarre to most grant reviewers. Few of them realized that he had spent 6 months at Princeton's Institute for Advanced Studies to find out what quantum physics had to say about electrons. The result:

> The author spent half a year [January 1, 1950–June 30, 1950[19]] at the Institute for Advanced Studies, at Princeton, enjoying this wonderful institution's boundless hospitality. He did so in order to be able to rub elbows with those who know most about electrons, hoping to find help for a better understanding of biological phenomena. [Albert Einstein was a member of the Institute's Faculty at the same time that

> Szent-Györgyi was there]. He found a profound and sympathetic interest in biology. However, when he revealed that living systems contain more than two electrons, physicists turned their backs on him in terror, mathematical difficulties becoming insurmountable. With all their computers they could not say what the third electron might do. The remarkable thing is that it knows exactly what to do. So that little electron knows something that all the wise men of Princeton don't, and this can only he something very simple.[20]

It was then, and still is, generally agreed that cancer is a problem of molecular biology and biochemistry, not quantum mechanics. In fact, few of his grant reviewers knew enough about quantum physics to evaluate his work, and they were not really interested in learning about it. It was much easier to dismiss him as an antiquated scientist who was behind the times, when, in fact, his mind was as sharp as ever and far ahead of the curve. There was a widely shared view that Szent-Györgyi had passed his prime and he should be more or less "put out to pasture" like an aging mare, by giving him a small grant so he could finish out his days "puttering around in the laboratory." I asked colleagues at Woods Hole specifically what their problem was with his approach. When pressed, they would confess that they really did not understand his ideas. This seemed a bit arrogant, dismissing a scientist's work without understanding anything about it. One of his grant reviewers described the situation: "His ideas on cancer research never seemed really promising to me…We regretfully came to the conclusion that the underlying conceptions did not look promising compared to research that was going on elsewhere."[21] In retrospect, "the promising research that was going on elsewhere" continues to this day, still with little real progress. To repeat, in the words of noted cancer doctor and researcher, David B. Agus MD, "… in my field (oncology), the progress stalled out decades ago." We will never know what the aging genius, Albert Szent-Györgyi, could have discovered had he been given the support he requested at the time he asked for it.

BIOMEDICINE HAS BEEN STUCK WITH THE MILLENNIA-OLD LEGACY OF LUCRETIAN OR "BILLIARD BALL" BIOCHEMISTRY

Atomism (from Greek ἄτομον, atomon, that is, "uncuttable" or "indivisible") is a natural philosophy that developed in several ancient traditions. The Greek atomists, Democritus (460–370 BC), Epicurus (341–270 BC), and Lucretius (99–55 BC) theorized that nature consists of two fundamental principles: atoms and void. Atoms come in an infinite variety of shapes and sizes, each indestructible, immutable and surrounded by a void, where atoms collide with the others or join together to form clusters. Clusters of different shapes, arrangements, and positions give rise to the various macroscopic substances in the world. Of course we now know that atoms are divisible into parts and those parts can be further decomposed.

The legacy of atomism is the concept that atoms are billiard-ball like particles that collide or join together to form molecules, which are also particles that diffuse more or less randomly through a relatively inert suspending medium, water (corresponding to the ancient "void"). The brilliant English scientist, John Dalton (1766–1844), agreed with Democritus. All matter is made of indivisible and indestructible atoms. In honor of Dalton's work, many chemists and biochemists use the unit "dalton" (abbreviated Da) to denote the mass of atoms and molecules.

In 1957, Albert Szent-Györgyi pointed out that biochemistry generally assumes that no interaction can take place between molecules unless they touch one another. Scientists have applied a lock and key model, with variations, to virtually all situations in which molecules interact. Examples include olfaction, cellular regulations (as in embryogenesis, wound healing, regulation of normal and abnormal growth, such as in cancer and other diseases), and the enzyme-substrate interactions involved in cellular metabolism. With few exceptions, scientists have rarely considered the fact that molecules do not actually have to touch each other to interact. In fact, molecules cannot physically touch, as they do not have real surfaces as we experience them with objects we can touch. Albert Szent-Györgyi pointed out many years ago that, "The transmission of excitation energies between molecules through electromagnetic coupling is not a mere matter of speculation."[22]

Szent-Györgyi referred to atomism as "Lucretian biochemistry" and viewed its legacy as one of many persistent conceptual dilemmas:

> Lucretian biochemistry involves the assumption that no interaction can take place between molecules without their touching one another. Support is given in this book[23] to the idea that manifold interactions can take place without such bodily contact, either through energy bands or through the electromagnetic field, which thus appears with water and its structures as the matrix of biological reactions…In accordance with the basic concepts of Lucretian chemistry, biology dealt with molecules and their aggregates as isolated units, separated by the water which fills the space between them….Water is more than this; it is part and parcel of the living matter itself. One of the main functions of the protoplasmic structures [cytoskeleton and nuclear matrix] may be to generate in water those specific structures which make forms of electronic excitations and energy transmissions possible which would be improbable outside these structures.
>
> **–Albert Szent-Györgyi [statement in brackets added]**

We know that all molecules at temperatures above absolute zero are oscillating or vibrating, and that this results in the emission of characteristic electromagnetic fields. Spectroscopy (Figure 39.3) is the process by which the emissions or absorptions of different wavelengths of light are used to determine the atomic structure of molecules. The basic physics involves the production of oscillating fields by vibrating charged components of molecules under the influence of light at the resonant frequencies of the chemical bonds. When the electrons in a molecule vibrate, they produce electromagnetic fields that depend for their frequency on the ways they

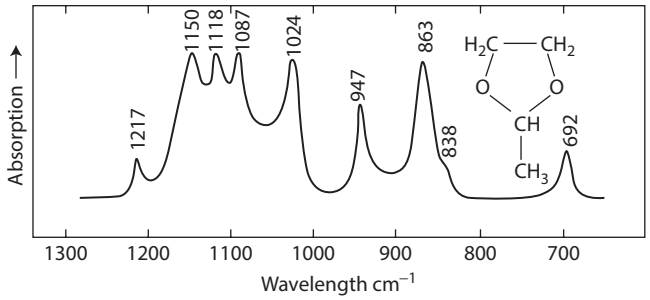

FIGURE 39.3 The infrared absorption spectrum of 2-methyl dioxalane, and its molecular structure. This use of infrared spectra for identifying unknown compounds has led to their being called, with much justification, the "fingerprints" of chemical compounds. (Whiffen DH. *Spectroscopy*, 2nd ed. p. 102. 1996. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

are connected to neighboring atoms. A carbon atom bonded to a nitrogen atom will have a different resonant frequency than a carbon atom bonded to sulfur atom, for example. An emission spectrum (Figure 39.3) has various peaks corresponding to the different atoms present in the molecule. Chemists and biochemists use spectra such as this to identify unknown compounds.

In terms of biological electronics, one essential role of water structure Szent-Györgyi referred to is impedance matching between the oscillating molecule and the propagating medium. Impedance matching is essential for efficient transmission of energy from one phase to another. It is the same phenomenon used when one attaches an 8 ohm loudspeaker to the 8 ohm terminals of an audio amplifier. Stated differently, water both conditions and it is conditioned by the molecules and molecular frameworks in cells and tissues. A part of the impedance matching involves the spin of water molecules.[24]

In physics, resonance is the tendency of a system to oscillate with greater amplitude at some frequencies than at others. When two objects are separated by some distance and have the same resonant frequency, the vibrations or oscillations of one can be transferred to the other. In the case of the tuning fork effect, striking one tuning fork that is designed to resonate at a particular frequency will cause other nearby objects with the same resonant frequency to vibrate as well. Currently, the most widely used tuning fork produces the note A above middle C = 440 Hz, because this is the standard concert pitch used to tune many orchestras. It is the resonant frequency of the violin's second string, the first string of the viola, and an octave above the first string of the cello.

Resonance phenomena occur with all types of vibrations or waves and in all types of media: there is mechanical resonance, acoustic resonance, electrical and electromagnetic resonance, nuclear magnetic resonance (NMR), electron spin resonance (ESR), and resonance of quantum wave functions. In the case of sound, the medium is air; in the case of electromagnetic fields, the medium is space. An individual atom or molecule will have many resonant frequencies. In the case of atoms, the *Handbook of Chemistry and Physics* has lengthy tables listing the resonant frequencies of all of the elements, which have been measured with an accuracy of a thousandth of an Angstrom unit. An Angstrom unit is equivalent to one ten-billionth of a meter. The four most abundant elements in living matter are hydrogen with 26 emission frequencies, carbon with 222, oxygen with 401, and nitrogen with 450.

Resonant electromagnetic interactions within and between living systems and their environments, and vice versa, have been difficult for many to grasp, in spite of all of the documentation and conceptual simplicity. This is remarkable, considering that action at a distance is an accepted part of Newtonian mechanics, and is widely thought to explain the motions of the celestial bodies. Moreover, spectroscopy is the method that enables astronomers, astrophysicists, and cosmologists to determine the chemical composition of distant stars and galaxies. If resonance can communicate chemical information over the vast distances of space, there is no reason in principal that molecules in the body should not communicate with each other through resonant electromagnetic interactions, particularly when all of the molecules are immersed in the ideal medium for impedance matching and vibratory transfer, water.

A legacy of Lucretian biochemistry is that it is generally accepted that the molecules reacting with each other inside of a living cell must diffuse randomly within the cytoplasmic fluids until they accidentally collide with enzymes that transform them as part of a biochemical sequence. The product of that collision is then supposed to diffuse randomly until it chances to bump into the next enzyme in the reaction pathway. It does not take a lot of analysis to realize that this type of biochemistry is far too slow to account for the hundreds of thousands to millions of processes taking place each second in a living cell.

A much more logical explanation for biochemical reactions in cells is provided by the *metabolon* concept introduced in the 1970s by Soviet and American biochemists. The metabolon is a structural-functional complex formed between sequential enzymes of a metabolic pathway, held together by noncovalent interactions with structural elements of the cell, such as integral membrane proteins or the cytoskeletal fabric. The metabolon changes our picture of biochemical sequences from dependence on slow diffusion of reactants from enzyme to enzyme to a model resembling the sequence of steps taking place on an automobile assembly plant. Metabolons enable rapid and efficient channeling of an intermediary metabolic product from an enzyme directly into the active site of the subsequent enzyme of a metabolic pathway. The concept was first conceived by Kuzin in the USSR[25] and adopted by Srere[26] of the University of Texas for the enzymes of the tricarboxylic acid (Szent-Györgyi-Krebs) cycle. This hypothesis was accepted in the former USSR and further elaborated for the complex of glycolytic enzymes (Embden-Meyerhof-Parnas Pathway).[27–29] The name "metabolon" was published in 1985 by Srere.[30]

To complement the metabolon model is the development of femtosecond time-resolved spectroscopy by Ahmed H.

Zewail that made it possible to see how atoms in a molecule move during a chemical reaction, using ultra-short laser flashes, on the time scale on which the reactions actually occur.

While the mechanical analogy between the enzyme complex and an automobile assembly plant is easy to visualize, there is yet another way of looking at the situation. Guenther Albrecht-Buehler[31] has pointed out that, "Biological molecules seem to have a size that keeps them poised in between the deterministic worlds of classical mechanics and the indeterministic world of quantum mechanics." In addition, "our intuition fails, based as it is on our experience with the macroscopic world, when it comes to judging the technical problems that cells have to overcome." Related to this is recent research from the Fleming group at the University of California at Berkeley revealing remarkable quantum processes taking place in the leaves of green plants:

> Wavelike electron energy transfer within the photosynthetic complex explains its extreme efficiency. It allows the excited electron to sample vast areas of phase space to find the most efficient path.
>
> **–Engel et al.[32]**

It will be fascinating to see if the metabolon turns out to be less a mechanical assembly plant than a quantum device, transforming metabolites as waves rather than as particles. Again, this is a plausible idea, given a widely accepted quantum wave model for the structure of matter.[33,34] The existence of matter waves was proposed by Louis de Broglie, who received the Nobel Prize for Physics in 1929. Matter waves have actually been created in the laboratory and are described as part of the 2001 Physics Nobel Lecture given by Wolfgang Ketterle.[35]

OUR OVER-SIMPLIFIED VIEW OF HORMONE-RECEPTOR AND SUBSTRATE-ENZYME INTERACTIONS

A look at what we have been taught about biological regulations shows that something vital is missing from the conventional picture. For example, we learn that living systems are regulated by a variety of types of messenger molecules such as hormones, neurohormones, neuropeptides, growth factors, endocannabinoids, and cytokines, to name a few. A recent review by Friker describes and defines the various classes of neuropeptides and related signaling molecules:

> Neuropeptides are the largest group of cell-cell signaling molecules, with over 100 different peptides known to function in this capacity. In addition, hundreds more peptides have been physically identified but do not have known functions, and some of these peptides are likely to have additional roles in cell-cell communication.[36]

In other words, our understanding of regulatory biology is far from complete. The "hundreds more peptides [that] have been physically identified but do not have known functions" represent an enormous opportunity for important research into a vital area of biomedical research. The living body probably has many more regulatory loops than are known at present. In addition, these loops interact with one another in important ways. As an example, the fabric of regulatory molecules called cytokines regulates the immune system's intricate responses to injury. Candace Pert and her colleagues have identified a psychosomatic network that joins the brain, glands, and immune system that is probably the biochemical substrate of emotions.[37] Shavit and colleagues have described how stress, opioid peptides, the immune system, and cancer are related.[38] Their summary diagram, Figure 39.4, shows the psychosomatic network, with the arrows connecting different components corresponding to particular signal molecules. From this discussion, a different image will emerge, in which some of the arrows represent electromagnetic/photonic interactions instead of diffusing molecules.

While molecules do tend to diffuse from regions of high concentration to regions of low concentration, statistically some molecules will move in the opposite direction. This means that when molecules are released from a source such as a secretory cell, as shown in Figure 39.5a, they tend to diffuse away in all directions. Latin, "diffundere" means "to spread out." The motions have little order to them; they bump and stagger about, the result of random bumping by surrounding molecules such as water (Figure 39.5c). The diagram shows a sugar molecule (glucose) being jostled about by the water molecules around it, drawn at about the same scale. The diagram to the right shows how a sugar molecule travels more than 3 meters per second, but it does not make much linear progress because it keeps bumping into water and other molecules around it. The jagged line represents the path taken by a single glucose molecule in a fraction of a second. This is referred to as a random walk. Eventually, signal molecules are supposed to encounter receptors on the surfaces of distant cells, activate the second messenger systems within the cells, and trigger changes in cell behavior (Figure 39.5b). Cellular processes are thought to be regulated up and down, depending on the concentrations of the messenger molecules. However, there are profound problems with these schemes.

The compartments through which regulatory molecules diffuse, both outside and inside of cells, are usually viewed as dilute saline solutions, sometimes called volume conductors. These images are incomplete and inaccurate and lead to much confusion. Diffusion of regulatory molecules is a relatively slow and random process because there is little motivation for the signals to move in any particular direction, that is, toward or away from their respective receptors. The only directionality for diffusional processes is created by the gradient in concentration. Generally, steeper concentration gradients yield faster diffusion. Small molecules diffuse more rapidly than larger ones. The process is quantified by Fick's Laws of diffusion.

A key issue is that signal molecules and their target cells do not float about freely in a large volume of dilute fluid,

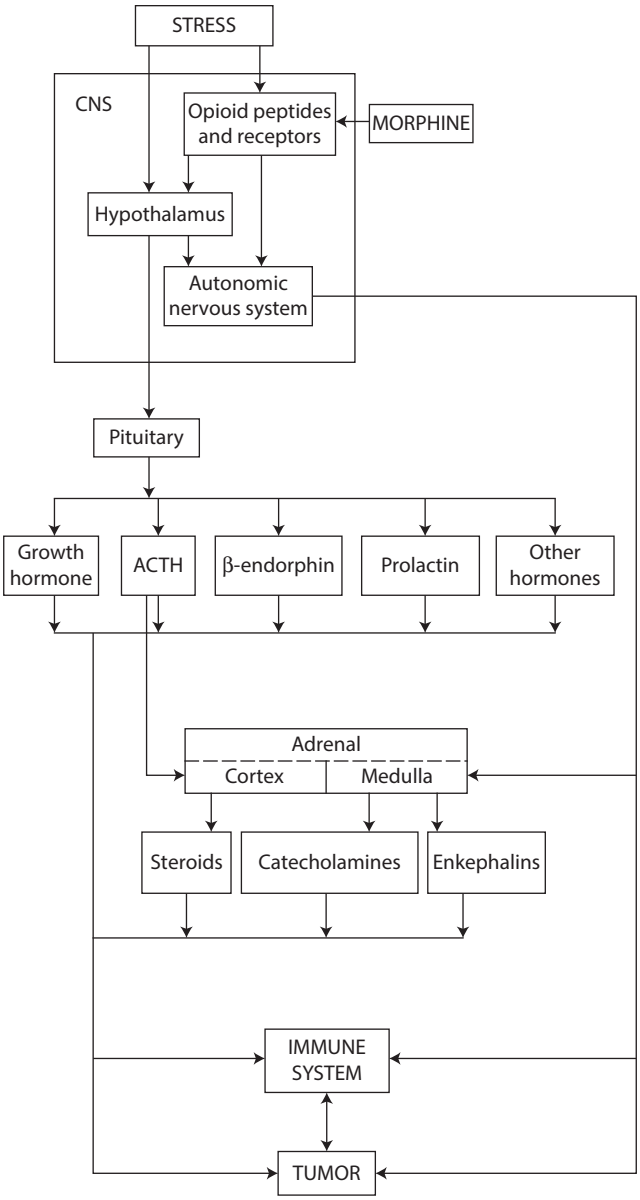

FIGURE 39.4 The neural and neurohumoral mechanisms by which stress and morphine might affect the immune system and tumors. The diagram also documents some of the interacting systems of systems Pert et al.[37] termed *the psychosomatic network*. The arrows connecting different components correspond to particular signal molecules. From this discussion a different image will emerge, in which some of the arrows represent electromagnetic/photonic interactions instead of or in addition to diffusing molecules. (From Shavit Y et al. *J Immunol* 1985;135(2):834s–7.)

which would be easy to model with Fick's Laws. Both the extracellular spaces and the cytoplasm of the cell are filled with highly charged polymers, or ground substances.[39] A modern understanding of the situation, due to the work of Gerald Pollack and colleagues, is that polymer and cell surfaces organize extended layers of water known as exclusion zones. These regions are virtually impenetrable to all but the smallest solutes.[40] Moreover, cells can be packed close together within some tissues. Many cells are organized into layers called epithelia. While some epithelia are only one cell thick, with their basal surfaces bathed in extracellular fluids, other epithelia consist of many layers of cells packed closely together on top of each other (Figure 39.6). Cells that are relatively isolated from the circulatory system and extracellular fluids (serosa) include four of the seven types of epithelia shown. These types of epithelia are found in many different tissues.[41]

Other problems with this scheme have been summarized by Guenther Albrecht Buhler in his valuable perspective entitled *In Defense of 'Nonmolecular' Cell Biology*. If one considers the average fluid volume around an individual cell and a hormone with a concentration of 1 pM (6×10^{11} molecules/liter) there will be approximately eight molecules in the space surrounding the cell. In the region around the receptor the hormone concentration, for all practical purposes, is approximately zero (Figure 39.7). Albrecht Buhler concluded that our usual concept of concentration, at or near receptor sites, is essentially meaningless. The idea that hormones and other regulatory molecules can diffuse from some source, through the tissue fluids, to a receptor on the surface of a cell, and then activate a cellular process, when the concentration of the regulatory molecule reaches a certain level, is highly improbable.

The way hormones and other signals activate receptors is usually viewed with the "lock and key" model. As everyone has inserted a key into a lock to open a door, the image of molecules behaving this way is easy to grasp. The model dates to 1894, when the German organic chemist Emil Fischer (1852–1919) was trying to explain the highly selective nature of enzyme-substrate interactions. "Only with a similar geometric structure can the molecules approach each other closely, and thus initiate the chemical reaction. To use a picture, I would say that the enzyme and glucoside must fit each other like a lock and key."[42] This picture caught on, and is with us today.

The problems with this model are rarely mentioned in textbook descriptions of biological regulations. Early issues with the scheme led to alternative descriptions, such as the template model, the induced fit model, and the flexible enzyme or "hand in glove" model.[43] Many researchers were able to demonstrate that receptors undergo significant conformational changes when contacted by a ligand.[44] However, these studies were done on pure and dehydrated protein crystals, and do not accurately reflect molecular events taking place in the aqueous environment of the intact organism. This is a large problem in biochemistry, because it is so easy to assume that events taking place in isolated enzymes can serve as models for processes in the intact organism.

The alternative to all of these schemes is direct electromagnetic signaling between molecules, which is extremely fast and highly specific when compared with the diffusion and lock and key models (Figure 39.8). The same stereochemical considerations that enable the key to fit into the lock apply equally to electromagnetic resonance between the signal and the receptor. Specifically, the signal molecule will have structures that vibrationally match components of the receptor, so they will be ideal candidates for multiple

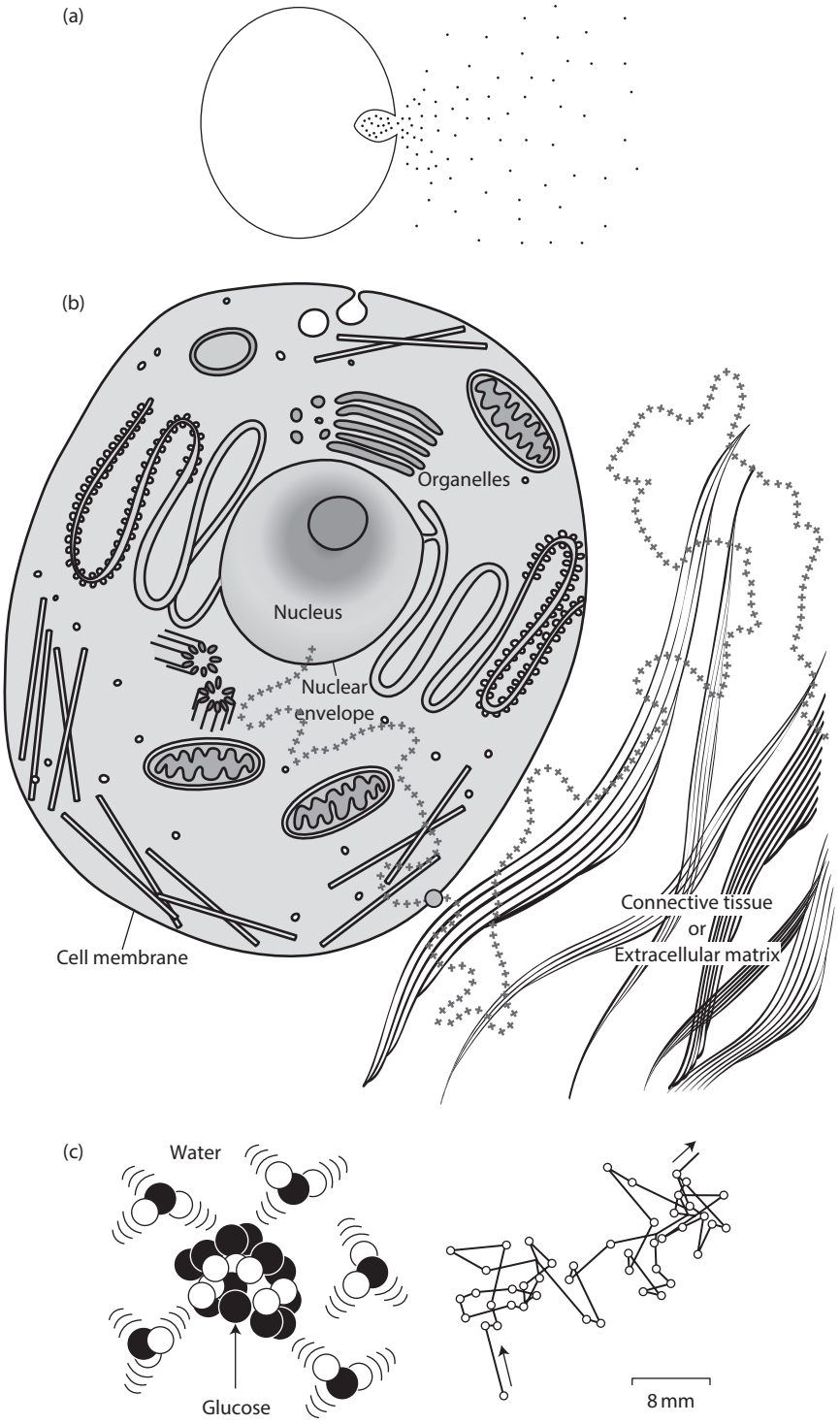

FIGURE 39.5 (a) When signal molecules are released from a source such as a secretory cell, they diffuse away in all directions. Latin, "diffundere" means "to spread out." (Drawing by J.L. Oschman.) (b) The accepted scheme for the diffusion of a signal molecule from a source, through the connective tissue, to the cell surface, where it interacts with a receptor (circle in membrane) that may trigger the release of a second messenger inside the cell to a site of action. (Drawing by J.L. Oschman.) (c) A sugar molecule (glucose) showing how it is jostled about by the water molecules around it. "Brownian motions" drawn at about the same scale. The diagram to the right shows how a sugar molecule travels more than 3 meters per second, but it does not make much linear progress because it keeps bumping into water and other molecules around it. The jagged line represents the path taken by a single glucose molecule in a fraction of a second. (From Oschman JL *Energy Medicine: The Scientific Basis*. Edinburgh: Churchill Livingstone, p. 123; Figure 9.1.)

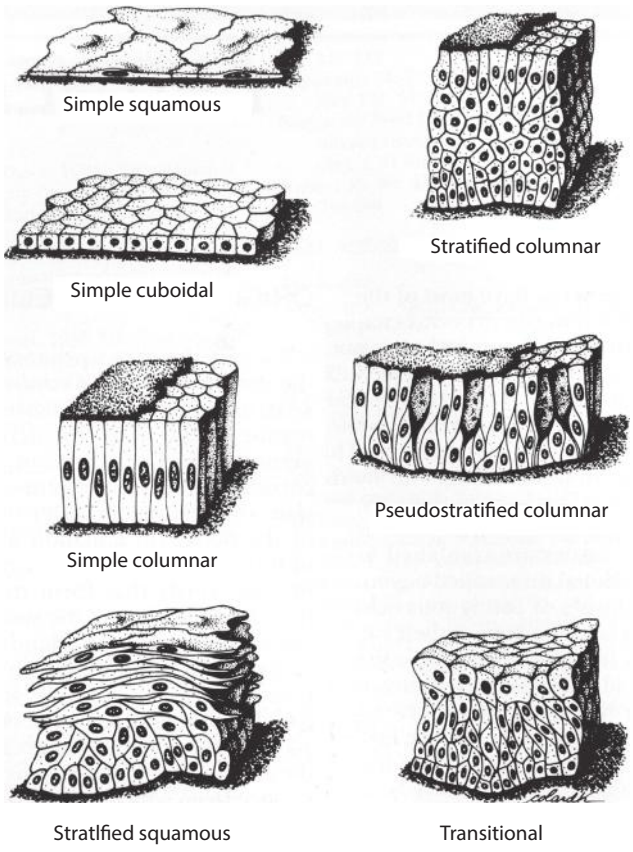

FIGURE 39.6 Cells in the body are generally packed closely together in layers called epithelia. These take a variety of forms, of which these are the basic types. While some epithelia are only one cell thick, with their basal surfaces bathed in extracellular fluids, other epithelia consist of many layers of cells packed closely together on top of each other. Cells that are relatively isolated from the circulatory system and extracellular fluids (serosa) include four of the seven types of epithelia shown. These types of epithelia are found in many different tissues, as listed in histology texts. (From Fawcett DW. *Bloom and Fawcett: A Textbook of Histology.* 12th ed. New York: Chapman & Hall; 1994. Figure 2.1.)

resonant interactions. It could be said that their electromagnetic "fingerprints" match. They can make functional contact without making physical contact – they can touch without touching.

A distinguished French scientist, Jacques Benveniste, gathered evidence for the electromagnetic signaling model, but was vehemently criticized for his proposal, even though there is nothing wrong with it in principle. Indeed, it makes much more sense than the random diffusion and lock and key models. Benveniste was twice awarded the "Ig Nobel Prize" from the *Annals of Improbable Research*, honoring "achievements that first make people laugh, and then make them think. The prizes are supposedly intended to celebrate the unusual, honor the imaginative – and spur people's interest in science, medicine, and technology."[45] In the case of Benveniste, the outcome was not funny and did not spur interest in his work. In fact, it contributed to the widespread dismissal of perfectly reasonable concepts.

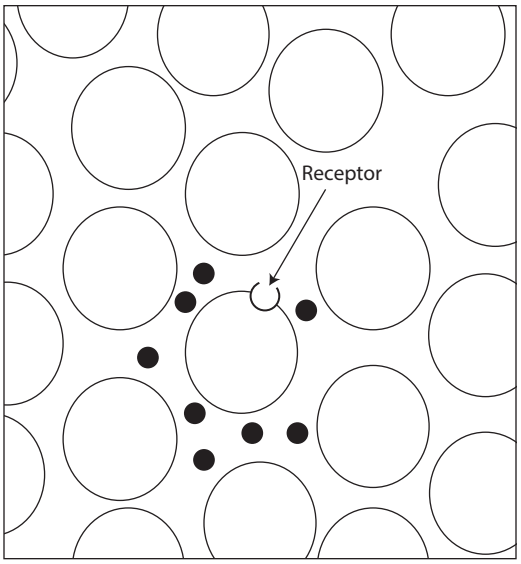

FIGURE 39.7 Guenther Albrecht Buhler in a valuable perspective entitled *In defense of* "*nonmolecular*" *cell biology* has raised a major argument against the view that regulations take place by diffusion of signal molecules to receptor sites on cells, where they activate cellular processes. While some epithelia are only one cell thick, others consist of many cells packed closely together (see Figure 39.6). If one considers the average fluid volume around an individual cell, the actual space available is such that hormone molecules (black dots) with a concentration of 1 pM (6×10^{11} molecules/liter) will have a concentration of approximately eight molecules in the space surrounding an individual cell. In the region around the receptor, the hormone concentration, for all practical purposes, is approximately zero. Albrecht Buhler concluded that our usual concept of concentration is essentially meaningless. (From Guenther Albrecht Buhler. Available online from www.basic.northwestern.edu/g-buehler/cv.htm; accessed January 6, 2014.)

LUCRETIAN BIOCHEMISTRY AND OLFACTION

The ability of cells, tissues, and organisms to detect the chemical and physical properties of their environments is central to sensory physiology, animal behavior, and the regulation of normal and abnormal cellular growth. The classic five senses of humans have evolved from rudimentary sensor molecules found in microorganisms. It is universally agreed that vision and hearing are both vibratory senses. What about olfaction?

A popular book by Chandler Burr, *The Emperor of Scent*, summarized the passionate arguments about whether olfaction is based on the mainstream shape or "lock and key" mechanism, or by the resonant frequencies of olfactants.[46] Electromagnetic signaling as described in this chapter provides support for the less popular but nonetheless plausible concept that olfaction is at least partly based on molecular frequencies.

Philip Callahan provided convincing evidence that olfaction in insects partly involve electromagnetic resonance between sex attractants (pheromones) and distant receptors

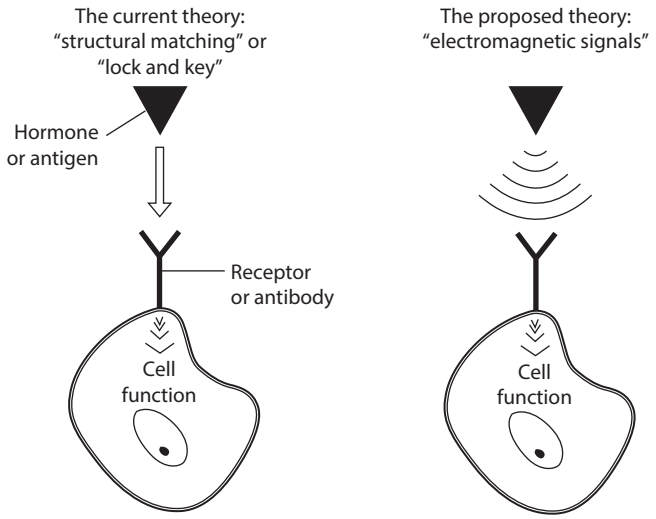

FIGURE 39.8 Two theories of molecular signaling. To the left, the conventional structural matching or 'lock and key' model of biological regulations. The three-dimensional structure of a ligand molecule, such as a hormone, antigen, or other signal molecule matches the three-dimensional structure of the receptor or antibody. Physical contact activated a particular function. To the right is Benveniste's proposed electromagnetic model. The signal molecule emits an electromagnetic signal (signature) which co-resonates with the receptor molecule, thereby activating it and triggering the cell function. (After Benveniste 1998, *From Water Memory Effects to digital biology.* Available online from www.spiritofmaat.com /archive/dec3/bveniste.htm; accessed January 1, 2014. Reproduced with kind permission from Dr. J. Benveniste.)

on the antennas of the animals.[47] His demonstration of this phenomenon resolved a long-standing mystery in entomology: how can a male moth sense and be attracted by a pheromone signal from a female moth that is miles or more down-wind from the male?

Entomologists and naturalists dating back to the early eighteenth century had suggested the possibility that insects communicate by "radiations" emitted from oscillating molecules. In 1894, a famous American entomologist, C.V. Riley attributed the insect's remarkable sense of direction to some unknown communication system, which goes beyond scent and hearing. Riley referred to certain subtle vibrations that could be detected by a sense organ that does not respond to light of the same frequencies that our eyes can see, but that responds to other frequencies to which we are blind. An equally famous French entomologist, J.H. Fabre, speculated in 1913 that the (then) recent invention of wireless telegraphy might have been anticipated by the Peacock moth, which can attract males from miles away, possibly by "electric or magnetic waves." Other entomologists concluded that neither sight nor smell is sufficient to explain the attraction of the male moth from long distances. Many of these naturalists concluded that insects must emit some sort of "special waves or rays" for long distance communication. In more recent literature, a British electrical engineer, E.R. Laithwaite, had noticed that the moth antenna has a remarkable resemblance to a radar antenna. In 1960, Laithwaite wrote *A Radiation Theory of the Assembling of Moths*. He also noted that a male moth can fly with the wind to find a female. Laithwaite concluded that there must be an electromagnetic attractant signal that travels independent of the wind. Callahan agreed, pointing out that the chances of a chemical molecule landing on the male antenna are far less than the chances of the antenna passing through the electromagnetic field emitted by the pheromone. Callahan took Laithwaite's antenna analogy a step further, by recognizing that the shape of the moth antenna resembles that of a direction finding antenna. Perhaps the insects are homing in on signals they detect by moving from side to side off the main beam, like pilots follow a directional beacon to an airport. Perhaps the zigzag flights of moths and butterflies are simply a scanning process, using direction-finding antenna arrays. Callahan found a variety of correspondences between the structures of various insect antennas and radio and microwave antennas. For References, see Oschman and Oschman.[40]

The breezes are carrying the so-called attractant molecules *away* from the male moth – not *toward* him. Callahan's answer is that the insect antenna is actually a radio antenna that detects the electromagnetic signals produced by vibrations of the pheromone molecules that are energetically "pumped" by infrared radiation present in the night sky.

One of Callahan's fascinating points was the correlation between the structure of the insect antenna (Figure 39.9a) and a log-periodic microwave antenna (Figure 39.9b). Such antennas have segments of different lengths, and the spacing gets closer and closer from the base to the tip. Each segment "slides" from one resonant frequency to another so that it covers a wide range of frequencies. Figure 39.9a shows the comparable arrangement in the antenna of the male Cecropia night-flying moth.

Callahan was not the first to suspect electromagnetic attraction in insects. The history of the subject is fascinating and instructive (see box).

In other words, insects "smell" pheromones electromagnetically by tuning into their infrared emissions. Callahan's research and that of his predecessors also resonated with Szent-Györgyi's concept of bioelectromagnetic communications in which molecules interact without touching. Callahan also asked why a moth is attracted to his destruction by a candle flame. The question had baffled many entomologists. The English poet, Thomas Carlyle, attributed the moth's self-destructive behavior to passionate love.[48] In a way, Carlyle was correct.

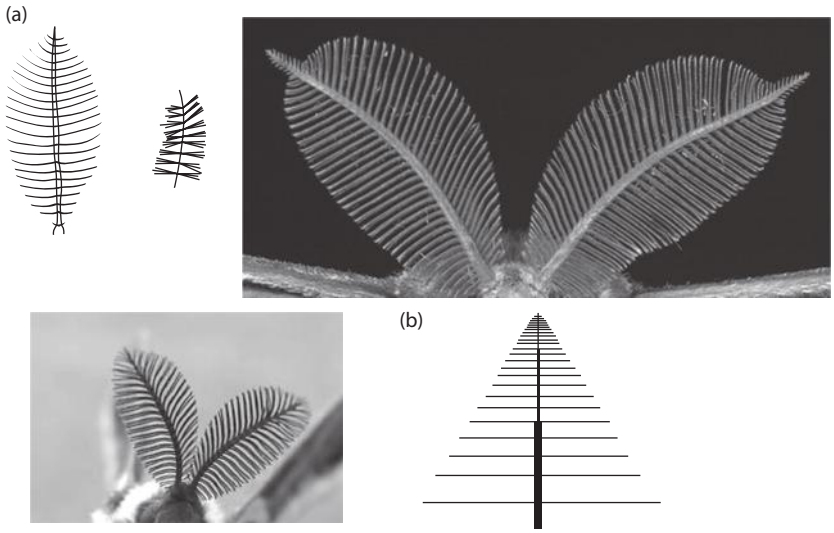

FIGURE 39.9 One of Callahan's correlations was between the structure of the insect antenna (a) and a microwave log-periodic antenna (b). Such antennas have segments of different lengths, and the spacing gets closer and closer from the base to the tip. Each segment "slides" from one frequency to another so that it covers a wide range of resonant frequencies. (a) The antenna of the male Cecropia night-flying moth. (From Callahan P. *Tuning in to Nature: Infrared Radiation and the Insect Communication System*. 2nd ed. Austin: Acres, USA; 2001. p. xvi.)

After many years of fascination with the moth and the flame, Phil Callahan decided that there must be something besides visible light coming from the candle. A candle is made of wax, and the insect is coated with wax. Perhaps, Callahan thought, heated waxes emit some unknown frequency that the moth can sense. Careful research confirmed these ideas. He waited patiently until sensitive spectroscopic technology became available. Callahan was then able to confirm that the candle produces infrared emissions corresponding to the emissions of pheromone molecules. Some of these infrared emissions in the 6–30 μm region are shown in the fast Fourier transform (FFT) spectrum below the candle drawing in Figure 39.10.

The mystery of scent and the mystery of cellular regulations are related in an important way. Specifically, in both cases, we are interested in how molecules interact with each other. Control of cellular activities depends on various regulatory molecules interacting with appropriate receptors; olfaction involves the scent molecules interacting with receptors in the nose. In both cases, the legacy of Lucretian biochemistry has essentially closed down interest in the study of resonant as opposed to billiard-ball interactions. Most olfactory physiologists accepted the "lock and key" approach that was an extension of enzyme kinetics. However, studies of enzyme kinetics are usually carried out with isolated molecules suspended in a salt solution, or with pure crystallized proteins, as mentioned above, and not with molecules in their natural environments. This could very well be the blind spot that hampers cancer research, as described by Agus, Szent-Györgyi, and many others. Unquestioning acceptance of the lock and key model for molecular interactions, combined with biomedicine's nearly complete lack of interest in energetic or electromagnetic interactions in living processes, combine to sustain a mental block against considering possible resonant frequency effects.

Chandler Burr's fascinating documentary chronicles the struggles of biophysicist Luca Turin in his efforts to get scientists to consider a molecular frequency rather than a molecular shape model of olfaction. While Turin's hypothesis was reasonable and thought provoking, it was dismissed without discussion by virtually all of the leading olfactory physiologists. Burr took the step of contacting these individuals and confirmed that nearly all of them disagreed with Turin, but none of them had actually read Turin's paper. Burr asked one of these experts if it was not a bit tricky to criticize a paper one has not read. The response was that Turin's idea is "wrong on its face" (whatever that means). Another said, "shape is an ironclad given." One of the leading authorities, however, said that he did not believe in vibration, but he did not believe in shape either. This could be the correct direction, as years of watching passionate scientific arguments have shown that a better answer often emerges when it is realized that both sides of the argument are partly correct.

Turin's first publication was also rejected by the editors and reviewers of a leading science journal, *Nature*. The shape versus frequency discussion was thus shut down by a journal's decision that essentially concluded that Turin was wrong, instead of allowing the scientific community to examine his ideas. Burr's documentary convinced many that Turin was not being treated fairly, and that some sort of conspiracy was afoot to protect the mainstream lock and key or Shapist model. Certainly, Burr's book allowed the layman to see the intrigue that goes on behind the doors of academia.

We believe Turin's model of scent is interesting, important, and worthy of further investigation. His idea is that the nose is a spectroscope. The same idea had been put forward earlier, in 1938, by Dyson.[49] One of Turin's contributions was a possible quantum mechanism for the detectors in the

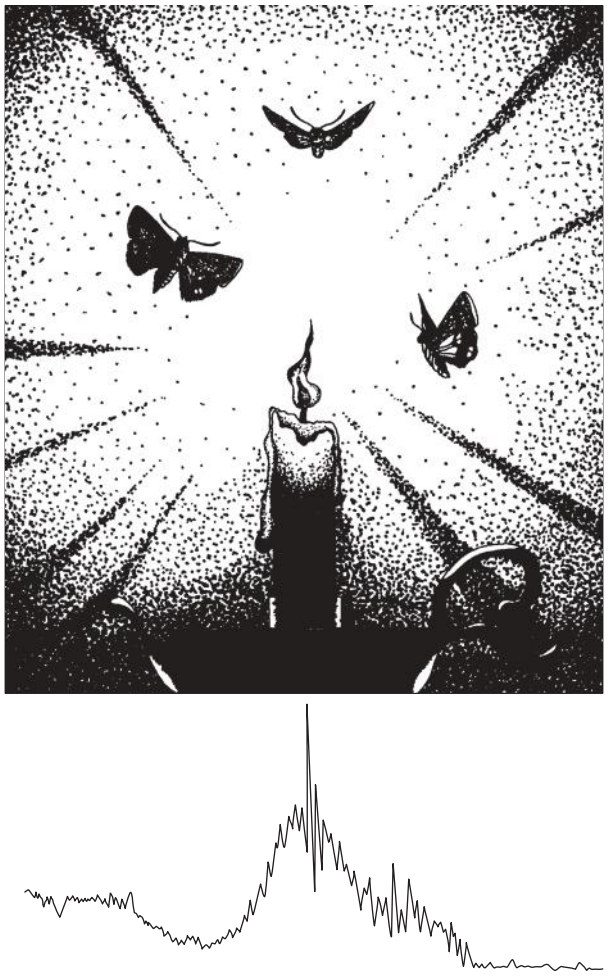

FIGURE 39.10 Moths attracted to the flame of a candle (top), and candle's infrared emission spectrum in the 6–30 μm region (bottom) showing one of the peaks that is also found in the spectrum of the pheromone. (From Callahan P. *Tuning in to Nature: Infrared Radiation and the Insect Communication System*. 2nd ed. Austin: Acres, USA; 2001. p. 117.)

nose. His proposal involved the scent molecules fitting into a receptor of the appropriate shape, followed by electron tunneling through the odorant molecule. The frequency of the molecule would then be determined by the way electrons traversed the odor molecule. Specifically, electrons would lose energy during their excursions through the scent molecules, and this energy loss could be used to "calculate" the resonant frequency or frequencies of the odorant. He got the idea from an electron tunneling spectroscope that had been invented by Ford Motor Company, an experimental tool that yields vibrational spectra with high resolution and high sensitivity. Inelastic tunneling spectroscopy had been described by a group from the Cavendish Laboratory in Cambridge in 1985.[50] A method of single molecule spectroscopy was published by another European group in 1998.[51] Turin provided detailed and elaborate discussions of how this mechanism could work.[52,53] In 2006, physicists from the University College London carefully tested the physical viability of Turin's proposal using electron transfer theory. They found that the mechanism was viable ("there are no physics-based objections, and it fits with well-known features of smell").[54] They referred to Turin's scheme as a "swipe card" mechanism. In an interview, one of the physicists, Marshall Stoneham stated that the popular shape model fails badly for small scent molecules (similar molecules smell different, differently-shaped molecules smell the same…"[55]).

In support of a frequency model and against a lock and key model is the fact that correlations between the three-dimensional structure of odorants and their odors have been elusive. In his review, Turin cites leading authorities who are convinced that such correlations may never be possible.

One devoted Shapist, Karen J. Rossiter, in a comprehensive review of structure-odor relationships, pointed out that three out of 20 examples of the correlation between molecular shape and odor presented problems for Turin's theory. However, she neglected to acknowledge that the other 17 examples contradict the mainstream shape theory and actually support Turin's ideas.[56]

Josephson effects and electron tunneling can occur in biological systems.[57] However, Turin's scheme partly involves shape as well as frequency, as the odorant molecules must fit into a space before they can have their frequencies "read." Apparently, Turin is not aware of, or has not considered, the possibility that the electromagnetic signatures emitted by odorants trigger the responses without physical contact with the receptors. If this is the case, the odor molecules might not even have to enter the nose. This is of course a radical idea, but one that is supported by the work of Callahan, in which the pheromone molecule does not have to come within miles of the male insect's antenna to be detected. Similarly, the emission spectra of scent molecules could be read from a distance, with scent information carried by electromagnetic fields and/or by more subtle signals composed of scalar or torsion waves. In looking at possible subtle energy involvement, it may be significant that the membranes of olfactory sensing cells are traversed seven times with helical receptor molecules. To us, this arrangement looks like a helical dielectric antenna array. The interest here is in the fact that space has a spiral or helical grain, which supports the conduction of torsion or spin waves.[58] The sensory receptors may well be frequency detectors, not drastically different from the frequency detectors in the eye and ear responsible for vision and hearing, respectively. We believe this is a more likely possibility for olfaction, especially in light of Callahan's work mentioned above.

Richard Axel and Linda B. Buck received the 2004 Nobel Prize in Physiology or Medicine for describing the genes that code for a large family of odorant receptors. Each of these receptors contains a protein that traverses the cell membrane seven times. Their view is that when an odor molecule fits into the receptor, the receptor protein is altered and a G protein is activated. The result is a nerve impulse to the olfactory bulb. While their work that led to the Nobel Prize was very important, it did not prove the molecular shape model for olfaction. They were convinced of the accuracy of the shape

rather than the frequency model, but their genetic studies did not bear on that subject one way or the other.

Turin's electron tunneling hypothesis may not be necessary. The most parsimonious explanation of olfaction is that the nose contains a large number of olfactory receptors, as described by Axel and Buck. These are frequency receptors tuned to hundreds of different frequencies. When one of these receptors is stimulated, it activates a G protein that triggers a nerve impulse to the olfactory bulb. It is in the bulb, then, that the signals from the various frequency receptors are analyzed to determine the spectral characteristics of the odorant, and the result of this neural processing then leads to a sensory experience. This explanation is parsimonious because it enables a similar class of vibration receptors to function in olfaction, hearing, and vision.

CONCLUSIONS

The fitting together of diverse perspectives is an interesting process, only rivaled in fascination by the way important discoveries have been passed over by mainstream science. We often forget that others who have not been steeped in this subject for the past 30 years or so may simply not know how various controversies unfolded, and how widely accepted opinions were later found to be erroneous. There are seemingly convincing statements in the literature, from prominent scientists, that have subsequently been proven to be partly or completely incorrect, yet they are frequently cited as facts. Some of these statements are based on simple and seemingly obvious logic that, upon closer examination and testing, has proven to be false. For example

- *Statement:* The energy fields surrounding the human body, if they exist, are far too weak to have any biological significance. Response: Biomagnetic fields are now measured with sensitive magnetometers and they provide clinical diagnostic tools, such as the magnetocardiogram and magnetoencephalogram.
- *Statement:* If a strong field does not seem to influence an organism's behavior or reproductive cycle, a much weaker field is also unlikely to have any biological effect. Response: Living systems are sensitive to fields in specific frequency/power windows. If the field is too strong or too weak, it will not have an effect (Adey).
- *Statement:* If a field induces oscillations that are smaller than those produced by thermal noise, the field can have no biological effects. Response: Stochastic resonance enables noise to actually *amplify* weak signals.[59]
- *Statement:* An electromagnetic field cannot interact with a living system unless the wavelength of the signal corresponds to the length of the body or the length of some part. Hence, a 60 Hz signal, with a wavelength of more than 3000 miles, cannot possibly affect a human being. Response: Frequencies from 0 to 100 Hz are in what is known as the "biological range" as this is where we find the electrocardiogram, brain waves, and other biological rhythms. Moreover, harmonics and sub-harmonics of a frequency can produce effects as well.[60]

The scholar new to this field of inquiry can become confused without some reference to the history of the subject, which we have begun to provide here. The topic of subtle energy effects has been controversial and confusing in part because opinions and discussions have sometimes been influenced by political and economic issues that should not be a part of basic research. There are also professional "skeptics" who seem to have the peculiar and disruptive goal of stimulating and maintaining controversy and confusion around new and worthy ideas. Understanding bioelectromagnetic medicine and subtle energies, therefore, requires an historical perspective that deals with the sources of the controversies and confusions, as well as with the pressures that sustain them. Moreover, the inquiry is multidisciplinary, and therefore, much more challenging to the specialist than to those who routinely work at the interfaces between disciplines, such as the biophysicists, quantum chemists, and quantum biologists, as well as the complementary and alternative therapists who often strive to connect their clinical experiences with scientific insights.

Many have been puzzled to the point of incredulity by claims of exceedingly weak electromagnetic field (EMF) effects of low energy photons that are thought to have insufficient energy to influence the chemistry or temperature of a cell. How can nonthermal effects of such tiny EMFs possibly occur? This chapter summarizes the view that such subtle effects are actually the keys to the vital communications that take place back and forth between cells, tissues, and the environment. The mechanisms involved are various quantum processes including quantum coherence as described by Herbert Fröhlich, spin resonance as described by Mae Wan Ho and Emilio Del Giudice, biophotonic communications as described by Fritz Albert Popp and Marco Bischof, and wavelike energy transfer that takes place in chloroplasts of green plants as documented by Fleming and colleagues. It is also suggested that disruptions of these exchanges require study to determine if they are the sources of electromagnetic sensitivities and serious diseases such as cancer.

A consequence of ancient thinking, dating to Democritus, Epicurus, and Lucretius, is the concept that all matter is composed of "imperishable" atoms, tiny indivisible particles that can neither be created nor destroyed. 'Billiard-ball' units, atoms, or molecules, move in straight lines in all directions, in accordance with the "iron laws of necessity" that were eventually replaced with Newton's laws of motion. This led to the incorrect conclusion that interactions cannot take place between atoms or molecules unless they touch one another.

The ancient atomist ideas were pivotal for the development of Western science. A legacy of this natural philosophy is the modern molecular view of regulatory interactions in which signal molecules, such as hormones, neurotransmitters, neuropeptides, or pheromones diffuse, wiggle, and

bump about randomly until they chance to approach an appropriate receptor site, at which point electrostatic and other short-range forces draw the signal molecule into the receptor, much like a key fits into a lock. The "key" obviously has to have a structure or shape that matches the "lock." For this model, shape is crucial.

We now know that atoms are not solid and indivisible, and we also know that the "lock and key" model is an incomplete picture of regulations. A distinguished neuroscientist, the late Candace Pert, had this to say about the "lock," "In truth… receptors are far more fluid and amazing than locks."[61] The random meeting between hormone and receptor, or enzyme and substrate, taking place in a sea of other randomly moving molecules, has a statistical probability approaching zero (Albrecht-Buehler). Under these conditions, the simplest biological event or step in a metabolic pathway or regulatory process should require some thousands of years to take place. Albert Szent-Györgyi and others have recognized that living processes are simply far too fast and too subtle to wait for molecules to wander around aimlessly until they happen to bump into the right targets. Electromagnetic or vibrational signaling is not only physically possible; it is the ideal mechanism for the rapid and precise communications taking place in living systems. For this model, electromagnetic resonance, not shape, is crucial. One can envision a web-work of electromagnetic signaling processes extending throughout the body, enabling the coordination of a wide diversity of functions and processes.

The lock and key model is so familiar and easy to visualize and so deeply ingrained in our scientific culture that many have had difficulty comprehending energetic interactions in which molecules interact by co-resonance, even though the same people maintain contact with distant friends via cell phones and other communication devices based on electromagnetic signaling. Many also use electromagnetic car keys that unlock their car door from a distance. This is a perfect model for electromagnetic signaling because, regardless of how routinely you use the magic button on your car key, you can still insert the key into the lock to open the door. In living systems, as in radio, television, cellular telephone communications, electronic car keys, and astronomical spectroscopy, long-range electromagnetic fields exchange messages across distances because of matching emission and absorption spectra. Nonresonating, unwanted, or random signals are excluded simply because they do not resonate. All of this is fully consonant with the laws of physics. Resonance is a truly remarkable phenomenon, but it is not magic. Those who dismiss the various vibrational therapies as physically impossible need to take note of this fact.

Phillip Callahan recognized that infrared signaling has many applications beyond insect communication. The concept of bioelectromagnetic communications is receiving increasing attention in the scientific community. For example, see *Bioelectrodynamics and Biocommunication* by Ho, Popp, and Warnke,[62] and a series of studies on cellular infrared cellular "vision" by Albrecht-Buehler.[63] Over the years, a number of other scientists have published key papers on this topic. As examples, see the work of Benveniste,[64] Smith,[65] and Popp.[66]

We believe thoughtful consideration of the research of Callahan and Turin and the related concepts presented here will help resolve both the centuries-old mysteries of how smell works and the crucial issue of how interference with biological communications can trigger chronic diseases. Lack of willingness to look beyond the lock and key model has stalled progress in many areas of biomedicine. This could be one of the "fundamental facts or dimensions missing from our biological thinking" as stated by Albert Szent-Györgyi. Chandler Burr's book dramatized the passion by which some hold on to the lock and key model. Figure 39.11 reproduces Figure 39.4 with the addition of some graphics to represent

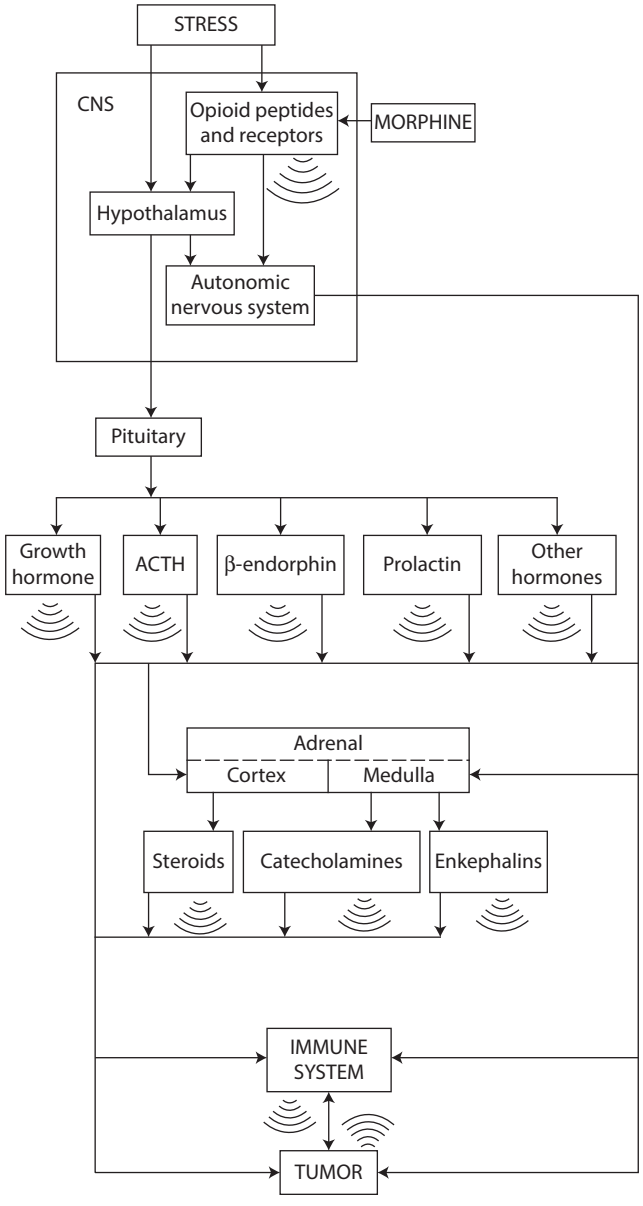

FIGURE 39.11 Figure 39.4 is re-drawn to include some of the possible electromagnetic or photonic connections between various signal molecules. Solid arrows are diffusing molecular signals, and radiation patterns represent proposed photonic interactions. (From Shavit Y et al. *J Immunol* 1985;135(2):834s–7.)

possible electromagnetic emissions from signal molecules as discussed here.

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40 Beyond Spacetime-Only Physics

*William A. Tiller**

CONTENTS

INTRODUCTION

In addition to the 60 or so years of orthodox, spacetime-only science in both industry and academia,[1] and, in parallel, for the past almost 45 years, this author has explored domains of nature that lie beyond our spacetime-only world.[2] This latter has been an "outside the box" adventure. My goal for this personal adventure has been to help build a reliable bridge of understanding that seamlessly joins today's orthodox science on the one end, passes through the domains of the human psyche, the domains of emotion and mind, and is firmly imbedded on the far end into the bedrock of spirit. Further, the goal was to make this bridge strong enough and reliable enough that humankind would be willing to walk across it and enjoy the great adventure with me, not only the general public but my orthodox science colleagues. During this exploration "outside the box," many new discoveries were made that have been reported on elsewhere.[3–9]

Today's orthodox science and, thus, orthodox medicine, presently holds at least five major beliefs

1. Mathematically, all true science findings must be internally self-consistent with each other via a distance-time-only reference frame (RF).
2. No human qualities of consciousness, intention, emotion, mind, or spirit can significantly influence a well-designed target experiment in physical reality (thought to be first proposed by Descartes in ~1600 AD).
3. Nothing with physical mass can travel at or faster than the velocity of electromagnetic (EM) light through physical vacuum ($c = 3 \times 10^{10}$ cm/s).
4. Today's quantum mechanics (QM) can be meaningfully applied to any phenomenon of nature.
5. The "big bang" creation of our physical cosmos grew out of a completely empty physical vacuum.

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In terms of belief 1, ~150 years of serious experimental observations of anomalous human cognition and anomalous human forces have been found to be not internally self-consistent with orthodox science, and, thus, have been conveniently ignored and "swept under the rug" by the orthodox science and medical communities.

Our standard model of orthodox physics involves the four fundamental forces of gravity, electromagnetism, the short-range nuclear force, and the long-range nuclear forces, which are fully consistent with belief 2. These have led to long-range forces that decay with respect to distance from atoms, molecules, planets, and stars. However, modern-day research at the Princeton Engineering Anomalies Research (PEAR) laboratory, which is internally self-consistent with that found by many other researchers around the world and over many years, is not internally self-consistent with the orthodox standard model and its independence of human consciousness.[4–9] What is also very striking about these "anomalies" research findings is that human consciousness appears to be nonlocal and independent of distance and time. They do not appear to be dependent in any causal fashion upon the physical brain.

In terms of belief 2, about a decade ago this was seriously tested via four carefully designed, different, target experiments via four different specific intentions, one for each target experiment, imprinted into an intention host device (IHD) and placed about a foot away from its continuously running companion target experiment. The experimental results of these four experiments[4–9] were robustly successful in proving that, in today's world, this orthodox physical belief is very, very wrong!

For belief 3, Einstein's theory of relativistic mechanics is a great creative triumph; however, it is cast in a distance-time-only RF with no adjacent higher-dimensional domains into which mass-type substance might "tunnel" completely and avoid the $v/c = 1$ barrier. Further, the theoretical work of Terletskii[9] has shown that the relativistic mechanics (RM) equations can be solved in the superluminal velocity domain, just as they can in the subluminal domain.

For belief 4, in today's QM, the wave functions for electrons in atoms are generally calculated via Schroedinger's

wave equation, which is a second-order partial differential equation in distance and time. It does a beautiful mathematical job for problems that are limited to distance and time. That is, with regard to humans, it can, in principal, deal with the electromagnetic (EM) "meat" of human bodies but not at all with the higher order capabilities of humans, such as consciousness, intentions, emotions, mind, etc. Thus, in its present form, it is unable to deal with human capabilities, such as psychotherapy and the healing arts, which involve these higher order human capabilities.

Julian Schwinger, along with Feinman and Tomanaga, shared a Nobel Prize for their discovery and mathematical development of quantum electrodynamics (QED). Schwinger had a PhD student, Paul Werbos, who made the prophetic point[9] that (i) all forms of QED, Copenhagen, Bohmian, Schwinger-type, or Werbos-type, yield the same kinds of predictions and none of them can explain "remote viewing." Further, (ii) he tells us that the world has spent billions of dollars to use QED in the military to see things very far away and it has failed to do so. The point, here, is that our present formulation of QM, as great as it is, is inadequate to encompass the effects of human consciousness into our orthodox science worldview. Thus, it is time to formulate a larger perspective or scientific RF for viewing nature that both accounts for all the old experimental data and provides the possibility of quantitatively accounting for the new data in an internally self-consistent way.

Turning, now, to belief 5, about 50 years ago, astrophysicist John Wheeler theoretically predicted[9] that, for QM and RM to be internally self-consistent, the physical vacuum must contain a latent energy density of 10^{94} gm per cc of equivalent EM energy ($\Delta E = 1.c^2$). This would mean that the calculated energy stored within the physical vacuum volume of a single hydrogen atom contains about a trillion times that of all the EM energy stored in all the stars, planets, and cosmic dust of our entire physical cosmos (a sphere of radius ~15 billion light years). This is inconsistent with the "empty space" assumption of the big bang.

An empty physical vacuum assumption is fully consistent with the experimental observations that (i) the physical vacuum is transparent to EM light and (ii) that EM photons of all frequencies travel with constant velocity, c, through physical vacuum of whatever length. From this, one can deduce that physical vacuum is a nondispersive medium for EM waves which, in turn, means that EM light is not interacting with anything that might exist in the physical vacuum. The big bang modelers assumed that this meant the physical vacuum was "empty." However, an equally plausible assumption is that the "stuff" John Wheeler postulated to reside in the physical vacuum all travels at velocities faster than c so that this "stuff" can easily get out of the way of EM photons traveling at $v \precnsim c$.

Also about 50 years ago, Eisberg[9] showed that, if one considers the DeBroglie particle/pilot wave concept of the 1920s ($\lambda = h/p$ and $\nu = E/h$ where λ = wave length, ν = frequency, h = Plank's constant, p = particle momentum and E = energy), for which he won a Nobel Prize, and one also uses a relativistic particle energy ($E = [c^2p^2 + (m_oc^2)^2]^{1/2}$ where m_o = rest mass of the particle), one finds that $v_p = v_g$ where v_g = the velocity of the wave group and that $v_{pw} = \nu\lambda$ so that $v_{pw}v_g = c^2$ (see Figure 40.1). Thus, as v_p is always less than c, v_g is always less than c and the pilot wave velocity, v_{pw}, is always greater than c.

As our average, present human sensory system and all of our EM measurement systems have subluminal limits at v = c, this means that the v_{pw} of DeBroglie, to be properly counted mathematically, must be treated as a mathematically imaginary entity from a subluminal measurement perspective. This fact will have great relevance later.

The orthodox science community do not like this v_{pw} conclusion and prefer to say that the medium through which the DeBroglie pilot wave travels is a dispersive medium, wherein an anomalous absorption process operates. However, such an anomalous process is quite unlikely to operate in the physical vacuum because an EM wave travels at velocity, c, independent of frequency, so, at best, a special absorption process could work well only at one frequency, not at all frequencies.

To close this section, let us consider the Higg's Boson predicted to give mass to all the fundamental particles of today's orthodox physics particle menagerie. It is thought to have been discovered in June, 2012, at Cern in Geneva with a formation energy of ~125 BeV. For this author, I assume that this forms a key type of closure for today's orthodox physics, which has created all the instruments whose EM signals travel at v < c. Thus, with all of the foregoing discussion, it appears as if the "standard model" and the "big bang theory," both dealing with v < c phenomena, are complete—a great achievement! However, it also means that, although natural phenomena in the v > c domain are open to legitimate scientific investigation, our orthodox science community presently has no tools available for such studies!

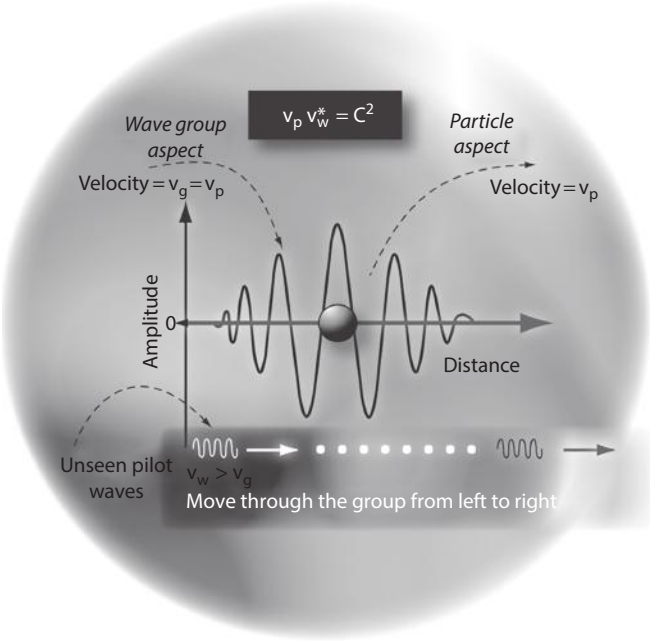

FIGURE 40.1 Schematic of true pilot waves.

A METAPHORICAL LADDER OF UNDERSTANDING

One of this author's working hypotheses is that nature is radiating information to us on many, many different frequency bands of quality, with most of these qualities unknown to us either by today's scientific tools or our own manifested cognitive sensory abilities. Figure 40.2 is a simple illustration of this metaphor (see Chapter 9 of reference 9).

The bottom-most rung of this ladder of understanding is thought to have been created by the diligent research of the last 400–500 years by the orthodox scientific and medical communities who have adopted a distance-time-only RF for nature that is independent of human intention, I*, and human consciousness, C*, as significant experimental variables. This community of dedicated souls have laid an excellent foundation of nature's manifold expressions with respect to an RF that includes the subluminal EM realm but excludes I*, C*, and many other experimental variables that we are not yet sufficiently conscious of to discriminate and to which we should attach serious meaning.

The second rung of Figure 40.2 is thought to be reserved for eventually quantitative investigations of nature, wherein I* and C* are significant experimental variables. At the moment, the third, fourth, etc., rungs are thought to be reserved for discoveries and theoretical constructs, etc., for the emotion domain, and mind domain, etc., which are aspects of nature's extensive expressions.

As a working target for future theoretical constructs and experiments, Figure 40.3 is a possibly relevant expansion of Dirac's original concept of how positive energy, matter/antimatter, electric, and subluminal substances could have been created via cosmic ray interactions with some type of negative energy plenum substance (existing in the physical vacuum).

Although Dirac received a Nobel Prize for this work, the orthodox science community rejected his hypothesis of a negative energy sea because they could not understand what a "negative energy" could possibly mean. This question will be answered a little later.

FIGURE 40.2 A metaphorical description of "the ladder of understanding."

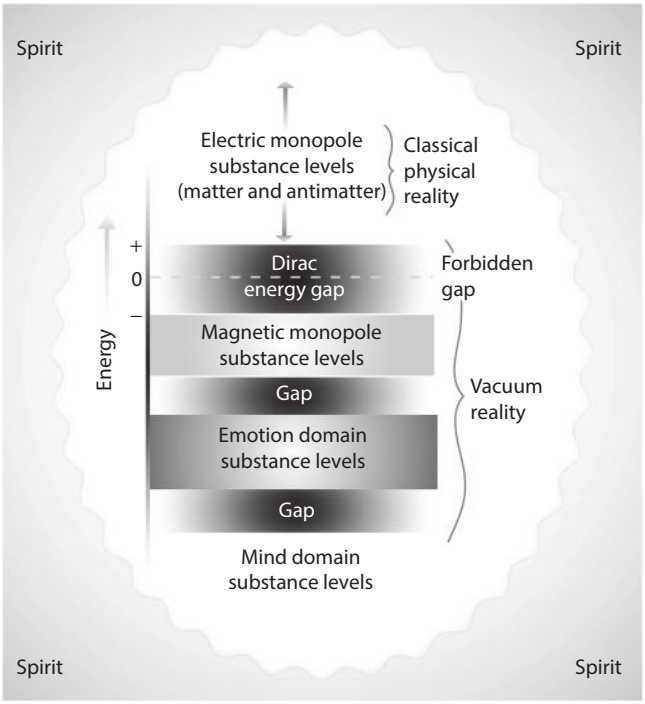

FIGURE 40.3 An energy level diagram embracing both classical physical substances and "unseen" vacuum substances.

WE ARE ALL SOULS AND NEED A BIOBODYSUIT VIA WHICH TO EXPERIENCE SPACETIME

Using Figure 40.3, this author proposes that Figure 40.4 is a meaningful approximation to our total self (see reference 9, pp 147–9).

Our soul self is the mid-region of Figure 40.4 and consists of a composite of emotion, mind, and some spirit domain constructs. Our personality self is a two-layer biobodysuit region of Figure 40.4 with (i) the outermost layer consisting of electrical atoms/molecules, cells, organs, bones, etc., with sensory systems that allow meaningful interaction with the outside, distance-time world, and (ii) the innermost layer is thought to involve magnetic information waves functioning in the physical vacuum of Figure 40.3.

This second inner layer of the personality self is where the acupuncture meridian system is thought to function. As many have experimentally discovered, there is no histological evidence of the acupuncture meridian system and its many acupuncture points in the outermost layer. At present, the only serious evidence of this important structural system is of an electrodermal nature.[15] The acceptable experimental evidence is a significantly enhanced electrical conductivity of the skin immediately adjacent to the loci of the Asian-predicted locations of the acupuncture meridians and points. In turn, such enhanced electrical signatures in the outermost substance layer of our personality self is thought to be induced via the flows of magnetic currents (Qi) in the various acupuncture meridians. The latter, in turn, are thought to be generated via connection to the soul self through the human

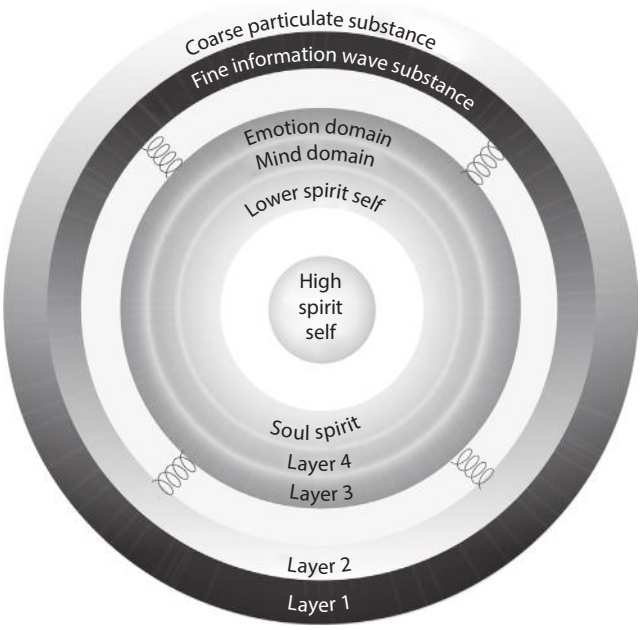

FIGURE 40.4 A metaphor for the whole person. I like to visualize a sphere comprised of three concentric zones that are at least weakly coupled to each other. The outermost two layers is the personality self. The middle three layers is the soul self. The core region is the high spirit self (or God Self).

chakra system. Finally, in Figure 40.4, the central region is the high spirit self (or the God Self) to which the soul self is connected. In this way, via a series of step-down transducers, the God Self can also experience its creation of the distance-time domain.

The primary entity in this Figure 40.4 construct is thought to be the soul self that (over time) experiences many bio-bodysuits through its evolutionary process and via which it co-creates a relative universe, as distinct from the absolute universe which is thought to function in the God Self.

When our souls are "born" into the spacetime domain, the innermost magnetic substance layer (the old "etheric" layer) of our personality self is thought to form first and become the conventionally "invisible" template upon/around which the coarse, electric atom/molecule layer forms. All electrical charge movement occurring in this outermost layer induces magnetic fields circulating around such electric current paths. These induced magnetic signatures are always of a dipolar nature rather than of a monopolar nature (see Figure 40.5, reference 9, p 70). Thus, although we have experimentally isolated individual plus and minus signed electric charges and electric currents flowing in this outermost layer, only induced magnetic dipoles (N–S species) are present in this outermost layer.

Our experimental data[3–9] strongly suggests that magnetic monopoles and magnetic currents are present and functioning in this "invisible to electromagnetic sensors" template layer of the personality self.

INTENTION-INDUCED SPECIFIC MATERIAL PROPERTY CHANGES, DUPLEX SPACE CHANGES, AND EM GAUGE SYMMETRY STATE CHANGES

In the previous volume of this book,[6] the material property change aspects via specific IHDs was well-covered. All four IHD target experiments led to robust results having the general form illustrated in Figure 40.6.

Here, Q_M represents the magnitude, M, of a typical physical measurement, Q. Plotted versus the degree of locale conditioning time produced by continued IHD use. The direction of change in Q, is always in the direction specified by the IHD. The magnitude of change is always the sum of two parts, (i) the original electric atom/molecule part, Q_{M0}, and (ii) the magnetic information wave part, $\Delta Q = Q_{M1} - Q_{M0}$, associated with the inner personality self-layer of Figure 40.4, and the specific intention imprinted into the IHD.[6] The zeroth-order approximation to the mathematical expression for Q_M can be given most simply by

$$Q_M(t) = Q_e(t) + \alpha_{eff}(t)\, Q_m \qquad (40.1)$$

Here, Q_e is our spacetime-world value, Q_m is our reciprocal space-world value, α_{eff} is the coupling ingredient, thought to be from the emotion domain of Figure 40.3, α_{eff} varies from 0 to 1 and t is time.

When $\alpha_{eff} - 0$, the two basic kinds of unique substances inhabiting these two levels of physical reality appear to interpenetrate each other but, normally, they do not interact with each other. Our working hypothesis is that this occurs because, at one level, we have our normal subluminal EM behavior but, at the new level, we have superluminal behavior. We label this normal state as the uncoupled state of physical reality. In the uncoupled state, with our five physical senses, we can perceive objects in our normal physical spacetime environment. However, this new level of substance is currently invisible to us and to our traditional measurement instruments because it appears to function in the physical vacuum at superluminal velocities (the seemingly empty space between the fundamental particles that make up our normal world).

It is the use of these IHDs that affect the experimental space in such a way that meaningful coupling begins to occur between these two very different kinds of substance. Then the vacuum level of physical reality becomes partially visible to our traditional measurement instruments. We have labeled this condition the coupled state of physical reality.

Figure 40.7 metaphorically illustrates some key differences between materials in the two states of physical reality. In Figure 40.7a, the normal uncoupled state of physical reality is illustrated metaphorically on the left via a classical picture of the atom with electrons moving in well-defined orbits at subluminal velocities while the noninteracting superluminal velocity moieties from the physical vacuum are illustrated as randomly moving dots of light. When the IHD has fully "conditioned" the experimental space to the coupled state, my working hypothesis is that the coupled state material

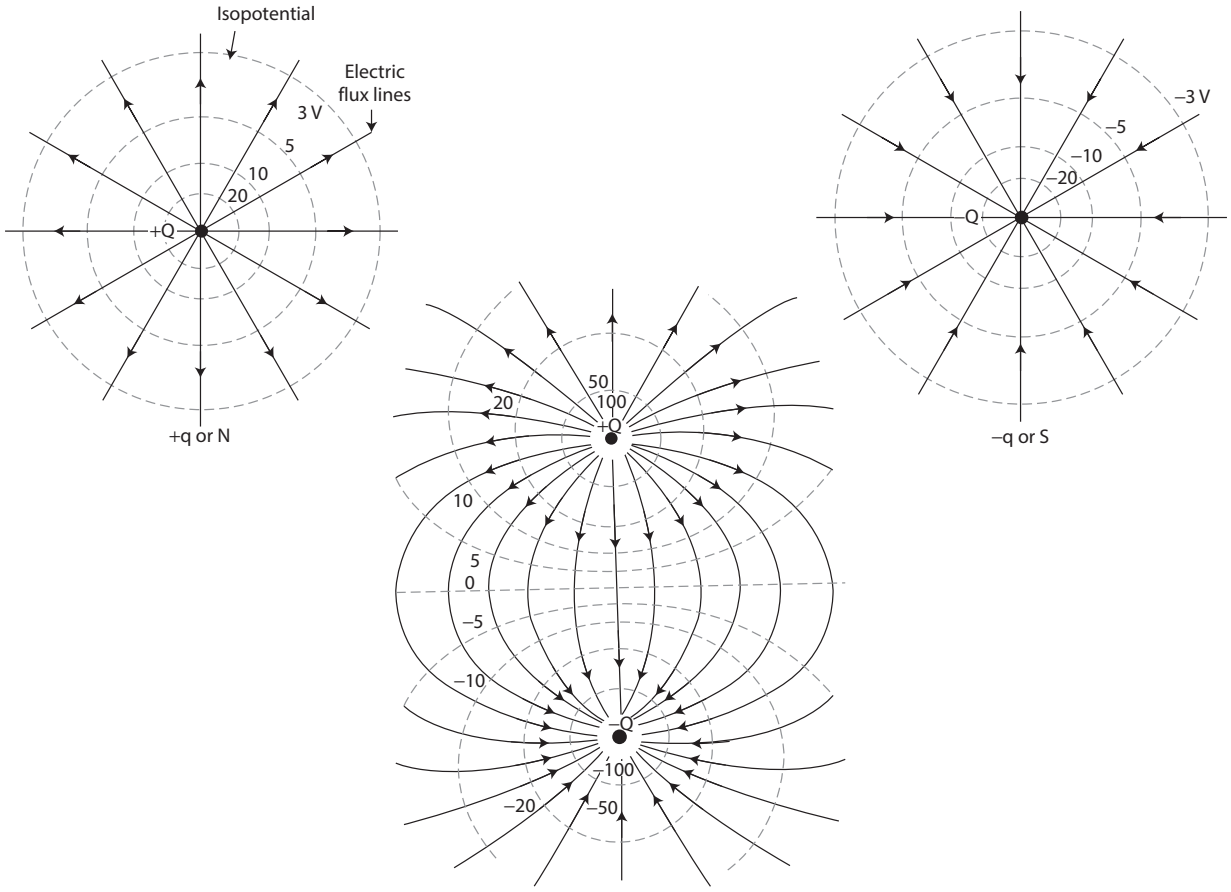

FIGURE 40.5 (Top) Illustration of monopoles (+q or −q for electric, N or S for magnetic); (bottom) illustration of a dipole (+q −q for electric, NS for magnetic).

looks more like that illustrated on the right of Figure 40.7a. A macroscopic picture of this overall process as it develops in the experimental space is illustrated in Figure 40.7b. This is thought to lead to a composite of coupled state domains embedded in a matrix of noncoupled state material.

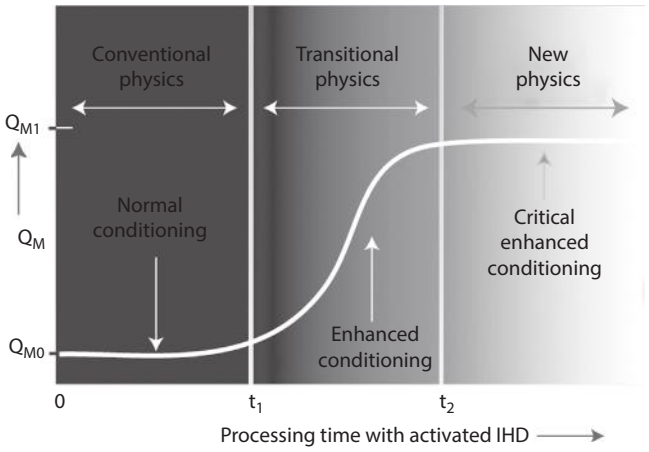

FIGURE 40.6 For any typical physical measurement, Q, the qualitative magnitude change, Q_M, is plotted versus the degree of locale conditioning produced by continued intention host device use.

What appears to be happening here is that the active IHD is capable of acting on the experimental space itself and lifting it to an altered (higher) gauge symmetry state of nature, wherein novel, new phenomena of nature can manifest and materialize (see below).[16,17]

Although this may seem to be a type of alchemy, it is not an equilibrium thermodynamic change. Rather, it is a metastable state of thermodynamic change that has been created. A close analogy is the laser process, wherein the lasing crystal must be continuously pumped via an incoherent light flux to lift the atom's or molecule's electrons to the appropriate excited state for the coherent light emission to continue. Stop the incoherent light pumping and the lasing process stops. This is also a dynamic, metastable thermodynamic state process. In our IHD case, we must periodically (~3 months) re-imprint the IHD in order to regenerate our special coupling ingredient that slowly leaks away into the environment.

Gauge theory development has probably been the most important advance in orthodox physics in the past 50 years. It deals with the interaction of external fields with internal symmetry states in nature.

For our normal spacetime reality, this involves the dynamic movement, in phase space, of the electron wave function phase angle, θ, with respect to either the absence

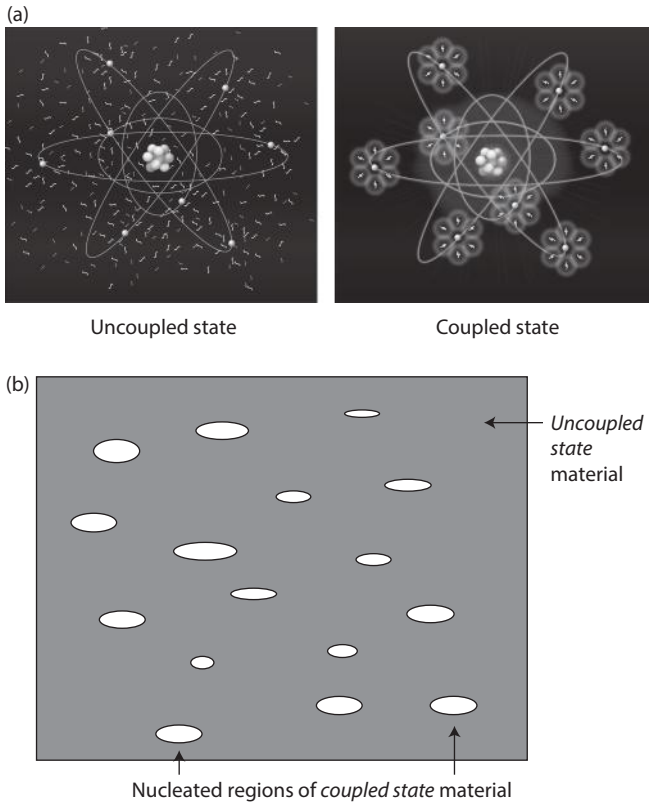

FIGURE 40.7 (a) The physical reality metaphor. (b) Nucleation and growth of the macroscopic coupled state of physical reality.

or presence of an external field (see Figure 40.8).[16,17] This is dependent upon fiber bundle mathematics and group theory considerations leading to a unique locus of θ in a planar ring of phase space at each (x, y, z, t) point in spacetime for the U(1) gauge symmetry state.

The geometrical structure of gauge theory can be illustrated via the very convenient and illustrated picture of Figure 40.9. Here, the external space (distance-time RF) is represented by the horizontal plane in Figure 40.9 and the internal symmetry space is drawn vertically at each point, (x, y, z, t). A vertical line in the figure depicts the case of a one-dimensional internal space like that of the U(1) group (our normal macroscopic EM world designation). This internal space is called a "fiber" by mathematicians. In this picture, the spatial location of a particle is given by a coordinate point in the horizontal plane while the orientation in the internal space is specified and the angular coordinate in this "fiber" space reveals this. As the particle moves through spacetime, it also traces a path in the internal space above the spacetime trajectory (see "phase" in Figure 40.8). When there is no external gauge potential (a specific thermodynamic potential in general—but for a U(1) gauge symmetry space, it is usually an EM potential), the internal space path is completely arbitrary and the phase angle, θ, can hop around without constraint.

The SU(2) Gauge state, illustrated in Figure 40.8, involves two relevant phase angles, θ and ϕ, which move in a three-dimensional sphere in space at each (x, y, z, t) point. For group designation SU(n), Gauge theory states that $n^2 - 1$ independent parameters are involved in the relevant interaction so

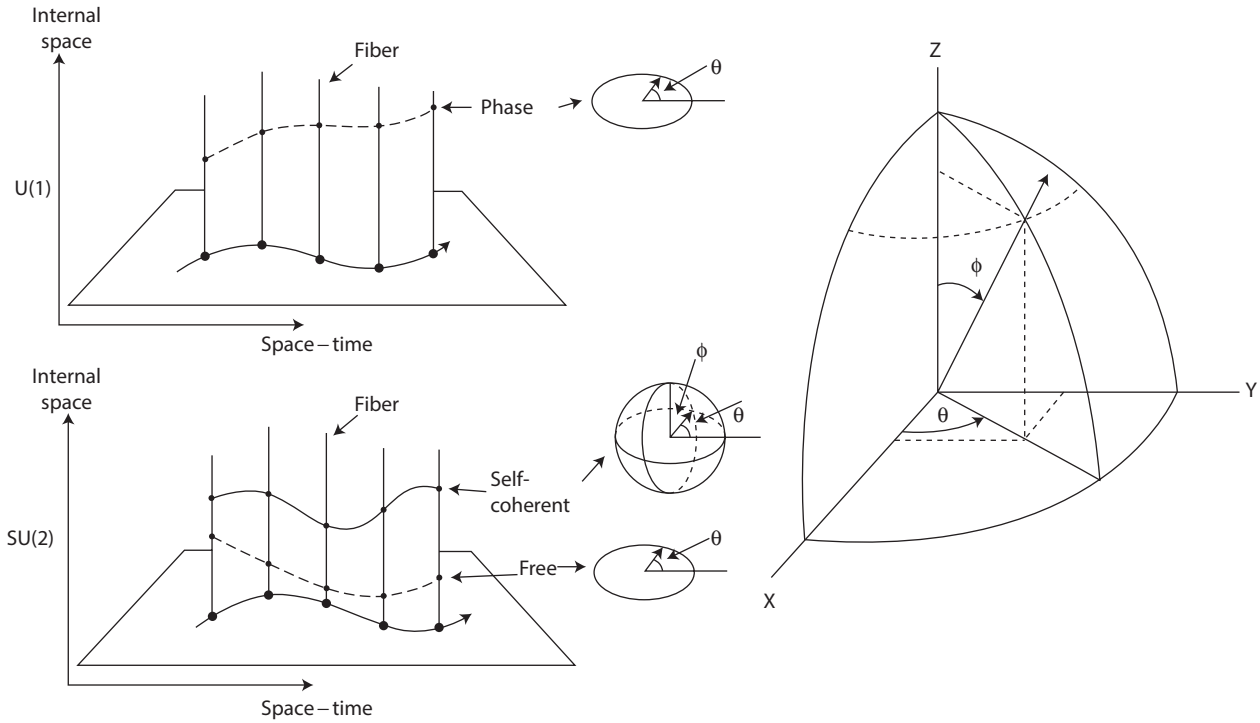

FIGURE 40.8 Illustrations crucial to meaning articulation for the U(1) and SU(2) EM gauge symmetry states.

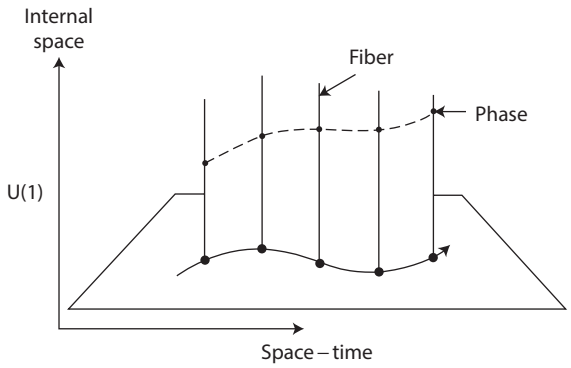

FIGURE 40.9 Geometrical picture of the internal symmetry space. Space-time is the horizontal plane and the internal space direction is specified by phase angles in the internal space or "fiber."

that, for n = 2, three parameters are critically involved. For the orthodox science neutron/proton exchange reaction, this is an SU(2) Gauge state with the neutrino acting as the third parameter, and this trio is also a member of QED.

In the case of our coupled duplex space, the electron/magnetic monopole interaction is thought to occur to produce an SU(2) Gauge state with what I have labeled a "deltron" as the necessary third parameter to stabilize this particular symmetry state. Loss of the deltron from this complex via "leakage" leads to "symmetry breaking" and transition to a U(1) Gauge state for the electron plus a different U(1) Gauge state for the magnetic monopole (but undetectable to our spacetime instrumentation because of its basic superluminal character).

For an SU(3) Gauge state system, $3^2 - 1 = 8$ independent interacting entities are involved in the Gauge interaction. We know this as Murray Gelmann's eightfold way of quark-quark interactions, now labeled as quantum chromodynamics.

Briefly continuing this theme, this author and his colleagues have been investigating some of the healing capabilities of "Buddha relics."[18–20] These artifacts are generally a product of the cremation event of various Buddha Masters, some from thousands of years ago. In our experiment,[20] we found it possible to cognitively and consciously interact with some of these seemingly dormant relics and request that they modulate their basic Gauge symmetry state so that our measurement devices could register a quantitative change in our experimental space.[20]

One of the relic tours was hosted in the home of the Manek family[18,19] over a 3-day period in late July, 2010. During this period, Raj and Nisha Manek placed 11 unimprinted host devices (UEDs) within approximately 2 feet of the stored relics, plugged into a wall socket and switched on electrically for a possible imprinting via the subtle energies radiating from these relics. About 3 months later, this author and his wife, Jean, were visiting the Manek home in Southern California and subjectively felt a residual "space conditioning" within the room in which the relics had been displayed for the public display and personal experiencing.

This author speculated that perhaps these relics had been created by Buddhist Masters via a specific intention, somewhat like what this author and his colleagues had been doing for over the past decade.[6,7] A further thought was that perhaps an experimental test of such a retained intention might be possible.

Six months later, W.A.T. asked N.M. if he might borrow one of her Buddha relics-exposed, but originally unimprinted UEDs, to perform a specific experiment. The answer was "yes!" The serious experiment was carried out in the confines of the Tiller Scottsdale house casita, an empty, unused, separate, and unconditioned room. This Buddha relics' exposed "UED" was placed in the room, plugged into a wall socket, and switched on. Three different types of detector systems were utilized as continuous, monitoring sensors: (i) air temperature, T_{AIR}, (ii) a magnetometer for magnetic flux, B_H, and (iii) a pure water pH-measuring system. Initially, no instructions of any kind were given to the system.

Only the pH-sensor was in any way responsive to this presence of the Buddha relic-exposed UED but only slightly as can be seen in Figure 40.11 for the first ~2300 h when only a very slow growth rate in pH(t) occurred. Discussions between W.A.T. and N.M. indicated that the Gauge symmetry state of these relics might be as high as SU(20), whereas the pH experimental set-up was primarily designed to detect the SU(2) Gauge level of "space conditioning" via human intention. Perhaps our detector system was significantly mismatched with our "relics" Gauge state system.

My wife, Jean, came to the rescue by suggesting that I should write a statement to clarify fully what I am asking the relics-exposed UED to specifically do! The relevant part of that statement was the following:

> This IHD has been exposed for 3 days some time ago to the Maitreya Buddha relics and this has, to some degree, been information-entangled with that loving kindness essence. This loving kindness essence is thought to still reside with this particular IHD at some very high gauge symmetry level of nature and thus still retains a significant thermodynamic free energy per unit volume state value relative to our normal U(1) Gauge State. It is respectfully requested that this **excess** thermodynamic free-energy aspect of this loving kindness essence be made manifest in this casita space so that its thermodynamic magnitude can be experimentally measured via the active pH, T_{AIR} and magnetic field sensors present in this space.

We used this intention statement in a subsequent meditation and activation of this "unconditioned" space. The remarkable change in Figure 40.10 after ~2300 h was extremely encouraging.

In the following ~2 months, ΔpH increased by about +2.5 pH units, or about +60 meV. In thermal energy terms, this number is extremely large. It would take an effective temperature increase of about $\Delta T_{eff} \approx 700°C$ to produce such a thermodynamic energy effect. As the actual temperature in that room did not change by more than ±10°C, this measured thermodynamic free energy change was probably due to a large decrease in thermodynamic entropy, ΔS, via an increased coherence in the strongly "conditioned space."

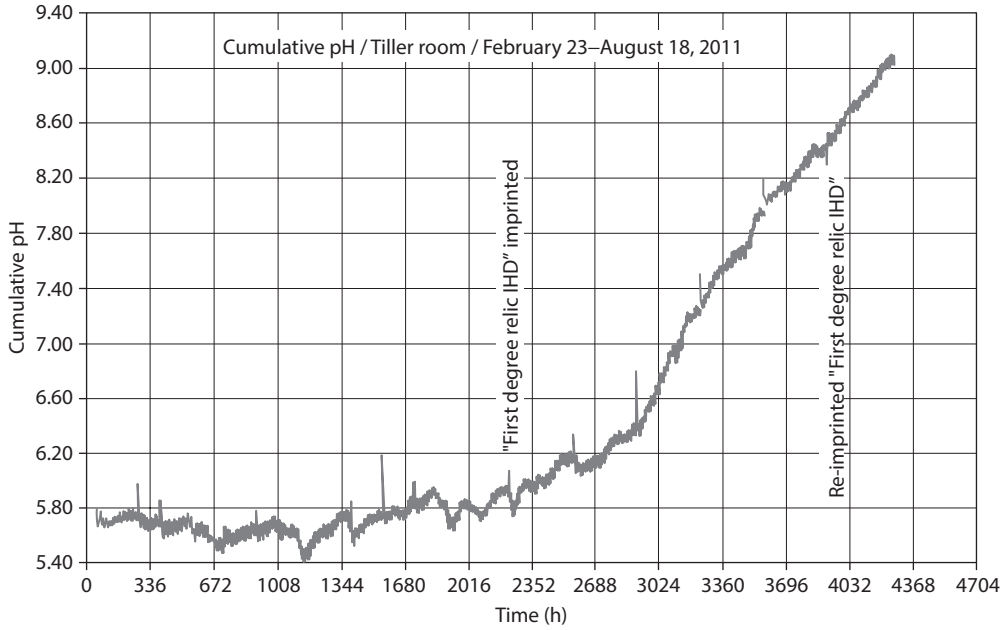

FIGURE 40.10 Plot of Tiller room cumulative pH change from the NM "first degree" (secondary) relic. Two weeks = 336 h. The almost vertical spikes are associated with electrode recalibration and fresh water exchange.

As a closing segment to this section, if the actual gauge state of the Maitreya Buddha relics was about SU(20), then $(20)^2 - 1 = 399$ independent interacting moieties are required to stabilize this Gauge state. Perhaps this is why such a Gauge state can remain stable for thousands of years.

KEY EXPERIMENTAL FINDINGS WITH RECONNECTIVE HEALING WORKSHOPS

In early February, 2006, Dr. Eric Pearl, of "Reconnection Healing" fame asked me if we might be willing to monitor his upcoming healer training workshop in Sedona, Arizona, USA, with our "thermodynamic free energy" detector based on our pH-measuring system. By then, we had found that it was theoretically possible to calculate the relationship between pH and the pH-electrode voltage (see Figure 40.11). Thus, it became possible via the collection of standard pH data to detect when the Gauge state of a space was moving away from our normal U(1) Gauge condition and the aqueous H^+-ion was exhibiting an excess thermodynamic free energy state that could be quantitatively measured. In essence, with no intentional chemical additions, a + 1.0 H unit change in water is equivalent to a 23.6 meV change in the water so that Figure 40.11-type date allows us to calculate $\delta G^*_{H^+}$-changes due to subtle energies.

Our basic experimental procedure is illustrated in Figure 40.12, while Figure 40.13 shows the first 9 h of pH data gathering that started ~5–6 h before the workshop was to commence. The uppermost curve, T_W, is the water temperature;

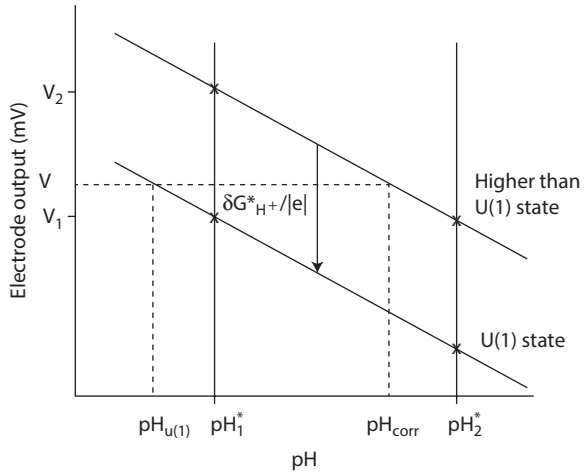

FIGURE 40.11 The electrode electrical output versus pH plots for both our normal, world electromagnetic symmetry state, the U(1) state ($\delta G^*_{H+} = 0$), and a higher than U(1) electromagnetic symmetry state.

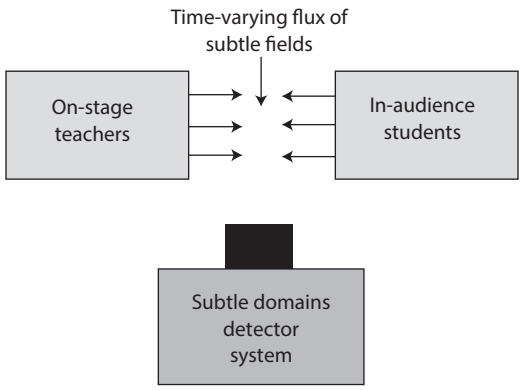

FIGURE 40.12 The general methodology is illustrated here.

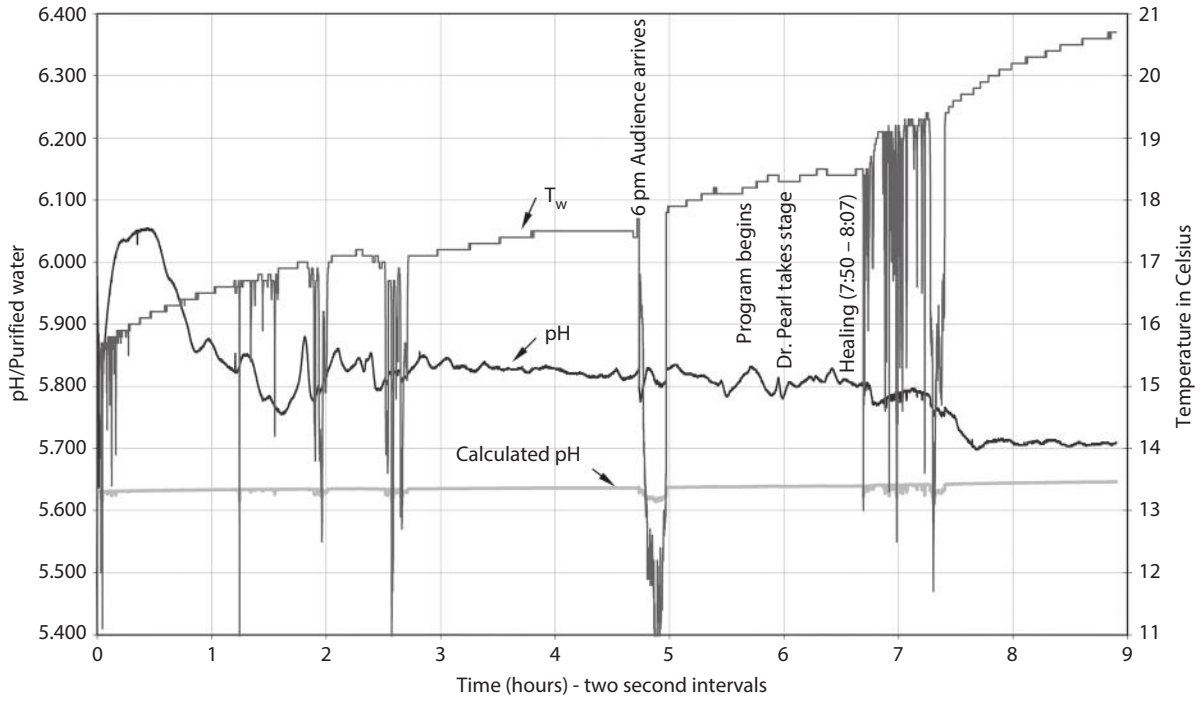

FIGURE 40.13 Very anomalous water temperature, T_W, behavior was observed at this Sedona healing workshop.

the middle curve is the digitally measured pH, while the bottom curve is the theoretically calculated pH = $pH_{U(1)}$.

The T_w-anomalies (the downward shooting lines) in Figure 40.13 started to appear ~5 h before the audience arrived in the large room. We have experienced this kind of phenomenon in our Payson laboratory many times before and found that this type of anomaly correlates strongly with the presence of high $\delta G^*_{H^+}$-values.

It is important for the reader to realize that this T_w-data indicates that this particular space had somehow been "lifted" to a very high–value well before any of the workshop participants had entered the room (perhaps information entanglement in time?). When a pH-calibration cycle was carried out with this same detector ~1 week after this workshop event, absolutely no anomalies appeared in either the pH or T_w plots and the room appeared to be completely back to the U(1) Gauge state.

Analysis of the gathered raw data to create a $\delta G^*_{H^+}(t)$-plot occurred about 1.5 weeks later. At time t = 0, δG^*_{H+} was found to be almost double what it would have been if α_{eff} in Equation 40.1 had been zero. At its peak (almost 2 days later), it had almost tripled the $\alpha_{eff} = 0$ value and, at ~1.5 weeks later, it had decayed back to ~double again.

If one asks the question "how much would one need to heat this room from an $\alpha_{eff} = 0$ state to yield its maximum $\delta G^*_{H^+}$-state, as found by our detector and describe the result as an effective temperature change, ΔT_{eff}, as illustrated in Figure 40.14, one notes that it would have required a change in $\Delta T_{eff} \approx 300°C$ over the workshop period. However, the actual change in workshop room temperature was no more than ~5–10°C.

One important implication of this result is that the $\delta G^*_{H^+}$ result occurring here is not due to a thermodynamic internal energy, ΔE, change but, rather, to an information change, ΔI*, process that automatically generates a thermodynamic entropy decreasing process wherein $\Delta S = -\Delta I^*$.[12,13]

At a later Reconnection workshop in Los Angeles (July 2007), two different pH-electrodes were utilized. They yielded the $\delta G^*_{H^+}$-plot results of Figure 40.15. Here, one notes that each electrode has its own "personality" (depending on electrode history as well as make and manufacturer) with electrode I being more responsive than electrode II.

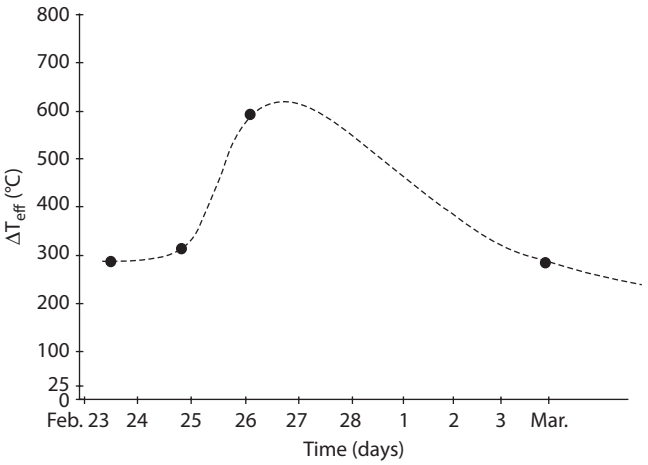

FIGURE 40.14 Possible data plot of the excess thermodynamic free energy for the healing workshop room as a function of time via converting $\delta G^*_{H^+}$ to an energy equivalent, effective change, in temperature, ΔT_{eff}, for a normal room.

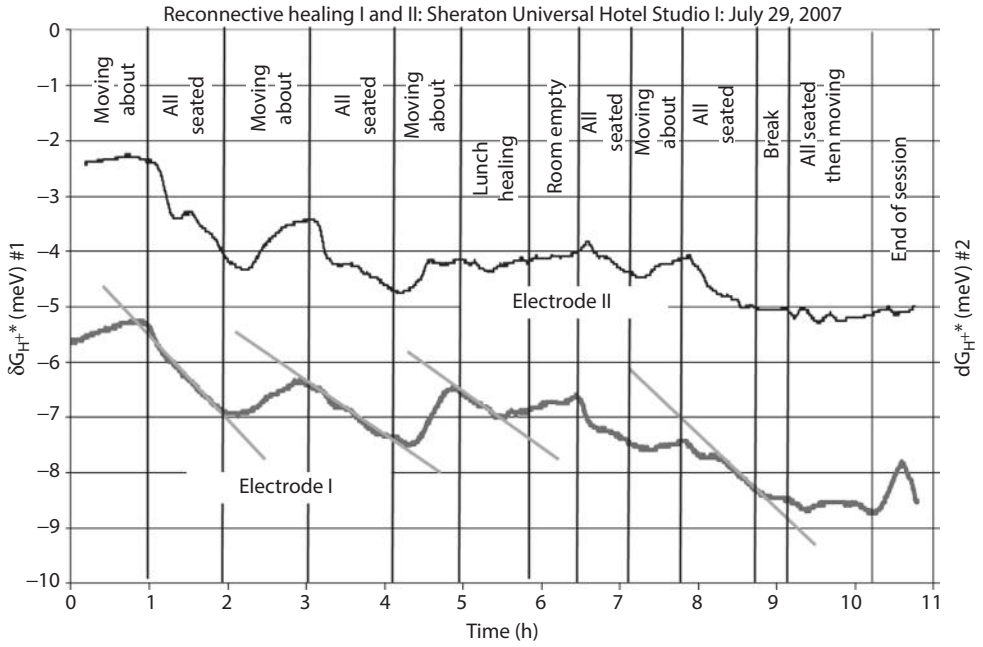

FIGURE 40.15 $\delta G^*_{H^+}$ for the space versus time.

Following the electrode data, one notices a strong correlation of periods of almost constant downward slope ($|\delta G^*_{H+}|$ is increasing) of $\delta G^*_{H^+}$ with time when either Dr. Pearl or the teaching assistants were lecturing on stage. It appears as if an entrained coherence between the on-stage speaker and the audience is meaningfully controlling the pH-measurement equipment. This entrained coherence is quickly broken when the speaker and the audience take a short break and begin to move around the room and talk with each other. This, in turn, causes a reversal of the slope in the $\delta G^*_{H^+}(t)$-plot every time this short relaxation break occurs.

One of the closing observations of this section, is that (i) during speaker on-stage presentations to the audience, one observes that the magnitude of $\delta G^*_{H^+}$ always seems to increase at a constant slope with time. This signals a constant rate of information production, $d\Delta I^*/dt$, and thus, an equal rate of thermodynamic entropy annihilation ($d\Delta I^*/dt = -d\Delta S/dt$ which leads to $-TdI^*/dt = \delta G^*_{H^+}$). Also, (ii) during the audience standing, moving around, and talking to each other, the magnitude of $\delta G^*_{H^+}$ always seems to decrease. This signals that net excess positive thermodynamic entropy production is occurring during these semi-chaotic intervals of relaxation.

The closing item is a quantitative thermodynamic free energy description in terms of its component parts. The Gibb's free energy G, is given by

$$G = PV + E - T\left(So + \sum_{m=4}^{z}\sum_{n=0}^{\infty}\Delta I^*_{nm}\right) \qquad (40.2)$$

Here, P = pressure, V = volume, E = internal energy, T = temperature, S = entropy, ΔI^*_n = nth increment of information created, and m is the dimension wherein the increment of information is created. At our normal reality (m = 4-distance-time), the U(1) Gauge state, the Boltzman Constant is so small that ΔI^*_{14} is quite small. As m increases, this author expects that the analogue of the Boltzman Constant is significantly increased.

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41 Bioelectricity Circulation and Bioelectric Resonance Therapy

The Bridge between Traditional Chinese and Western Medicine

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CONTENTS

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WHY ARE ENERGY THERAPIES STILL CONSIDERED TO BE ALTERNATIVE MEDICINE?

Why are energy therapies that have been utilized for centuries still considered to be an alternative medicine technology? Two major reasons are described in this paper. One is that there are no theories to explain the varied benefits of energy therapies, which differ from biological (structural) medicine. The second reason is that the efficacy of most of these approaches is not superior to pharmaceuticals. In biological medicine, biological structures at the levels of molecules, cells, and organs are always the direct targets of interventions and resultant changes are used to evaluate efficacy. Thus, what are the direct targets of different energy therapies, molecules, cells, organs, or some other undiscovered system? Superficially, all energy therapies are applied directly to the human body, however, where do the different energies go? The bioelectricity circulatory system (BECS) was discovered based on our existing understanding of biology and bioelectricity research,[1–4] and this nonstructure system may be the system that directly responds to energy therapies.[1,2,5–11]

THE BECS—A REVOLUTIONARY DISCOVERY OF BIOELECTRIC PROPERTIES

Bioelectricity is an old concept that encompasses electrophysiology, in which cell potentials and organ electricity have been scientifically studied, mainly with regard to their generation and properties.[11] However, the holistic (overall) bioelectrical current flow and its mutual transformation to environmental energies were not studied until the last few years, when we began to study channel bioelectricity and its relation to health, diseases, and treatment technologies.[1–4,12–29]

Research in the 1980s by the late Professor Björn Nordenström from the Karolinska Institute in Sweden had shown that specific direct current (DC) microcurrents can restore an abnormal ion electrical balance to treat cancers.[7] He also proposed an electrical circulatory system based on biologically closed electrical circuits (BCEC) between normal and cancer tissues.[7,10] It was unique that he had begun to consider electricity as the direct target of his treatment, but he later modified his treatment to take advantage of certain electrochemical benefits.[7,10]

Our studies in the past few years have revealed a BECS,[1–4] a nonstructure system (upper part of Figure 41.1). The BECS is a system involved in generation, flow, and exchanges with environmental energy, based on different structure levels. Therefore, the BECS can be described at molecular, cellular, and organ levels, as well as at a holistic (the overall flow of bioelectricity) and an environmental level (energies outside the body) (Figure 41.1).[1–4,12,13] BECS (upper part of Figure 41.1) are the counterparts of the biological structures (lower part of Figure 41.1). In order to identify biological structures, body hardware is introduced to refer to biological structures, while body software is introduced to refer to the BECS.[1–4,12,13] The relationship between the BECS and traditional Chinese medicine (TCM) has also been studied and reported.[1–4,12,13]

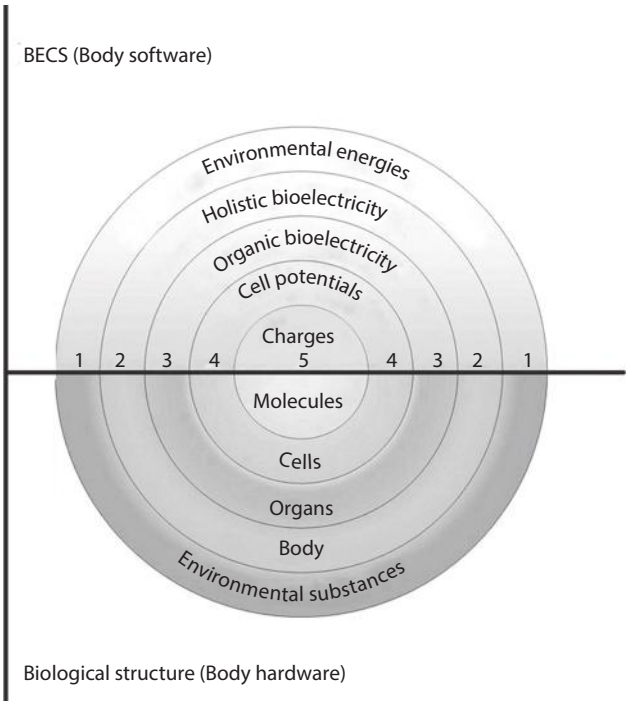

FIGURE 41.1 General classification of the substances of the human body.

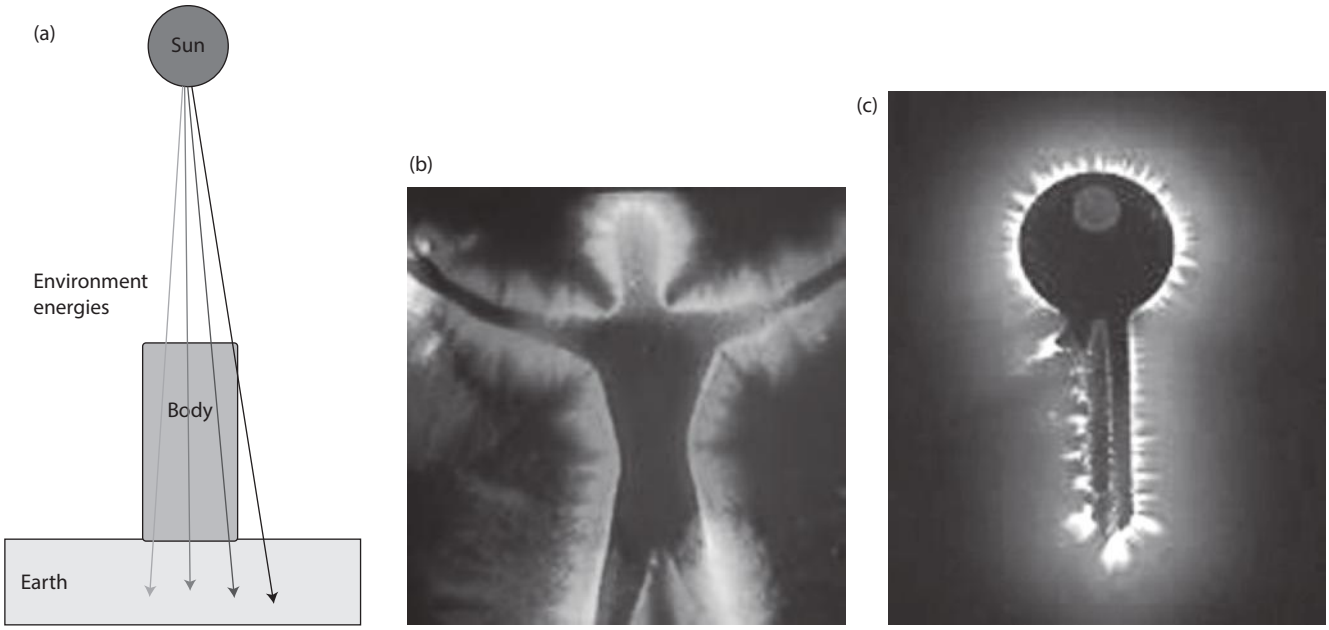

FIGURE 41.2 Energy and life: (a) the relationship between sun, human and earth, (b) the corona of human, and (c) the corona of a metal key.

WHY BIOELECTRICITY?

Life energy can be described in four subtypes: bioelectricity, biomagnetic, biothermal, and biolight. Why bioelectricity? First, electricity flow emits magnetic, thermal, and light energies, and bioelectricity has been thoroughly studied at frequencies, powers, and waves in electrophysiology established over centuries.[11] Second, it is common knowledge that a flat line electrocardiogram (ECG or EKG) is used to define death.[4]

The sun emits electricity, magnetic, light, and thermal energies, and therefore both the earth and our bodies can receive those energies (Figure 41.2a). Many scientists believe that energy is a sign of life, as illustrated (Figure 41.2b) by the energy corona observed with gas discharge visualization photography.[5] But why does a metal key (Figure 41.2c) without any characteristics of life also have an energy corona?

We believe that the energy corona might not be the life energy, but rather a physical phenomenon formed by the reflected environmental energies at object edges, such as the human body, keys, or other inanimate objects. The differing physical characteristics of such objects would change its original frequencies when subjected to varied environmental forces. The resulting corona colors and outline reflect these changes, which helps explain why a key and other inanimate objects can exhibit a strong corona.

RESOURCES OF THE BECS

As shown in Figure 41.3, the resources of the holistic bioelectricity of the BECS can be divided into two parts: one part is generated by cells and organs inside the body, and the other part is converted from the environmental energy outside the body (Figure 41.3). The bioelectric current of the inner body connects to the outside energies (Figure 41.3).

The external sources of bioelectricity are converted forms of the energy from the sun (including energies from the universe) and the earth (Figure 41.4). The body receives energy

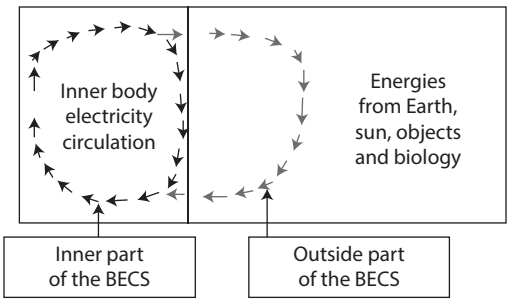

FIGURE 41.3 Illustration of BECS (inner body part and outside body part).

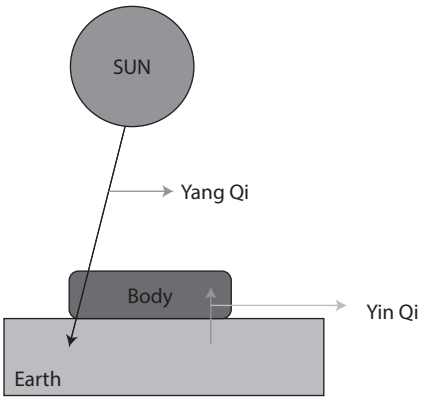

FIGURE 41.4 Outside major energy resources of the human body.

from the sun during daytime from sunrise until sunset. This energy is what has been called *Yang Qi*. At night, the body receives energy from the earth, and this energy is what has been described as *Yin Qi*.

THE BECS, FUNCTION, HEALTH, AND DISEASES

Based on the composition of components in the body, medicine can be classified into two categories (Table 41.1). One is biological medicine (western medicine and TCM) and the other is bioelectrical medicine (life medicine and TCM). The core theory for biological medicine considers that alterations in biological systems at different levels result in different diseases (Table 41.1), including molecular, cellular and organ diseases. And for bioelectrical medicine, the core theory is that changes in the BECS lead to various symptoms and functional diseases at these different levels.[1,2,4,12] The BECS is the life and biological structure is the vector of life (Figure 41.5) and different bioelectricity levels reflect different life stages or conditions.

Bioelectric Changes at the Molecular Level Lead to Water Distribution Problems and Metabolic Diseases

Inorganic and organic molecules, DNA, and protein molecules inside the body have unique electronic properties based on their charges and distribution.[1,2,4,12] Water-soluble molecules have ionic states that are based on their positive and negative charges. At the molecular level, the amount of positive and negative charges, their distributions, movement, and mutual interactions constitute the process of metabolism (Figure 41.5).[1,2,4,12]

First, the concentration of molecular charges and their distribution forms the basis of water circulation in the cell matrix. Cell membranes are composed of phospholipids. If the polarity of the phospholipids is weakened, then the binding force between phospholipids decreases. As a result, the cell membrane will become deformed or ruptured and there will be an increase in cell membrane permeability that allows intracellular enzymes to leak out. For example, in hepatitis, the permeability of liver cell membranes increases due to injury, and certain enzymes have higher blood levels because of this.[1,12]

Second, the functions of proteins are determined by the activity of their charged regions. If their charges are neutralized, the proteins will be inactivated and their function will be impaired.[1,12]

Third, the generation of resting and action potentials of a cell depends on the movement of potassium, sodium, calcium, and magnesium ions in and out of the cell membrane.[11] Without the flow of ions, there would be no cellular potentials, and no cellular functions could be performed.[1,11,12]

Fourth, a high concentration of molecular charges outside blood vessels causes edema whereas a low concentration causes dehydration. In contrast, lower concentrations of molecular charges in the blood cause edema, but higher ones can prevent edema or induce tissue dehydration. When acute injury occurs, the dead cells release a variety of charged molecule to tissues outside blood vessels, leading to a high concentration of charges in the injured tissues. Therefore, water from blood flows in to dilute the charges and achieve balance. The resultant alterations in molecular charges can lead to metabolic disorders.[1–4,11,12]

Bioelectric Changes at the Cellular and Higher Levels Result in Organ Functional Diseases

Cellular potentials include resting and action potentials. Cell potential generated from one cell can be transmitted to neighboring cells.[11] The frequency of action potentials represents the cell function, or the vitality of the cell. Abnormal action potentials will make the cell and organ dysfunctional (Figure 41.5).

An organ is composed of different types of cells, and some have active bioelectricity, whereas others do not. The

TABLE 41.1
Bioelectricity Medicine, Biological Medicine, Related Diseases, and Treatment Technologies

Term	Theory	Body Substance Target	Related Diseases	Related Technologies
Bioelectricity Medicine (Life Medicine)	BECS changes at different levels lead to different diseases, including various symptoms and functional diseases	Molecular charges	Swollen and metabolic disease	BERT, acupuncture
		Cellular potentials	Organ functional diseases	BERT, acupuncture
		Organ electricity		BERT, acupuncture
		Holistic electricity	Pains and other symptoms	BERT, acupuncture
		Mutual transformation with environment energies	Insomnia, epilepsy, autism, depressions, and so on	BERT, acupuncture
Biological Medicine (Western Medicine)	Structure changes at different levels result in diseases, including molecular, cellular, and organ diseases	Molecules	Molecule contents and structure change diseases	Drugs and herb medicine
		Cells and organs	Organ structure change diseases	Surgery
		Body	Appearance changes	Surgery
		Environmental substances	Poisons	Prevention of in-taking

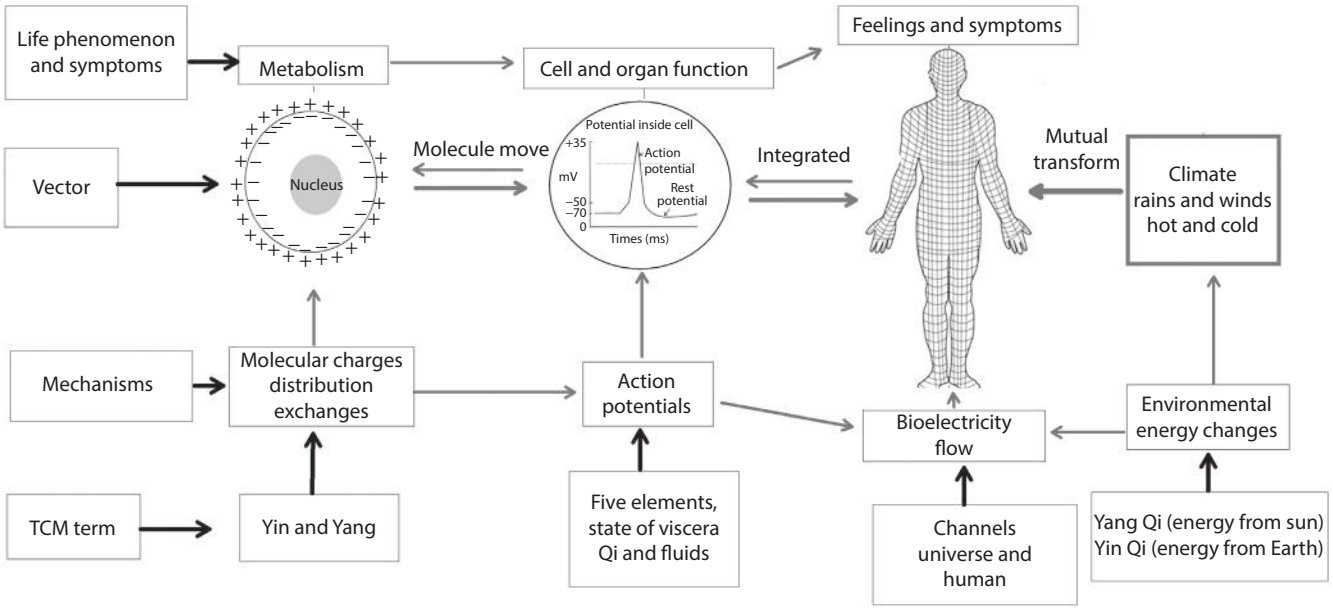

FIGURE 41.5 Analysis of the relationship between bioelectricity at different levels, life status and TCM.

type and quantity of cells with active bioelectricity in organs determines the features and strength of their function. All living cells have electrical transmembrane potentials. Blood cells have about 7 millivolts, muscle and nerve cells have −70 millivolts.[11]

The total bioelectricity generated by a variety of cells within an organ is the organ bioelectricity. Decreased action potentials in one organ result in a decrease in the strength and/or frequency of action potentials, followed by diminished or slower function.[11] If, however, the frequency or strength of the action potentials increases in the cells in one organ, then the overall function of this organ would be excessive.[11] For example, when the bioelectricity of skeletal muscle has a low frequency, myasthenia occurs, and when the frequency becomes too low, the muscles become paralyzed. However, when the frequency is higher than normal, spastic paralysis and seizures can occur.[1–4,12]

Holistic Bioelectricity Changes are Symptoms

In the human body, the bioelectricity generated by molecular, cellular, and organ activities cannot be detected separately; rather, all of this bioelectricity forms holistic bioelectricity, a circuit flow system.[1–4,12] Holistic bioelectricity plays a role in coordinating the functions of different tissues and organs, and also in the bioelectricity storage of molecules, cells, tissues, and organs (Figure 41.5).[1–3,12]

Because of bioelectric flows and circulation, the body has its own natural magnetic field, thermal energy (temperature), and luminescence (body brightness). The circulation of holistic bioelectricity generates and maintains body temperature.[12] Therefore, a low or high temperature is caused by abnormal bioelectric circulation. When life ends, normal temperature disappears.[4,12] Changes in strength, wave type, and frequency of holistic bioelectricity can cause symptoms or health problems (Table 41.1). The status, circulation, and mutual transformation of external energies of holistic electricity are self-feelings and represent the functional status.[1–4,12]

Body Bioelectricity Mutual Transformation and Related Diseases

Body bioelectricity will alter with changes in environmental or climate energies. Thus, we are awake during the day and sleep during the night. The human biological clock, in fact, represents the relationship between the BECS and the environmental energies from the sun that change throughout the day. Communication between bioelectricity and environmental energies is the foundation of human adaptability to the environment (Figure 41.5).[1–4,12] When people live in one place for a long time and then move, they are likely to suffer because of discomfort due to poorer or slower communication with new environmental energies. These can cause various symptoms seen in patients with autism, depression, and insomnia. Finally, human bioelectricity can interact with the bioelectricity of other living things through environmental magnetic fields, which is why some humans can communicate with certain animals and possibly plants.[1]

THE BECS AND TRADITION CHINESE MEDICINE

The concordant relationship between BECS and TCM has been thoroughly studied[1] and reinforces the validity of both of these concepts. (Figure 41.5).

"The Yin and Yang Principles"

The principles of *Yin* and *Yang* were stated in Chapter five of an ancient Chinese book, the *Huang Di Nei Jing*.[30] It said that "*Yin* and *Yang*, is the road between Heaven and Earth,

the disciplines of all matters, the parents of changes, the line between life and death, the codes for wisdom and intelligence." To treat diseases we will have to treat the Yin and Yang.

TCM Three Principles

TCM treatment depends on addressing its three fundamental principles: geography, timing, and individual states. The BECS explains why different geographic regions have different environmental energies and why energies can vary at the same geographic place at different times of the day and seasons of the year. Even in the same location, same time and season, different individuals will have different bioelectricity levels.[1] The BECS justifies the three principles of TCM (Figure 41.5).[1]

Geographic Regions

Diagnosis and treatment should be carried out paying special attention to environmental characteristics. In different geographic environments, where environmental energy intensity fluctuates, the state of human bioelectricity changes with time. As a result, the diagnosis as well as the effects of treatment will differ.[1]

Timing

Timing treatment acknowledges that diagnosis and treatment should be made according to the hours of the day as well as the seasons of the year. In a single day, the environmental energies change with time and therefore the bioelectricity differs in the morning, mid-day and evening. Therefore, different diagnoses and treatment results will occur at different times. Seasonal changes can significantly affect an individual's bioelectricity.[1]

Individual States

This principle mandates taking into account the patient's age, gender, and physical characteristics when considering diagnosis and treatment. The same gender, age, and health conditions, however, do not ensure the same states of bioelectricity. Individuals with these identical demographics may require different medicines or doses of medication due to variations in their personal bioelectricity level. This is also true in Western medicine, since the effectiveness of a drug for the same disease can vary considerably in patients with the same complaints. Similarly, why do identical twins with the same genes and environment develop different diseases or levels of intelligence? Why does intelligence or resistance to disease vary with age in the same individual? All these phenomena can be explained by the differences in the BECS.[1]

TCM Yin and Yang Theory

Yin and Yang describe two sides of one matter. For a biological body, Yin is structure and Yang is nonstructure (BECS), and the interdependence and the convertibility between them is the dynamic status towards balance (Figure 41.5). Once an imbalance occurs, illnesses will ensue. At a holistic level, active bioelectricity flow is Yang, and otherwise it is Yin. At an organic level, Yang basically represents the higher organ bioelectricity resulting in higher function and lower bioelectricity/function is Yin. At cellular levels, the action potential is Yang and resting potential is Yin. At molecular levels, Yin is the negative charge while Yang is the positive charge, and when the number of positive changes is higher than negative charges it is also Yang, while the opposite is Yin.[1]

TCM Five Elements Theory

Five elements describe the interaction of the bioelectricity between different organs. Different metabolic rates in tissues and organs result in distinct bioelectricity rates and intensity. Therefore, the bioelectricity generated by dissimilar organs can affect each other, like bioelectricity generated from the liver during hepatitis can affect the stomach and cause vomiting (Figure 41.6).[1,12,13]

TCM Channels Theory

Channel is the generation, flow and the flowing basement of bioelectricity (Figure 41.5). Bioelectricity fluctuates over time, with an intensity lower than a volt (normally between 0.1 and 0.5 V), a frequency between 25 and 500 Hz, mainly at 50 Hz.[1,2,13] The flow of bioelectricity balances and nourishes organs and tissues, and holistic bioelectricity also stores bioelectrical energy for use when a tissue has a shortage of bioelectricity. When balanced, there are no symptoms; otherwise, symptoms will occur. In other words, changes in bioelectrical strength and frequencies generate both symptoms and illnesses, and this is described as "blocked channels cause pain" in TCM.[1,2,13,30] Based on the channel bioelectricity theory,[1,12,13,30] acupuncture actually impacts on bioelectricity. In essence, once the metal acupuncture needle is inserted into the body, the bioelectricity reacts instantly. Therefore, the feeling of acupuncture is the conduction of bioelectricity, namely "Getting Qi." This can also be the exchange between

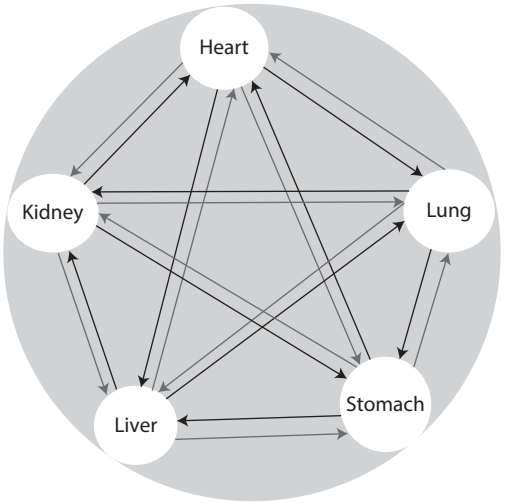

FIGURE 41.6 The five elements in TCM theory.

the bioelectricity of patients and that of the acupuncturist and environmental energies.[1]

TCM State of Viscera Theory

This presents the mutual relationship of bioelectricity between internal organs and the body surface area. Bioelectricity from different organs is able to flow to certain locations of the body's surface, establishing the relationship between the organs and body surfaces (Figure 41.5). Similarly, bioelectricity from the stomach can flow onto the tongue and manifest as different colors or thickness of the tongue surface.[1]

Body Qi and Fluids

Body Qi is the bioelectricity-related energies and "Qi-Gong" is the process of a human body transforming environmental energies into bioelectricity (Figure 41.5). When the converted bioelectricity intensively flows inside the body, it is "Getting Qi." Natural healing is the mutual transformation process of environmental energies to human bioelectricity.[1] "Qi is the driving force for fluid circulation, and when Qi stops, fluid stops" in TCM theory;[1] Qi is the bioelectricity, and it is understandable that electricity is the driving force for fluids including blood circulation.[1]

Here the electricity forces are the driving forces for positive and negative ions to move, and if the movement is conducted between cell membranes, the active cell potentials are enhanced and the functions are improved. If the movement of ions is induced in the fluid outside the cells, it will help cellular communications and also assist organ functions.[1]

TCM Universe and Human Theory

This describes the interaction between body bioelectricity and the environmental energies (Figure 41.5). From birth, people began to stand on the earth and under the sun, subjected to this energy network. With constant changes in the environmental energies, bioelectricity also changes correspondently. People also receive energies from the earth, which is referred to as "connected to the earth Qi.[1]"

TCM Herbs and Bioelectricity

The effectiveness of Chinese herbs has been proven for many conditions. The mechanisms of action that may be responsible are partially explained by biological studies.[1] However, Chinese herbal medicines mainly provide water and inorganic ions to modify the distribution of the molecular electrical charges inside the body, gradually improving the generation of cellular potentials, organic electricity, and the flow of holistic bioelectricity (Figure 41.5). This then leads to a balance in bioelectricity.[1] Other effective ingredients from the herbs used are scarce and mainly glycoside-based substances.[1]

BERT

The Nature of Bioelectricity Resonance Technology

First, the nature of BERT is a new technology that targets the natural body bioelectricity, and BERT is designed to correct altered bioelectricity by targeting molecular, cellular, organic, holistic bioelectricity and its mutual transformations with environmental energies. BERT is different from other energy therapies that treat body structures and is based on the body's natural physical properties.[1]

BERT Parameters and Its Treatment Principle

The frequencies used for BERT are 50–150 Hz with a sine wave of adjustable amplitude. The treatment principle involves circuits along both sides of the diseased site. The applied AC microcurrent ranges from 3 to 25 mA and can be adjusted according to the patient's feelings. A frequency of 25, 50, or 100 Hz is chosen, and the current is applied using an electronic pad placed on the skin on two opposite sides of the diseased area.[1]

SHECON, the Bioelectricity Resonance Equipment[1,31]

SHECON, the bioelectricity resonance equipment (operator panel shown in Figure 41.7), is the only product based on

FIGURE 41.7 Operator panel of SHECON.

bioelectricity medical theory (innovational patent in the year 2010). SHECON can correct abnormal bioelectrical signals and apply the corrected signals to the patients.

BERT Practice Instruction

BERT treatment involves both longitudinal treatment, in which the electro-pads are placed along the body axis, and horizontal treatment, in which they are placed across the lateral body axis (details shown in Table 41.2). First, it is important to localize the lesion site based on the patient's description and then determine the treatment locations. Second, the SHECON electro-pads are placed on the determined locations to begin the treatment. During the treatment, the SHECON index (the number shown in panel 8 in Figure 41.7) increases steadily, indicating that the treatment is effective and that the disease is under control. A lack of change of the index indicates the presence of blocks around the lesion. A decrease of the index indicates that the disease is being treated but will take a longer time to cure.

BERT APPLICATIONS AND EVALUATIONS

Theoretically, BERT can be applied to all diseases related to all bioelectrical active tissues, including the nervous system; the muscular system (skeletal muscle, smooth muscle, and heart muscle); the glandular system, including the liver, kidney, and similar organs; blood; and the immune system. These tissues can be swollen and present other symptoms.[1,2,11,12,13,14]

Effective evaluation indicators consist of two parts. For functional disease and/or symptoms, the effectiveness was evaluated mainly by the patient's satisfaction, and for illnesses with structural changes, the effectiveness was evaluated by comparing biological indicators before and after treatment.

TABLE 41.2
BERT Instructions

Positions	Methods	Applied Diseases
Waist horizontal treatment	1. Place two red electrodes on parallel close locations between the 4th and 5th lumbar vertebrae and place two black electrodes on the two sides of the navel. Fasten the electrodes with bandages. 2. Set the time to 20 ms, mode to 2, and protection to 6. 3. The SHECON index should be approximately 6–18, depending on the individual patient.	Almost all diseases happening in organs below the waist, including lower back pain, diarrhea, constipation, arthritis, cold extremities, leg cramps, hemorrhoids, prostate disease, necrosis of the femoral head, and so on.
Waist longitudinal treatment	1. Place two red electrodes on the waist and two black electrodes under each foot near the Yong Quan acupoint. Fasten the electrodes with bandages. 2. Set the time to 20 ms, mode to 2, and protection to 6. 3. The SHECON index should be approximately 5–15, depending on the patient's feelings.	Dysmenorrheal and most gynecological disease. Most male diseases. Male and female functional diseases and so on.
Stomach horizontal treatment	1. Place the black electrodes on the stomach and the red ones on the back. 2. Set the time to 20 ms, mode to 2, and protection to 6. 3. The SHECON index should be approximately 5–20 depending on the patient's feelings.	Almost any diseases related to organs inside the abdomen. Liver problems including hepatitis, hepatocirrhosis, gallbladder infection, liver cancer. Kidney problems covers kidney stones, nephritis and kidney cancers. Stomach problems cover stomach ache, gastric ulcer and bleeding, gastritis; and intestine problems, pancreas, and pains and so on. Other problems including pancreatitis, and so on.
Stomach longitudinal treatment	1. Place two red electrodes on the back at the stomach and the black ones under the feet. 2. Set the time to 20 ms, mode to 2, and protection to 6. 3. The SHECON index should be approximately 5–20, depending on the patients' feelings.	
Neck horizontal treatment	1. Place the red electrode on the right side of the neck and the black on the left side of the neck. 2. Set the time to 10 ms, mode to 2, and protection to 3. 3. The SHECON index should be approximately 5–10, depending on the patient's feelings.	All diseases happening in any organs above the diaphragm including eyes, lung, heart, brain and cervical vertebrae. Covering diseases like headache, dizziness, insomnia, dry eyes, depression, cardiovascular diseases, heart problems, and pains, asthma, lung cancers and so on.
Diseases locations	1. Place the red electrode on the right side or back side and the black on the left side or front side. 2. Set the time to 10 ms, mode to 2, and protection to 2–6. 3. The SHECON index should be approximately 5–10, some places even higher depending on the patient's feelings.	For any diseases.
Restrictions	Never put the pads across the heart area.	

TABLE 41.3
SHECON Complementary Evaluation Technologies

Biological indicators	Pathology changes Molecular changes
Bioelectrical indicators (symptoms) —Dr. Wang evaluation technology (or 100-point scoring reduction system)	Number of effective symptoms Symptom degree change evaluation 1. The symptom degree is assigned as 100 before treatment. 2. A score is given after the treatment by comparing with that of before and compared. 3. Any symptom degree reduced by less than 20 is marked as not effective. 4. Score between 21 and 60 is effective. 5. Score between 61 and 90 is significantly effective. 6. Score between 91 and 100, or no symptom is cured.

The SHECON Evaluation Technology shown in Table 41.3 includes two types of indicators. One is based on biology at the pathological and molecular levels. The bioelectricity indicators include the number of symptoms and the changes in each symptom. The number of symptoms before treatment is compared with that after treatment. For symptom degree changes, a 100-point scoring system was developed and applied. The symptom degree is assigned as 100 before treatment, and the score given after treatment is used to rate its success. Any symptom reduced by less than 20% is marked as ineffective, between 21% and 60% as partially effective, 61%–90% as significantly effective, and over 91% essentially cured.

BERT EFFECTIVENESS OBSERVED

Disease Spectrum

For more than four years of clinical application in more than 10 centers, BERT has shown significant effects on many diseases; Table 41.4 shows the diseases observed in 10 centers before 2011. Many patients treated by BERT had previously received various other treatments and showed no improvement (Table 41.4). All patient's symptoms were evaluated.

Pain is Caused by Holistic Bioelectricity Changes Rather Than Structure Changes

Pain is a symptom, and most illnesses tend to be accompanied by pain. BERT has a significant effect on pain symptoms. As we proposed that all symptoms, including pain, are caused by holistic bioelectricity changes rather than structural changes, all cases treated were not classified by Western medical etiologies. Among the 870 cases treated for various types of pain, such as trauma pain, acute abdominal pain, and cancer pains, 833 cases were treated with remarkable effectiveness and the effective rate reached 96% (833/870).

TABLE 41.4
Nineteen Different Diseases Treated by BERT

	Name of Diseases and Symptoms	Number of Cases	Effective Cases	Effective Rate (%)	Treatment Duration (minutes)	Number of Treatments
1.	Toothache	114	106	93	20	1–3
2.	Lower back pain	347	316	91	40	1–30
3.	Shoulder pain	102	99	97	20	1–10
4.	Stomach pain	82	76	93	40	1–5
5.	Headache	33	32	97	10	1–3
6.	Trigeminal neuralgia	17	15	88	20	1–10
7.	Cancer pain	18	15	83	40	1–10
8.	Sore throat	72	61	85	20	1–5
9.	Insomnia	46	40	87	40	1–30
10.	Meniere's syndrome	11	11	100	20	1–5
11.	Epilepsy	9	9	100	40	10–30
12.	Depression	12	12	100	40	30
13.	Eye tearing	19	18	95	10	1–7
14.	Swelling (edema)	21	21	100	40	1–30
15.	Liver function	11	11	100	40	5–30
16.	Paralysis	223	221	99	40	5–30
17.	Cold extremities	18	17	94	40	1–5
18.	Cervical spondylosis	74	69	93	20	1–30
19.	Gynecological inflammation	17	15	88	40	5–20
20.	Sinusitis	23	19	83	20	10–20
21.	Prostatitis	22	18	82	40	5–20
	Total	1291	1201			

Among the 114 observed cases of toothache (see Table 41.5), 106 cases were cured by one treatment, and the efficacy rate reached 93% (106/114). The analysis was based on the treatment duration and showed that 42.1% were completely cured by a 5 minute treatment, 34.2% were cured by a 10 minute treatment, 11.4% were cured by a 20 minute treatment, and 5.1% were cured by two 20 minute treatments. Only eight cases did not show any effectiveness (Table 41.5); and, of these, there were two cases with wisdom teeth, two cases with broken teeth, one case with cut gums, one case with an artificial crown, and two cases with no clear description.

TABLE 41.5
Distribution of Treatment Duration and Treatment Time for Toothache

Treatment Duration (minutes)	Number of Treatments	Number of Cases	Cured	Rate
5	1	48	48	42.1%
10	1	39	39	34.2%
20	1	13	13	11.4%
20	2	6	6	5.1%
30	1	8	0	7.1%

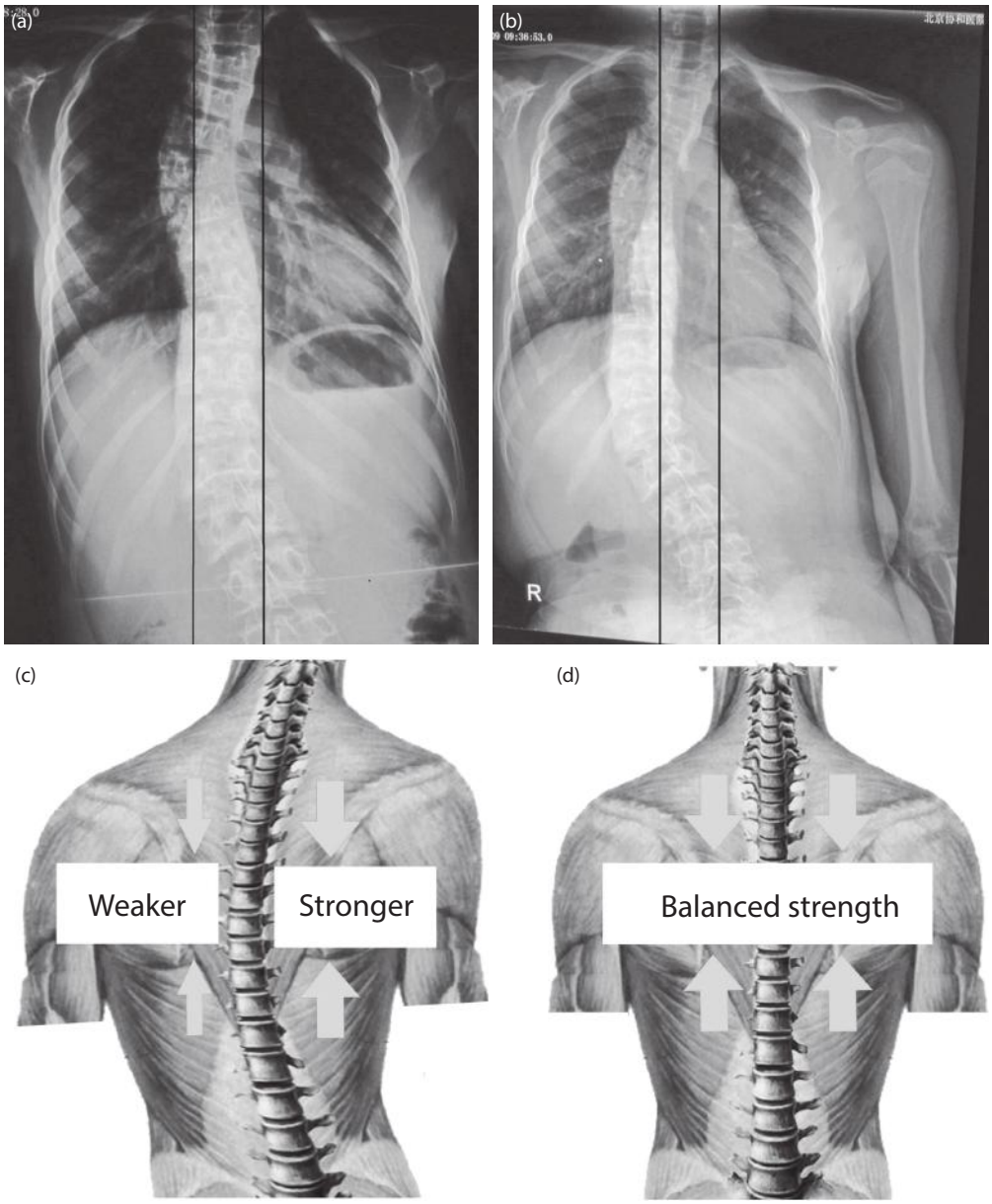

FIGURE 41.8 Severe scoliosis treatment result and its mechanism. (a) is the spinal cored curved due to the stronger muscle strength on the right side and weaker on the left (c); after treatment, the spinal cored curved is much corrected to straighter (b) due to the muscle strength back to normal (d).

Spine Vertebral Disorders are Caused by Imbalanced Skeletal Muscle Strength

The spine consists of the vertebral bodies, vertebrae and muscles, and the position of the spine is maintained by the muscle strength and the vertebral bodies. Imbalance in muscle bioelectricity results in symptoms normally clinically diagnosed as muscle strain, stiff neck, lower back pain, and similar afflictions. If the imbalanced muscle strength lasts for a long period, the position of vertebral bodies will change and lead to diseases, such as a bulging spinal disc, herniated disc, intervertebral canal stenosis, spinal vertebrate degeneration, and so on. After BERT treatment, in 871 cases of spinal vertebral disorders, all of which caused pain, 798 cases were effectively treated and pains completely vanished, with an efficacy of 94% (798/871).

A 10 year old girl suffered from severe scoliosis with no available effective treatment technology. After 20 treatments with BERT, most symptoms disappeared, and 6 months later, the spinal curvature was significantly corrected (Figure 41.8).

Edema is Caused by an Imbalanced Distribution of Molecular Charges

In TCM, it is described that "Qi is the driving force for fluid." Qi is bioelectricity and bioelectricity circulation can force water to move. We have found that body structure and bioelectricity are two components that are interdependent. We proposed that swelling is induced by the changed distribution of molecular charges outside cells (Figure 41.9). BERT can force the bioelectricity to circulate and cause blood to travel faster, thus, water can flow away from the swollen area and swelling disappears.

There have been 238 treated cases of edema-related illnesses, including injuries with swelling, knee edema, gout, and post-traumatic edema. Among the 238 cases, 228 cases were treated effectively, and the effectiveness rate reached 96%. All cases showed significant reduction of both pain and swelling. A female patient had suffered from knee edema in her left knee for approximately five years. After 10 daily treatments, the edema completely disappeared. The circumference of the knee was 57 cm before the treatment and reduced to 48 cm after treatment.

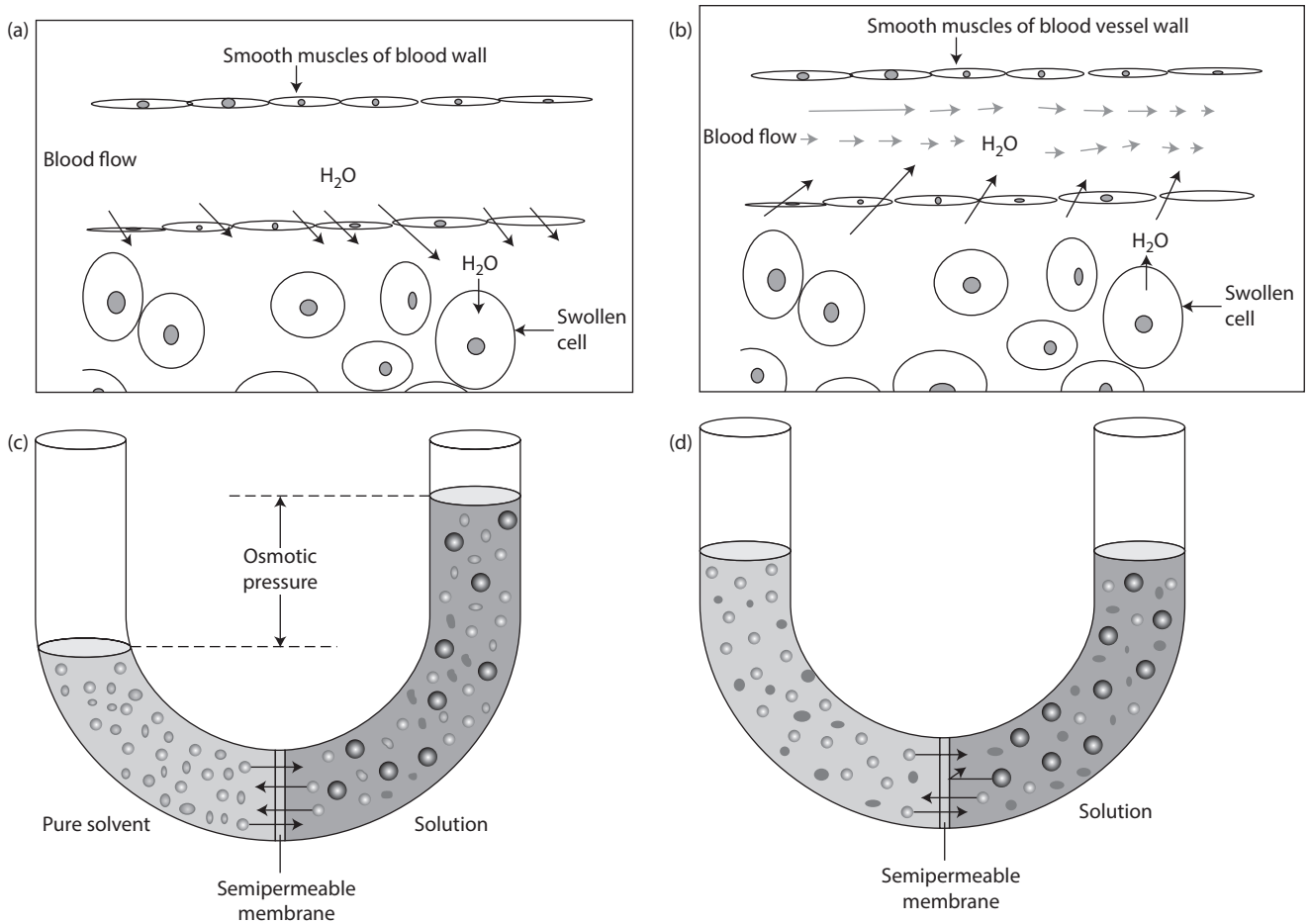

FIGURE 41.9 Edema treatment mechanism. (a,c) A high concentration of molecular charges outside blood vessels causes water from blood flow out and causes swollen; while lower concentrations of molecular charges outside blood vessel, water would flow into the blood and induce tissue dehydration (b,d).

DISCUSSION AND CONCLUSION

The BECS May be the Target of All Energy Therapies, and BERT is the Technology Based on the BECS

Although energy therapies have been used for centuries and are still widely used in clinics, except for BERT, they cannot cure various diseases that respond to Western medicines. This is largely due to the lack of a clear treatment target. The discovery of a bioelectricity circulatory system (BECS) now promises to correct this disparity.

As described before, in all medical technologies, either Western or TCM, structure is the only target for diagnosis and treatment. With the discovery of the BECS, BERT is the technology targeting the BECS considering all levels of bioelectricity. Now it has been clearly demonstrated that the BECS is the essence of life.[4] The suggestion is made that any technology, including drugs, surgery, and energy therapies, should be re-evaluated bearing the importance of the BECS in mind as well as possible harm to this vital system.

The BECS is the Essence of Symptoms and Functions, and Symptoms and Functions are Isolated Systems from Biological Structures

As indicated previously (Figure 41.1), medicine should be classified into two categories (Table 41.1). One is biological medicine (Western medicine and TCM) and the other is bioelectrical medicine (life medicine and TCM). Because bioelectricity depends on biological structure, an abnormal BECS will often progress to structure changed diseases that are recognized by Western medicine at molecular, cellular, and organ levels. On the other hand, structure changes can also alter BECS changes at molecular levels, cellular levels, organ levels, and holistic levels. Only those structure changed diseases that have affected local holistic bioelectricity can produce symptoms.

Why Can BERT Cure a Wider Disease Spectrum Including Symptoms and Functional Diseases?

All medical technologies consider the body as the main object of treatment, and there are no strict boundaries among them. Studies show that molecular charge changes can lead to water distribution disorders and metabolic diseases.[1,12] Cellular potential alteration and organ electricity changes will lead to organ functional disorders. Symptoms are related to blockage of holistic bioelectricity flow and faulty communication with environmental energies.[1–4]

BERT is designed to treat the BECS at molecular levels by balancing the distribution of molecular charges, restoring cellular potentials by forcing the movement of small molecules, organ levels, and holistic levels by forcing the bioelectricity circulation.[31] It is proven that those diseases are related to bioelectrically active tissues. Normally, bioelectricity active tissues cover the nerve system, muscle system including skeletal muscles, smooth muscles and heart muscles, gland system, and blood system.[11] However, when some tissues like bone have excess water, BERT can reduce the swelling. That is why BERT can cure both fevers and cold extremities, as well as multiple symptoms like pain, swelling, fever, and so on.

Why Can BERT Cure All Kinds of Inflammation, Including Bacterial and Aseptic Inflammation?

In modern medicine, inflammations are classified into bacterial inflammation and aseptic inflammation. However, by definition, all inflammation is accompanied by swelling (*tumor*) as well as pain (*dolor*). The other components are heat (*calor)* and redness (*rubor*). Often the swelling causes the pain and when it is controlled, the inflammation and other symptoms disappear (seen in Figure 41.9). This suggests that some infectious and noninfectious diseases can be cured faster and more easily with BERT than with standard therapies.

Why is BERT Effective on Many Smooth Muscle Cell-Related Diseases Like Cardiovascular Disease, Stroke, Hemorrhoids, Varicosity, Kidney Stones, Gallbladder, Bladder Problems?

The location of smooth muscle cells has been thoroughly studied and it has been demonstrated that their contraction is related to smooth muscle cell action potentials.[11] This ability is termed smooth muscle cell elasticity. When this elasticity is decreased, the walls of heart and brain blood vessels soften and collapse, resulting in diminished blood flow. In the rectum, blood vessel walls expand due to the heavy weight of blood and form haemorrhoids. Varicosities in the leg may result for the same reason. For smooth muscle cell-related diseases, the best way to correct the problem is by administering the correct frequency and strength of BERT to restore normal bioelectricity. This is the reason why BERT is effective in these diseases.

Why is BERT Effective on Skeletal Muscle Cell-Related Diseases Like Paralysis, Muscular Atrophy and Spinal Vertebral Diseases?

Skeletal muscles are the source of body strength. Skeletal muscles are connected to bones and their contractions, which are controlled by nerves,[11] are what cause bones to move. When contractility between different muscle groups becomes imbalanced, it will lead to varied problems depending on location. In the lower extremities, there is difficulty in standing or walking properly, and similar functional difficulties occur in the arms, hands, and fingers. Those muscle contraction imbalances are often seen in patients suffering from stroke, other paralytic disorders and epilepsy. When muscles lose their action potentials, they will have no contractions and no strength. For spinal vertebral muscles, a disturbance in balance will force vertebral bodies to curve

towards the side of the weakest muscles resulting in different symptoms depending on the resultant change in their position (Figure 41.9). BERT can restore the muscle potentials and thus restore muscle strength. Symptoms disappear and regular function resumes as vertebral bodies are restored to their normal positions (Figure 41.9). Surgery cannot restore muscle strength and should not be considered until after a trial of at least 10 BERT treatments has been evaluated.

Why Can BERT Cure Pains Including Those due to Cancer?

Many diseases can cause pain during their course, and this is often a serious problem for cancer patients. Before the discovery of the BECS, pains were considered a manifestation of biological structure changes. As a result, drugs, surgery, and even energy therapies based on biological structure are often not effective or have undesirable side effects. However, when pain is viewed from the perspective of holistic bioelectricity changes, BERT can easily restore holistic bioelectricity flow and pain can be rapidly eliminated.[1,12]

Why is BERT Very Effective Both for Fever and Cold Extremities?

Fever is a symptom or sign that can occur in many different diseases and treatment varies depending on its cause. Since cold extremities are not considered to be a significant health problem there is no standard treatment. The BECS paradigm proposes that holistic bioelectricity circulates inside the body and helps to regulate body temperature by emitting heat. When circulating in a higher strength, it produces an elevation of normal body temperature, or fever. On the other hand, when circulating at a lower strength, the reverse happens and can lead to cold extremities. Prior to BERT, fever has never been treated by energy therapies, and cold extremities have never been cured. With BERT, most fevers can be controlled with one treatment, although it may take 10 or more treatments for cancer patients. For cold extremities, five to 10 treatments usually produce very good results.

Comparison between BERT and Acupuncture

Acupuncture is a technology using metal needles that are inserted into the body at specific points based on meridian channel location theory. Some believe that, since metal is the best conductive material, acupuncture might work by its effects on body electricity.[1,2] BERT is based on channel bioelectricity theory and therefore it might be viewed as an advanced form of acupuncture that does not require a needle as a vector. The vector here is the SHECON BRE, as the bioelectricity is a circulatory system. As a result, BERT can easily resonate the bioelectricity (more channels at one time) deeper inside the body and produce much faster and longer-lasting effectiveness (Table 41.6).

TABLE 41.6
Comparison between BERT and Acupuncture

	BERT	Acupuncture
Vectors	SHECON	Needles (best metal ones)
Theory basis	Channel bioelectricity in bioelectricity medicine	Channels theory of TCM
Pathology	Bioelectricity changes at different levels lead to different diseases in bioelectricity medicine and channel is the holistic bioelectricity.	Blocked channels lead to pains in TCM
Clinical objectives	BECS back to normal	Channel open
Application	Diseases related to bioelectricity active tissues including nerve system, muscle system, all glands, and blood system. And all diseases involving swelling.	Pains mainly and some chronic diseases
Effectiveness	Fast and high efficiency	Some fast and some slow

Comparison between BERT and Other Energy Therapies

Healthcare providers, researchers, and patients have wondered about the difference between BERT and other energy therapies. Actually, it is this question that initiated our research. To answer this question, we have researched on the direct targets of all energy technologies. As described above, the BECS is a nonstructure system in the body that differs from the biological system, and the BECS is the life essence.[1,2,3,4] Therefore, any energy therapies should consider the existence of the BECS, otherwise they may be harmful to the BECS, which is the essence of life. It is important to recognize that live cells only respond to a frequency lower than 500 Hz. The major differences between BERT and other energy therapies are listed in Table 41.7. A major difference is that BERT is designed to treat the BECS while others are designed to treat biological structures. BERT protects the BECS, while other energy therapies that stimulate structure may disrupt it. More detailed information can be found in Table 41.7.

BECS Monitoring Technology, the New Check-up Technology of the Future

Pulse diagnosis is one of the most useful TCM technologies. Practitioners use their own bioelectricity to detect the bioelectric information of a patient simply by placing their fingers on the patient's wrist pulse to diagnose the cause of their illness.[1] According to the BECS theory, different organs generate different bioelectric patterns, which can partly flow

TABLE 41.7
Comparison between BERT and Other Energy Therapies

Parameters	BERT	Energy Therapies
Direct targets	BECS	Body biological structure
Research foundation	Bioelectricity medicine	Unclear
Mechanism	To resonate the body's own bioelectricity frequencies, strength, and waves, balance molecular level, restore the cellular potentials, fast the organ and holistic level and its conversion with environmental energies	Stimulation
Frequency	25–150 Hz	2 Hz–50 kHz
Control	Adjustable	Non-adjustable
Application of electronic pads	Pads placed opposite the disease location	Mainly on pain areas, some with needles, some not
Effectiveness	Within 1–5 times, fast and long-lasting	Alternative medicine

to the body surface where these differences and their origins can be detected.[1]

FUTURE STUDIES AND WHY THE BECS MAY BE THE BRIDGE TO UNITE WESTERN MEDICINE AND TRADITIONAL CHINESE MEDICINE

The discovery of the BECS has established the fundamentals required for humans to understand our bodies. The biological structure system is the hardware; the nonstructure system is the software, the BECS. The BECS is the essence of life; if bioelectricity disappears, life terminates. The BECS is the other significant fundamental understanding of TCM. Bioelectricity changes cause symptoms and illnesses. TCM theory, including "Yin and Yang," channels, and similar phenomena, represent the earliest recognition of the existence of the BECS and describe the BECS using different terminology. Western medicine has also begun to study some manifestations related to the BECS, including psychology, praxeology, and similar fields. However, Western medicine lacks an understanding of the essence of the BECS.

Medical research related to the BECS will be a fruitful area to pursue. Bioelectrical medicine is much more than complementary or alternative medicine and may be the future of medicine as it eliminates many of the limitations of current therapies. The soon to be released book *Mechanism of Medicine*[32] (in China) contains numerous illustrations demonstrating that bioelectricity changes first to produce a state of diminished health that then progresses to structure diseases. On the contrary, structure changes also can lead to bioelectricity changes, which is why some structure diseases produce symptoms while others do not.

The BECS is invisible but it exists inside our body and represents the nature of life. Although Western medicine became aware of bioelectricity three centuries ago, it did not recognize or appreciate its relationship to life, health, and disease. Therefore, little research was devoted to this and few technologies were developed for clinical applications. ECG is widely used to detect body surface bioelectricity. However, bioelectricity circulates throughout the body and ECG must have carried information from all organs, which is why TCM can monitor all body organ information by pulse diagnosis. In TCM, the BECS had been thoroughly studied but termed as Yin, Yang, channels, five elements, and so on. With the discovery of the BECS, Western medicine and TCM can be united in one system that looks at the whole body working together in an integrated fashion, rather than selected organs that require multiple technologies.[1,2,3,4,12] The BECS represents a much more holistic approach, since it recognizes that the whole is more than the sum of its parts.

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42 The Role of the Pineal Gland in Bioelectromagnetic Medicine

*Leonard A. Wisneski**

CONTENTS

FUNDAMENTAL RESEARCH: INTRODUCTION

The pineal gland is arguably both the most misunderstood and underrated endocrine gland in the human body. Until 40 years ago, almost nothing was known about the pineal; it was considered unimportant and physiologically useless. Yet, René Descartes stated that the pineal is the "seat of the soul," and Eastern religions have described the pineal as the mysterious "third eye," the seat of wisdom, or the source of inner light. Although these beliefs were based on some rudimentary knowledge of the pineal as being photosensitive, the alignment of the pineal with spirituality has, more likely than not, been a deterrent to serious scientific research, relegating the pineal to the realm of the unknowable (see Zrenner[1] for a history of the pineal gland).

Complicating matters further, Descartes's expression linking the pineal and the soul generally is misunderstood. The philosopher, who is undoubtedly even better known for his exclamation, "cogito ergo sum" (I think, therefore I am/exist), believed that the ability to think is irrefutable evidence that the mind exists. His dualistic philosophical system divides the universe into mutually exclusive but interacting elements of spirit/mind or God and matter. Descartes's "seat of the soul" expression stems from his belief that the pineal is the interface between the spiritual and the material worlds.

It is my contention that the pineal is the master gland and the major energy transducer (and physiological regulator) between the energy surrounding us and our internal physiology.

OVERVIEW OF THE PINEAL GLAND

Only in the last 30 to 40 years has an accurate understanding of the functions of the pineal begun to emerge. Most of this understanding has stemmed from the isolation of melatonin (*N*-acetyl-5-methoxytryptamine), the major pineal hormone.[2] The pineal has the ability to transform neural input into endocrine output. It is the tiny but mighty gland that is our liaison to the world around us. It converts light, temperature, and magnetic environmental information into neuroendocrine signals that can change the course of the body's functioning, often via its primary hormone, melatonin. Numerous studies now have shown the pineal to be the regulator and orchestrator of many neuroendocrine- and neuroimmune-modulating functions in the body.

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The pineal's most widely known function is its ability to use external light to generate an entrainment of the body to daily (circadian) and seasonal (circannual) rhythms of the sleep–wake cycle. The word *circadian* comes from two Latin words: *circa*, meaning around, and *dies*, meaning day. In addition to sleep–wake cycles, circadian rhythms are found in the body's metabolism, hormone levels, blood pressure, and core temperature, to name a few. The pineal and its major hormone melatonin are capable of activating and regulating major body systems, including the stress and immune systems (see Bubenik et al.[3] for a review of clinical utilizations of melatonin). In the following pages, I cover the structure and functions of the pineal, demonstrating its role as the body's primary neuroendocrine regulator and systems integrator.

PHYSIOLOGICAL CHARACTERISTICS OF THE PINEAL GLAND

In humans, the pineal gland lies above the superior colliculi and below the splenium of the corpus callosum at the posterodorsal aspect of the third ventricle. Embryologically, it arises from the ependyma (the membrane that lines the ventricles of the brain) of the third ventricle. In some lower vertebrates, the pineal arises from the median of the dorsal wall of the thalamus. It weighs 50 to 150 milligrams in humans, and is seven millimeters in length and five millimeters in width—about the size of a pencil eraser. Its name derives from the Latin word *pinea*, or pinecone, because of its cone-shaped appearance. Millions of years ago, vertebrates literally had a third eye on the top of their head, and today some invertebrates, such as lampreys, still possess a third eye. The pineal gland in both vertebrates and invertebrates has retained its photosensitive qualities.

The pineal gland undergoes a gradual process of calcification throughout life. Calcification actually begins in childhood. By early adulthood, it can be seen on a radiograph in about 53% of the population and is evident in approximately 80% of elderly individuals. Recent work comparing the degree of calcification, as measured by computed tomography, to urinary melatonin excretion shows an association between lower levels of melatonin and calcification.[4] Degree of calcification has also been correlated to daytime tiredness and sleep disturbance.[5] There is one remarkable study, published by the *British Medical Journal* over 15 years ago, that indicates a correlation between pineal calcification in humans and a poor sense of direction.[6] This report is intriguing when compared with studies on homing pigeons, whose pineal gland is paramount to survival, indicated by a brain weight of 10% (compared with 1% for humans). When homing pigeons have extensive calcification, they too lose their sense of direction. Perhaps, researchers should begin to study the correlation between pineal calcification and senility.

Unlike other structures of the central nervous system (CNS), the pineal gland lacks a blood–brain barrier, permitting direct reception of exogenous substances and endogenous hormones or neurotransmitters via the peripheral circulation. In addition, the pineal gland's major hormone, melatonin, is highly lipophilic, which means that it easily passes out of the pineal via cell membranes, including the epithelial cells in the blood vessels, the lymph vessels, the serous cavities, and the cavities of the heart. Consequently, melatonin is found not only in the blood but also in an assortment of fluids, including the saliva, cerebral spinal fluid (CSF), male seminal fluid, amniotic fluid, and the fluid in the anterior chamber of the eye.[7,8] The lack of a blood–brain barrier and the lipophilic quality of melatonin places the pineal gland in the optimal position for its responsibilities as the primary endocrine transducer and regulator of hormonal signals (i.e., as the master gland).

NEURAL PATHWAY FROM THE ENVIRONMENT TO THE PINEAL—THE RETINOHYPOTHALAMIC–PINEAL SYSTEM

In 1960, Ariëns Kappers identified postganglionic sympathetic neurons as the main source of pineal innervation.[9] In addition, a neural pathway has been established from the eye to the pineal gland. The pathway begins at the ganglion cells of the retina, which have axons that make up the retinohypothalamic tract. Electrical signals from the retinohypothalamic tract reach the suprachiasmatic nucleus (SCN), located in the hypothalamus. The SCN is our biological clock, which will be described in more detail later in this chapter. From the hypothalamus, long descending axons of hypothalamic neurons synapse on autonomic neurons of the intermediolateral cell column in the upper thoracic spinal cord. The signals continue via the paraventricular nuclei to the spinal cord, where preganglionic axons exit the spinal cord to terminate on neurons in the superior cervical ganglia. Postganglionic neurons from the superior cervical ganglia travel back up and terminate in the pineal gland. Unlike many invertebrates whose pineal glands are connected to the roof of the brain, in mammals these postganglionic neurons replace any direct nerve connection to the brain.

In the early 1960s, Richard Wurtman, his mentor Julius Axelrod, and coworkers determined that, in periods of darkness, the postganglionic (sympathetic) fibers from the superior cervical ganglia release norepinephrine (the major hormonal input) into the synaptic cleft, activating the retinohypothalamic–pineal system.[10–12] The pineal contains both neuroglial cells and pinealocytes. The pinealocytes are the all-important receptor cells within the pineal. Pinealocytes secrete various peptides and neurotransmitters (see next section) in addition to melatonin (the major hormonal output). When norepinephrine stimulates β-adrenergic receptor sites at night, melatonin is synthesized and secreted from the pinealocytes. The melatonin is quickly released into the CSF and venous circulation, probably by passive diffusion.[7,13]

SECRETIONS OF THE PINEAL

Neuropeptides in the Pineal

The pineal contains receptor sites for various neuropeptides, including those for norepinephrine (α- and β-adrenergic), serotonin, dopamine, glutamate, benzodiazepines,

γ-aminobutyric acid (GABA), acetylcholine, and nicotine.[14] As just mentioned, norepinephrine is the primary pineal neurotransmitter. Melatonin not only fits into its own receptor, but also into the benzodiazepine receptor.[15]

A group of researchers from Buenos Aires first showed that there are benzodiazepine receptors in the bovine pineal, and then a few years later they located them in the human pineal.[16,17] Both benzodiazepines and melatonin reduce anxiety, alleviate depression, and aid insomnia. Melatonin, however, has fewer side effects.[18,19] Recall that diazepam can suppress melatonin-binding sites, an action reversed by exogenous melatonin, and that peripheral benzodiazepine receptors can reverse the antidepressant action of melatonin.[19,20] In addition to the pineal, benzodiazepine receptors are present on platelets and monocytes, which implicates melatonin in the modulation of the cardiovascular and immune system—more on melatonin and the immune system will follow.[21,22] Clearly, a portrait emerges of a reciprocal and interactive relationship between these two molecules.

Hormones in the Pineal

The list of hormones found in the pineal is quite extensive (see Table 42.1 for a partial list). The pineal influences the secretion of these hormones, potentially resulting in significant functional and physiological changes. It is possible that some of the hormones are synthesized in the pineal and others arrive there via the circulation, but their presence still appears to have an impact on system function. For the most part, the pineal has an inhibitory impact on hormones and body function (e.g., it can reduce adrenal or gonadal weight), but there are some notable exceptions (e.g., it generally enhances the immune system). The extensive number of hormones found in the pineal, alone, is indicative of the broad influence of the pineal gland.[23,24]

TABLE 42.1
Partial List of Hormones Found in the Pineal

Melatonin
Serotonin
N-acetyl-serotonin (NAS)
Cortisol
Corticotropin-releasing hormone (CRH)
Aldosterone
Insulin
Thyrotropin-releasing hormone (TRH)
Growth hormone (GH)
Gonadotropin-releasing hormone (GnRH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)
Prolactin
Adrenocorticotropic hormone (ACTH)
Oxytocin
Somatostatin
Antidiuretic hormone
Prostaglandins
Melanocyte-stimulating hormone (MSH)

MELATONIN—THE MAJOR PINEAL HORMONE

Melatonin is the hormone that regulates our circadian, or sleep–wake, cycle. In 1958, melatonin was first isolated by Aaron Lerner, an American dermatologist, and coworkers.[2] Lerner isolated the melatonin, which was known to lighten skin melanocytes of amphibians and fish, from 250,000 bovine pineal glands.[25] Curiously, melatonin is also found in plants, particularly of the rice family, and some researchers claim that it can enter the blood and bind to melatonin receptor sites when ingested.[26,27] However, in a personal communication, Richard Wurtman at Massachusetts Institute of Technology (MIT) said, "At present, there is no evidence that any food, eaten in any quantity, significantly elevates plasma melatonin levels." In so many words, conclusive evidence simply has not been established. It is, however, an intriguing line of research, which in my opinion, warrants further study.

Endogenous circadian rhythms of not only melatonin, but also of core body temperature and cortisol, average 24.18 hours in both young and elderly humans.[28] Daytime administration of small doses of melatonin increases fatigue, decreases oral temperature, and impairs vigilance tasks.[29–31] An 80 mg dose of melatonin can raise normal nighttime concentrations by 350 to 10,000 times.[32]

As any new parent might guess, infants under three months of age secrete very little melatonin. Fortunately, this trend soon changes as humans reach peak concentration levels in the first to third years of life.[33] As mentioned, melatonin production progressively declines throughout life, showing considerable depletion with age: 250 pg/mL at ages one to three; 120 pg/mL at ages eight to 15; and declining gradually to 20 pg/mL by age 50 to 70.[34]

Melatonin Phase-Response Curve and Suppression by Light

Normally, melatonin follows a reliable bell-shaped pattern of peaking at night and returning to lower levels by morning. This phase-response curve may vary significantly even among healthy individuals (up to 30 ng per eight hour interval), but it maintains a fairly consistent pattern for any particular person, allowing for the gradual and steady changes that correlate to shifts in season.[35] Light does not actually cause the response curve (the SCN does), but rather entrains or alters it.

A "reset" of the phase-response curve or a "phase shift" occurs when an environmental factor (e.g., travel) or an exogenous substance (e.g., β-adrenergic blocking agents or melatonin) changes the time of melatonin secretion. A *delayed response* or phase shift takes place when the secretion of melatonin shifts to a later time, which could occur from exposure to bright light at night or β-adrenergic blocking agents. An *advanced response* or phase shift occurs when there is exposure to bright light in the latter part of the night

or very early morning hours. This results in a phase shift that causes melatonin to secrete earlier in the night.

Virtually all investigations into the function of melatonin utilized the experimental setup of determining whether a phase shift has occurred. Hundreds of studies that have been performed on plants, insects, and mammals, including humans, confirm the fact that exposure to bright light at night causes a phase delay, and exposure to bright light in the very early morning hours results in a phase advance.[36–38] The optimal time of melatonin administration to shift the cycle to an earlier time of day is between eight hours before and four hours after the increase in endogenous plasma melatonin production. The optimal time of melatonin administration to shift the cycle to a later time of day is between eight and 16 hours after the increase in endogenous plasma melatonin production.[39] This information is crucial to the effective clinical administration of melatonin and to achieving experimental results that are not needlessly spurious. In humans, gender does not appear in any way to affect light-induced melatonin suppression.[40] Table 42.2 shows the illumination levels associated with commonly encountered environmental situations.

As long ago as the early 1960s, researchers recognized that the enzyme hydroxyindole O-methyl transferase (HIOMT) (the last catalyst in melatonin production) is suppressed when animals are exposed to continuous light.[12] However, in a landmark experiment in 1980, Alfred Lewy and colleagues discovered, contrary to previous trials, that light does suppress human melatonin levels. The salient variable was that it took an intensity of light higher than ordinary room light to achieve the suppression.[41] By the end of that decade, the dose-dependent relationship between light intensity and the associated degree of melatonin suppression had been established. The suppression levels at intensities of 3000, 1000, 500, 350, and 200 lux were 71%, 67%, 44%, 38%, and 16%, respectively.[42] The different light intensities produced discrete suppression of melatonin within one hour of light exposure at midnight, regardless of the intensity. A light intensity of 1000 lux is sufficient to suppress melatonin to near daytime levels.[42] However, light intensity of 200 lux does not produce statistically significant melatonin suppression when compared with control samples.[43] Interestingly, Charles Czeisler, at Harvard Medicine School, has now shown that the pineal is most susceptible to the influence of light when core body temperature is lowest, that is, around 4 a.m. to 5 a.m.[44]

TABLE 42.2
Illumination Levels Associated with Environmental Situations

Event	Illumination Level (Lux)
Noontime, summer solstice, 35° N latitude	113,284
Noontime, winter solstice, 35° N latitude	58,895
Most extreme black storm cloud conditions	7000–11,000
Twilight begins	8200
Full moon	0.37 (max)
Typical school classroom (general lighting)	400–700
General office lighting (typing)	500–750

Source: Hughes PC et al. *Pineal Res.* 1987;5:1–67.

Clockworks—the Suprachiasmatic Nucleus

The SCN is our biological clock and it, not light, ultimately is the location of the on–off switch for melatonin synthesis.[45,46] However, light both entrains and suppresses the levels of melatonin via the SCN. The SCN is located in the hypothalamus and receives environmental input via the retinohypothalamic tract. A measurement of melatonin is the most effective way to track a change in the circadian rhythm of the SCN. The SCN is fundamental to each of three major components of the circadian system: entrainment pathways, pacemakers, and output pathways to effector systems.[47] It modulates our neuroendocrine systems according to the current light pattern by regulating the secretion of melatonin and other hormones of the pineal. Clearly, the biological clock is indispensable to the basic functioning of the human body. But how is light information conveyed from the environment to this tiny SCN nucleus? What do the clock parts look like? And what resets the clock when the days start getting longer in the spring and shorter in the fall and winter?

We know that light somehow travels to the SCN via retinal projections in the retinohypothalamic tract that arise from discrete retinal ganglion cells.[47,48] The portion of retinohypothalamic tract that carries the transduced light impulse to the SCN also ends at the anterior hypothalamus.[49] The SCN and melatonin production are closely related to immune performance.

The SCN is a paired structure with two subdivisions: a ventral core, which is located above the optic chiasm and receives transduced photic input, and a dorsal shell, which surrounds the core and receives input from nonvisual sources. Research has shown that the core and shell differ in their functioning in several respects.[50] Efferent fibers project from both the core and the shell to similar areas on the other side of the SCN, and messages that travel via efferent projections to the periphery vary, depending on whether they originated from the core or the shell.[50,51] Similarly, afferent neuronal messages going to the SCN contain functionally discrete messages that differ, depending upon whether they are being sent to the core or the shell. It may be that the projections from the SCN to the posterior hypothalamus mediate the arousal function of the circadian timing system.[52]

Local connections as well as afferent and efferent patterns offer insights into the pacemaker functions of the SCN. Circadian rhythm is determined by light via neural inputs and other information that flows through and out of the SCN. The rhythmic beating of these tiny nuclei is the timepiece of our lives. The physiological setup gives rise to strong speculation that the rhythm is the result of individual SCN neurons that are coupled (either between the core and shell or between the nuclei on each side, or both) to produce the circadian message.[51] In fact, there is evidence to support the theory that the SCN is functionally organized into two left- and right-side

oscillatory components that cycle in antiphase, with efferent projections to brain regions outside of the SCN that maintain the rhythm.[53]

Keep in mind a portrait of a timekeeper whose task it is to harmonize not only our daily cadence but our lifetime rhythms as well. Then, mentally step back and try to hold the image of this internal timekeeper in harmonic resonance with the physical earth as well as with seen and unseen energy. Thus the pineal gland, in conjunction with the SCN, serves as a transducer of circadian rhythmicity.

Clock Components

Single-Cell Oscillators

What are the clock components? A fascinating experiment demonstrated that nuclei from the SCN placed in a petri dish continued an electrical firing that maintained a 24 hour circadian rhythm.[54,55] The neurons in the petri dishes did not synchronize to one another, however, which meant that they fired off independently, without any oscillating pattern.[55] The SCN is composed of many of these autonomous single-cell oscillators, which when coordinated or synchronized generate a circadian output that affects our body rhythms, as we know them.[56]

In this section, we will look at some of the factors that produce synchronization among the autonomous circadian oscillators and how the synchronization influences the body rhythms (see Ishida et al.,[57] Jin et al.,[58] and Miller[59] for a review). Interesting research shows that circadian oscillators reside in peripheral tissues as well as in the SCN of the pineal, but the SCN also controls the rhythm of the peripheral oscillators.[56–61] As a result of this synchronization, the body maintains circadian rhythms for not only the sleep–wake cycle but for temperature, blood pressure, immune-cell count, and hormones that impact entire physiological systems, such as cortisol (stress) and prolactin (immune and reproduction).

Gene-Driven Feedback Loops

How do the opposing oscillations within the clock, for instance, for day and night rhythms, stay in sync? The entrainment of the SCN is triggered by a complex process (involving genes and proteins encoded to regulate numerous physiological processes) and then calibrated and reset by contact with light.[62,63] Circadian oscillator genes have transcriptional and translational autoregulated feedback loops with both negative and positive elements.[64–66] Various components of the negative feedback loop were first and more easily identified, but recently progress has been made in identifying the components of positive feedback loops, which are the core elements to circadian rhythmicity.

To understand the functions of a gene, researchers find genetic mutations of the wild-type or normal genes (which also provide an opportunity to clone the gene). They then insert or breed this mutation into test subjects (e.g., mice, fruit flies). How the mutation changes normal performance (e.g., causes phase advances, phase delays, or arrhythmic patterns) provides information regarding its inherent functioning. The research on clock genes began with two proteins from fruit flies (*Drosophila*) and one from a bread mold (*Neurospora*). The genes from the fruit flies are period (*per*) and timeless (*tim*), and the clock gene discovered from the bread mold is called *frequency* (*frq*).[67,68] The two fruit-fly genes were eventually located in the mouse.[69–71] Two proteins involved in restarting the SCN clock genes, Clock and BMAL1, also have been located in both the fruit fly and mouse.[72–74] The clock gene is an activator of the circadian system.

Joseph Takahashi and colleagues at Northwestern University were the first to identify the circadian clock gene in humans, which is expressed particularly in the SCN and cerebellum.[75] It appears that the clock gene in humans (as in mice) is required to maintain a rhythmicity in individual SCN neurons, but that a separate (but still unknown) mechanism within the SCN is synchronizing all of these neurons.[76] Think about it: your biological clock just keeps going—tick, tick, tick. These genes and proteins may well be the power source to the incessant, rhythmic ticking.

Ocular Phototransduction: Research on Individuals Who Are Blind

Photoreceptors receive the information to reset and adjust our biological clocks via the entrainment of light. We digress a moment before a discussion of photoreceptors to examine research performed on blind people, which gives important insight into ocular phototransduction. The majority of individuals who are blind have either an unusual circadian rhythm or a free-running rhythm (approximately 50% of those examined), but they show no impairment in the synthesis of melatonin. Free-running rhythms are characterized by a consistent delay in the circadian rhythm of about 60 to 70 minutes a day. Therefore, these people spend about half a month with their melatonin level telling them to sleep during the day and the other half of the month in a normal sleep–wake cycle.[9,77]

In 1995, Charles Czeisler and several of his colleagues at Harvard performed some very interesting research on 11 blind subjects who had no conscious perception of light.[78] They used the classic experiment of exposing the subject and controls to bright light at night to assess whether the normally higher nighttime melatonin levels would decrease. In three of the 11 blind subjects exposed to light, the melatonin levels decreased at essentially the same percentage as it did for the sighted controls. Curiously, it was only these three subjects who had reported no prior sleeping difficulties, while the remaining eight subjects reported a history of insomnia. These results strongly suggest that there is some photic function retained in the subjects whose melatonin is suppressed by light, despite the presence of damage that has eliminated the pupillary reflex and any perception of light. The researchers reasoned that the photoreceptive system that mediates melatonin expression must be distinctly different from the photoreceptive system that governs light perception "either quantitatively (i.e., in requiring only a few conventional receptors) or qualitatively (i.e., in using a novel

phototransductive system with a distinct subgroup of retinal ganglion cells)."

Studies on the ocular photoreceptive system in blind people appropriately led to the therapeutic use of melatonin to entrain their circadian rhythms. Research now shows that melatonin, given at a dose of 10 mg per day, can appropriately phase-advance the circadian cycle for blind people, alleviating the burden of insomnia.[39] It also appears that the dose of melatonin can be reduced to 5 mg once the individual is entrained to a nighttime sleep cycle. Research to determine whether the dose could be further lowered is warranted in light of the work by Zhdanova et al., who demonstrated that a dose of 0.3 mg was optimal in those individuals whose levels are subnormal.[79] Furthermore, researchers encourage a comprehensive evaluation of the circadian system before bilateral enucleation (i.e., removal of eyes damaged from disease or injury) is performed.[78]

How is the Clock Set? Capturing and Sending Light to the SCN

As we have indicated, light has something to do with how our biological clock adjusts itself, that is, how it makes the necessary corrections as days lengthen or shorten with seasonal changes. So, naturally, scientists want to locate the photoreceptors that pass this information from the environment to the SCN. The obvious place to look would be the light-sensitive rods and cones in the retina that provide us with our visual information. However, research on people who are blind gives us cause to question the role of rods and cones as primary phototransducers. Corroborating this supposition is a study that found that cone degeneration in aged mice did not render them incapable of circadian phase shifts and that their responses to light were similar to that of controls.[80] Following this study, two experiments established that mutant mice, lacking both rods and cones, still exhibited melatonin suppression when exposed to light.[81,82] This finding conclusively demonstrates that something other than rods and cones are conveying the light information; in other words, they are not the sought-after photoreceptors. Research on humans is similar and shows that there is a unique short-wavelength-sensitive photopigment involved in light-induced melatonin suppression, providing the first direct evidence of a nonrod, noncone photoreceptive system in humans.[83] So if not rods and cones, what might these photoreceptors be?

One possibility is cryptochrome, the vitamin B-based, light-absorbing protein pigment in the eye and SCN, which is sensitive to blue light.[84] It is found both in the retinal ganglion and the inner retina.[85] Cryptochrome was discovered in plants and identified as the protein that allows plants to bend toward light. Other possible photoreceptors are the nonrod, noncone vitamin A-based opsin photopigments, such as melanopsin.[86] The retinal distribution of melanopsin cells bears a striking resemblance to the retinal cells known to connect to the SCN in rodents. The inner retina seems to be the only mammalian site at which melanopsin is expressed, suggesting a role in nonvisual photoreceptive tasks.[87] So, in the end, melanopsin and cryptochrome are viable, but unconfirmed, photoreceptor candidates of the mammalian clock.

There are those working on finding the receptors who are convinced that multiple photoreceptors will be identified, which is a feasible conclusion given the complex interactions of the clock components.[88] It also is known that nonmammalian vertebrates possess multiple photoreceptors.[89] There are, however, others who have done work showing that a single photopigment may be responsible for photoentrainment, suggesting that it may involve a novel opsin.[90] Scientists know that the photoreceptors for melatonin synthesis have a spectral sensitivity (i.e., the range most sensitive to stimulating melatonin release) between 400 and 650 nm. This helps to limit the choices but, unfortunately, a definitive mammalian photoreceptor has not yet been established.

The SCN and melatonin are integral to lifelong personal patterns, potentially in a harmonic resonance with the environment around us.

CHRONOBIOLOGY

Chronobiology involves the science of our biological clock (i.e., the SCN) as it is expressed in our physiological rhythm. However, chronobiology also concerns the science of how our biological clocks are disrupted by or determine the daily rhythms of a particular illness and even the time of optimal medication administration. Franz Halberg, who some called the father of chronobiology, initiated the study of body rhythms in the late 1950s and continued to provide valuable research to the field until his passing in 2013.[91,92] Halberg ascertained literally dozens of circadian patterns present in humans and other species, including thyroid function in Peking ducks; rhythms of susceptibility to an insecticide (pyrethrum) in cockroaches and houseflies; and the peak times of the day that symptoms of asthma, schizophrenia, and narcolepsy are expressed in humans.[93–98]

In the intervening years, we have learned much about body rhythms and how they relate to particular diseases. These findings interface with our knowledge of the pineal and circadian hormonal secretions. For instance, the morning surge in sympathetic activity (e.g., increased epinephrine and norepinephrine secretion, higher blood pressure and heart rate levels) and increase in cortisol levels correlate to cardiovascular disease, including ischemia, myocardial infarction, stroke, and sudden death.[99–103] The fact is that humans tend to have a heart attack in the morning—generally between about 6 a.m. and noon—when the sympathetic system is fully active and our stress hormone system is at its peak.

Similarly, the progression of disease and the intensity of side effects for patients with colorectal cancer are enormously influenced by the time of day that chemotherapeutic drugs are administered and their correlation to concurrent radiation therapy.[104–108] Research stemming from a laboratory in Villejuif, France, has actually shown that lack of a distinct circadian rest–activity rhythm in cancer patients is a novel independent prognostic factor for survival.[109,110] The researchers encourage chronotherapeutic adjustments as

part of these patients' overall cancer treatment, that is protocols designed to adjust their circadian rhythms more in line with usual patterns and with normal levels of melatonin expression.

From a broader perspective, chronobiology is expressed in the patterns of both human and animal nervous, stress, immune, and reproductive systems. We have discrete daily, yearly, and lifetime biochemical patterns and rhythms. In the following section, we will begin to consider how the articulation of our internal hormonal energy is reflected in and reflective of energetic variations that surround us.

ELECTROMAGNETIC ENERGY AND THE PINEAL: PROPOSED ELECTROMAGNETIC RECEPTOR—A LINK TO EASTERN ENERGY CONCEPTS

Light can be described as the visible portion of the electromagnetic spectrum. We have already explained how light can modify our internal clocks, causing phase advances or delays. Is it possible that other portions of the electromagnetic spectrum can also entrain our biological clocks? An increasingly large body of research seems to support this hypothesis (see Wilson et al.[111] for a review of earlier studies). Russel Reiter and his colleagues, for example, have performed numerous experiments showing that the nonvisible portion of the electromagnetic spectrum decreases melatonin levels, just as visible light does. Reiter has shown that nighttime exposure of animals and humans to pulsed static and very low-frequency magnetic fields reduces melatonin production and plasma levels in a manner very akin to nighttime exposure to light, although it is not known whether the mechanism of action is the same.[8,112–115]

Reiter's research is significant because of the ongoing, and often heated, debate as to whether these low-frequency magnetic fields are detrimental to our health. Studies on humans show that nighttime residential exposure to 60 Hz lowers urinary melatonin levels, particularly in winter and especially in women taking various medications, including calcium-channel blockers and beta blockers as well as psychotropic medications.[116] A study performed at the Lawrence Berkeley National Laboratory and then replicated by the U.S. Environmental Protection Agency established that 60 Hz reduced the ability of both melatonin and of tamoxifen to effectively inhibit human breast cancer cells *in vitro*.[117,118] Although I have yet to see comparable *in vivo* experiments, I find this research disconcerting, particularly when juxtaposed with the research on women who work night shifts and have increased rates of breast cancer.[119,120] While the researchers from the night shift studies speculate that the cause may be increased release of estrogen induced by decreased melatonin, there is also the possibility that the increased incidence of breast cancer is simply related to the role that melatonin plays as an effective free radical scavenger.[115] Furthermore, it is plausible that similar amounts of melatonin are synthesized but that tissue that is exposed to larger amounts of free radicals from the electromagnetic exposure may be using the circulating melatonin at augmented rates.[121]

Duration of exposure to electromagnetic fields may be a key variable. While it is known that electromagnetic exposure in the 50 to 60 Hz range can suppress melatonin levels, there may be a set, but unknown, length of time before the suppression occurs.[122,123] Most of the experiments (that we have found) showing a correlation between exposure to electromagnetic fields and reduced melatonin levels indicate an effect only when they are carried out for weeks and not days.[124–126] However, contrary to this trend, researchers at the National Institutes of Health exposed pinealocytes from rodents to low-frequency electromagnetic fields and found an average melatonin suppression of 46% after only 12 h.[123]

In the mid-1990s, Ewa Lindstrom and her colleagues at Umea University in Sweden did a series of experiments on magnetic fields and lymphocytes. In one experiment, she found that cells (called *Jurkat cells*) from a leukemia cell line, subjected to low-frequency magnetic fields, responded in a manner similar to what would occur if the cells had been exposed to antibodies.[127–129] Lindstrom continues to perform research in support of these findings.[130] She suggests that her original findings may buttress the speculative, but provocative, findings of Liboff and colleagues, who are also doing research on electromagnetic fields and cell membranes.

Liboff claims to have shown that certain resonance frequencies, applied by pulsed magnetic fields, exist for several biologically important ions, including calcium (which is required for proper nerve function, among other things). Liboff calls this phenomenon ion cyclotron resonance. The resonance frequency is effective only if the magnetic field is within the earth's amplitude range.[131–133] The pulsed magnetic field induces the ion to revolve in a circular path, at right angles to the earth's magnetic field, as if it were being accelerated in a cyclotron. This research is profoundly controversial because it indicates that electromagnetic energy can cause changes in the membrane gradient. The notion that a calcium ion could pass through a cell's membrane without the interaction of some ligand goes against all that is understood about ion channels. However, it is current knowledge that all known receptors interact with their endogenous ligands through mechanisms that include electromagnetic properties. Ion cyclotron resonance may enhance the interactions between ligands and receptors, including the movement of important ions across cell membranes. We found one researcher who purports to have disproved both Lindstrom and Liboff's findings.[134] Liboff's research may not be well-known and, therefore, few scientists would be trying to replicate it or to determine why Coulton and Barker was unable to replicate it.

CONCLUDING THOUGHTS

Let us quickly review the information presented in this chapter. The pineal is the central component to an amazing tract of electromagnetic information, which is dependent on light impingement. Special phototransducing receptors convert light information to electrical signals, which then travel through our biological clock or circadian pacemaker (i.e., the SCN) to set and adjust our inner rhythms. The electrical

signals continue their journey, checking in with the hypothalamus, in case there is any input there, traveling down the brainstem, and finally traversing to the pineal. The power of the pineal is in its ability to then interpret and decipher the already decoded environmental input and disseminate it, via a neuroendocrine response, to all of the body systems. The pineal affects endocrine, autonomic, hypothalamic, and immune responses. The pineal is our all-purpose, comprehensive regulatory gland. It is primarily inhibitory but plays the crucial role of facilitating the translation of environmental messages (i.e., energy) into neuroendocrine signals that can be dispersed throughout the body. Ergo, scientifically, I would call the pineal our master gland.

It is my contention that our inner rhythms, which are influenced by environmental light, electricity, and magnetism, are a reflection of, or complement to, the sun-center geophysical signatures of our physical universe. The pineal gland senses magnetic alterations in the environment. The oscillating neurons of the SCN entrain the endocrine and nervous systems according to the cues received by the external environment. This occurs daily, but it also occurs in longer pacemaker rhythms, called *ultradian cycles*, such as puberty or menopause for women. Consequently, there is circadian and ultradian rhythmicity to each of our internal body systems. Ultimately, this interaction allows for something like a harmonic resonance between our internal rhythm (both circadian and ultradian) and the subtle energies, which are also called *spiritual energy* or referred to as *Qi* in the Chinese system of medicine. This harmonic resonance is perpetually present, but it is more accessible to our personal experience when we entrain our body and mind to a subtler energy frequency. It is why music can be so calming to our souls—it restores the endocrine symphony when we are distressed or stressed. The musical harmonics are entrained by the SCN and modulated by the pineal.

The pineal is the cornerstone of the biochemical interface with our environment *and* with the subtle energy that both supports and transcends our sense perceptions and sustains our body as much as any nourishment we consume. While the pineal is the energy transducer that sends hormonal and electrical messages throughout the body, the chakras, as described in Eastern religious and medical systems, are the energy transducers for subtle energy. Chakras, speculatively, are energetic portals that permit a subtler, but profoundly sustaining, energy to enter the body. Chakras, speculatively, open and connect into the autonomic nervous system (ANS), interacting richly with the endocrine system.

The seventh chakra (as described in Ayurveda or Eastern Indian medicine), which is located at the crown of the head, is in physiological terms associated with the pineal and the CNS. The seventh chakra would theoretically connect, via the CNS, to the autonomic nervous system and then to interact richly with the endocrine system. This construct allows for a systemic coherence of our internal and external environments.

Our understanding of time is based on scientific constructs that bundle up traversing energy in a linear fashion, yet mystics through the ages have made statements to the effect that "all things are one." If we have the courage to alter our belief systems a bit, we can begin to see that all things are part of a tapestry—the body, the mind, the spirit. So perhaps the pineal, as Descartes declared, is indeed the "seat of the soul," because it may well be the interface between our body and our soul—that is, the corridor by which we can experience our spirituality.

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43 Ion Cyclotron Resonance Applications in Medicine

*Abraham R. Liboff**

CONTENTS

INTRODUCTION

The notion that ion cyclotron resonance (ICR) plays a role in living things was formally introduced by the author[1] at a NATO meeting in Erice in 1985. This hypothesis followed a decade of fruitless attempts at trying to understand the experimental results independently obtained in laboratories headed up by Adey[2] and Blackman,[3] both groups showing that calcium ion transport in the central nervous system is perturbed by weak, low-frequency electromagnetic fields.

At the time, the radical nature of this ICR concept could not be overstated. Indeed, as a direct result, the author lost funding support, was denied access to better journals, and was even mocked at meetings. Nonetheless the simple truth and usefulness of this concept has long survived its severest critics.[4–6] There have since been dozens of confirmatory experiments, many with clinical and biological applications, all supporting the thesis that this effect is intrinsically interwoven into basic biological function.[7]

The impact of ICR on biological thinking is best summarized by two of its consequences. First, it implies that biological processes are intimately connected to the geomagnetic field (GMF), to the degree where we can think of this field as an *aufseher* that oversees and regulates cellular homeostasis. Second, it reveals that biological processes can be rationalized, in the sense that certain physiological responses are shown to (numerically) depend on very specific physical variables, namely the charge-to-mass ratios of key cations. In the following, we expand on this second aspect of ICR phenomena in biology and medicine.

THE ION CYCLOTRON RESONANCE SIGNATURE

Much of the difficulty surrounding the recognition of ICR as a biological effector has occurred because of reluctance to admit experimental evidence in support of this concept without any corresponding reasonable explanation. There is no question that pending a satisfactory theoretical resolution the ICR phenomenon remains strictly empirical in nature, despite more than 50 experimental corroborations in at least a half dozen laboratories.

For each of these reports one finds a unique resonance signature, namely the classical expression for the cyclotron resonance frequency Ω, expressed as a radial frequency (Equation 43.1),

$$\Omega = \frac{q}{m} B_{DC} \tag{43.1}$$

where Ω, in terms of radians/second, is equal to the product of the ion's charge to mass ratio and the magnetostatic field B_{DC}. This expresses the fact that a resonance condition exists when an ion moving in this DC field is also simultaneously exposed to a frequency *f*. In practice this is achieved by directing an AC field of frequency *f* parallel to the DC field. Probably the most important part of this relationship is its dependence on the physical uniqueness of the ion, specified by its charge-to-mass ratio. Thus the stimulation of different ionic types requires different combinations of frequency and magnetic field, in turn leading to different biological outcomes.

When expressed in terms of the more familiar frequency *f* given in Hz, the defining equation becomes

$$f = \frac{q}{2\pi m} B_{DC}. \tag{43.2}$$

Using the *q*/*m* values for a number of critically important biological ions it is possible to obtain unique conditions on frequency *f* and magnetic field B_{DC} that are associated with any given ionic type. These are shown in Table 43.1.

The usefulness of this signature is shown in Figure 43.1, where the resonance frequencies, in Hz, for a number of

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TABLE 43.1
ICR Conditions for Selected Biological Cations

ION	q/m (C/kg $\times 10^{-6}$)	f/B_{DC} (Hz/μT)
H^+	95.76	15.241
Li^+	13.90	2.212
Mg^{2+}	7.937	1.263
H_3O^+	5.066	0.807
Ca^{2+}	4.814	0.766
Zn^{2+}	2.951	0.470
K^+	2.467	0.393
arg^{2+}	1.235	0.197
glu^+	0.747	0.119

Note: The charge-to-mass ratio, q/m, is given in terms of Coulombs per kilogram.

biologically critical ions are plotted against the magnitude of the magnetic field. One immediately notices that these ICR frequencies are all very small for magnetic intensities falling within the range of the earth's magnetic field, roughly 25–65 μT. It is convenient to group these frequencies into the extremely low frequency, or ELF, range, commonly used in electrical engineering practice.

Equally important, frequencies this small can be readily involved in various endogenous activities in living things. The fact that biologically important ions can be readily connected to the earth's magnetic field does not in itself mean that the geomagnetic field ICR is actually interacting with living things. But it does imply that such interactions are quite possible. Indeed, since 1985, dozens of laboratory experiments testing this possibility have found robust biological changes do occur when applying magnetic fields as indicated in Table 43.1. A short list of such changes that have been reported is shown in Table 43.2.

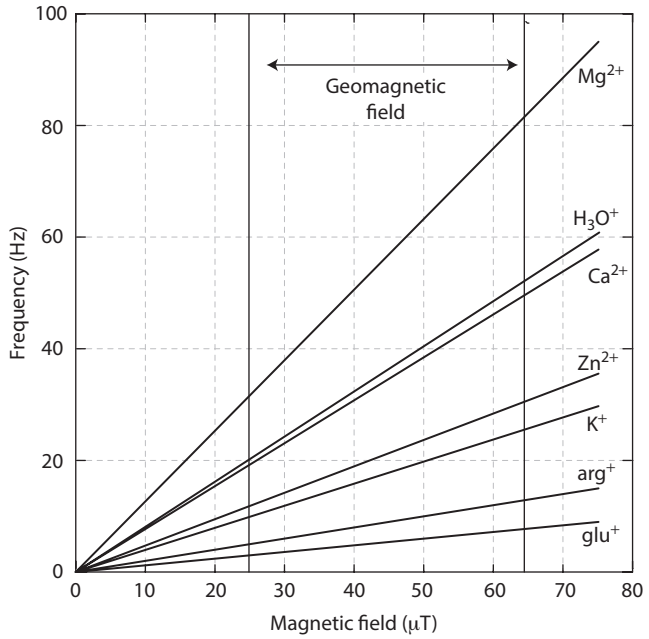

FIGURE 43.1 ICR frequencies plotted against B_{DC} for some critically important biological ions. The two vertical lines represent the approximate lower and upper bounds of the GMF at the earth's surface.

TABLE 43.2
Representative List of Reports Indicating Significant Biological Changes Due to ICR exposure

Biological Model	Year	Reference
Rat behavior	1986	Thomas et al.[8]
Diatom motility	1987	Smith et al.[9]
Production of glycosaminoglycans in cartilage	1991	Smith et al.[10]
Neuroblastoma cell metabolism	1992	Smith et al.[11]
Expression of Insulin Growth Factor II	1995	Fitzsimmons et al.[12]
Regeneration of planarians	1995	Jenrow et al.[13]
Analgesia in snails	1996	Prato et al.[14]
Rat EEG	1998	Vorobyov et al.[15]
Amino acid conductivity in aqueous solutions	1998	Zhadin et al.[16]
Protein hydrolysis	2001	Novikov et al.[17]
Growth rate in plants	2005	Galland and Pazur[18]
Stem cell differentiation	2009	Gaetani et al.[19]

Note: The wide range of model systems in which ICR effects are observed, supporting the notion that a very basic interaction is at work.

EXPLAINING THE ION CYCLOTRON RESONANCE EFFECT

Almost immediately as the ICR hypothesis was offered in support of the Adey/Blackman work, it was dismissed on theoretical grounds. Among other criticisms, the most important shortcoming was that the viscosity in biological substances is much too high to allow resonance processes. ICR is commonly observed in physics, but only in vacuums, or at the very least, in low pressure gases. As applied to living things with much larger tissue densities the situation is made even worse for charged particles resonating at very low frequencies.

Nevertheless, wide experimental support quickly made it clear that biological ions in many instances were indeed responding to the ICR signature. Possibly the most striking thing about the continued criticism was the consistent denial of observed facts, often expressed as a statement of disbelief in the experimental reports, even outright assertions[20] that they constituted an example of "Pathological Science." In retrospect these critics were lacking in the very quality that defines a scientist, namely curiosity about unexplained observations.

On the other hand, many scientists quickly accepted the abundant evidence and offered various attempts at

explanation. In his original paper, Liboff argued that the membrane ion channel was the likely interaction site. This was based on both the pivotal role played in cell metabolism by ion channels as well as the helical structure of the proteins that span the membrane in creating the channel structure. The latter fits the helical moiety of charged particles in cyclotron resonance. However there are various reasons why this picture is untenable, the most serious related to the great disparity between the ultrashort (10^{-10}s) transition times measured in channels and the resonance periods for low-frequency ICR (10^{-2} s). Additional explanations were suggested by Edmonds[21] and by Zhadin,[22] both focused on the precessional motion of bound charged particles in magnetic fields, but these failed to provide an experimental handle with which to judge these explanations.

Lednev added greatly to the theoretical basis for ICR interactions[23] by not only focusing on calcium-binding proteins but also expanding on Equation 43.1, finding a way to predict which values of the AC magnetic intensity are necessary for resonance to be observed. These proteins, best represented by calmodulin, are essential for cellular metabolism, playing a direct role in the use of calcium as a second messenger. The key factor in Lednev's Ion Parametric Resonance theory was its dependence on a previously neglected observable, namely B_{AC}/B_{DC}, the ratio of AC to DC magnetic fields. This is a very convenient experimental yardstick with which to assess data. This same variable was used in subsequent theoretical models, first by Blanchard and Blackman,[24] and later by Vincze et al.[25] In the first case a wider set of proteins, apart from calmodulin, was explored. In the second, the theoretical explanation was not related to interactive proteins, but rather to magnetic field effects on ionic drift velocity.

Notwithstanding these theoretical approaches, it was a key experiment carried out in Zhadin's laboratory[16] that helped to better understand the nature of the ICR effect. While studying the ICR effect on polar amino acids in solution a sudden sharp increase in conductivity was found at the resonance frequency (Figure 43.2). This strange effect, independently confirmed[26–28] at three other laboratories, points unequivocally to some sort of quantum-like phenomenon, the realization of which helps explain the inability of critics to find an answer by simply relying on electrical engineering.

Adding to the revelatory nature of Zhadin's experiment a second, equally profound fact emerged, namely that the ICR effect also occurs for AC magnetic fields that had previously been regarded as too small to be of any consequence. The experiment showed conclusively, and was confirmed elsewhere, that ICR magnetic fields as low as 40 nT are biologically effective, a fact that has enormous significance. To gain perspective one need only recall that in the early 1980s it was thought impossible that magnetic fields as low as 0.5 μT (5 mG) could in general influence biological systems, and more specifically, that power line magnetic fields could be tied to leukemia in children. Zhadin's experiment showed that when fields more than ten times smaller than this are deployed according to ICR conditions, they are biologically interactive.

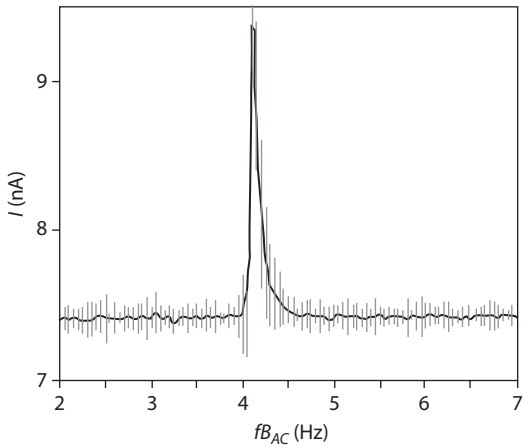

FIGURE 43.2 A sharp increase in current in the Zhadin experiment occurs at the ICR condition for glu+. For this specific run, $B_{DC} = 40$ μT and the alternating magnetic field $B_{AC} = 50$ nT. Frequency resolution is 0.05 Hz. (From Pazur A. *Biomagn Res Technol* 2004;2:8.doi:10.1186/1477-044X-2-8.)

Directly as a result of these data, Del Giudice et al. used quantum electrodynamics to propose a model[29] in which water exists in two states, one of which is enhanced by electromagnetic fields. They showed that microscopic water domains are formed which are devoid of internal ions. In this model the ions found on the surface of these domains are free, experiencing much smaller viscosities under magnetic resonance. Irrespective of whether the Del Giudice et al. model is exactly correct, present thinking regards electromagnetic effects on water structure as the likely basic reason for ICR interactions.

BIOMEDICAL APPLICATIONS

Shortly after the ICR hypothesis was proposed, a device was designed around this concept to treat the problem of nonunions in bone, and was then approved by the U.S. Food and Drug Administration (FDA). This condition, also called pseudarthrosis, is one in which a small section of skeletal tissue fails to knit, either following a fracture or because of congenital reasons. This problem can present considerable morbidity, often leading to amputation. Following the discovery[30] of piezoelectricity in bone by the Japanese surgeon/physicist team of Yasuda and Fukada, it became evident, for reasons still unclear, that small currents in the order of fractions of a milliampere, when applied to such discontinuities, are able to initiate the required bone growth process. Bassett subsequently explored the use of pulsed electromagnetic fields (PEMF) to deal with this condition,[31] obtaining a success rate of about 80%, and FDA approval, and at the same time demonstrating that this medical condition could be dealt with in a noninvasive manner. The ICR application[32] of fields tuned simultaneously to Ca^{2+} and to Mg^{2+} was fully as efficacious as PEMF, but required power levels 50 times smaller, thereby allowing for greater device portability during

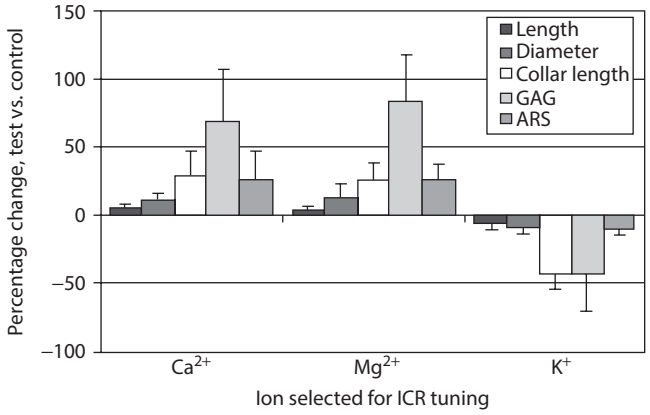

FIGURE 43.3 Experiment on ICR stimulation of explanted cartilage showing the remarkable mobilization of GAG following application of either Ca^{2+} or Mg^{2+} resonantly tuned magnetic field combinations, and the completely opposite result for K^+ stimulation. ARS: Alizarin red S-stained; GAG: glycosaminoglycans. (From Regling C et al. Paper presented at the *Orthopedic Research Society 48th Annual Meeting*, Dallas, 2002.)

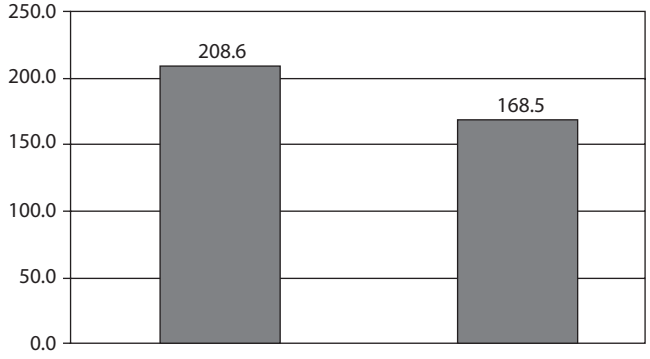

FIGURE 43.4 Relative effects of Seqex treatment on oxidative stress on 38 lymphoma patients; before treatment (on left) and after (on right). Numbers refer to the FRAS-3 scale, a measure used in the evaluation of oxidative stress levels. (From Rossi EW et al. *Electromagn Biol Med* 2007;26:277–81.)

treatment. A second FDA-approved ICR treatment is presently also used as an adjunctive procedure following spinal surgery. The ability of ICR-tuned magnetic fields to repair bone apparently derives from its profound effect (Figure 43.3) on cartilage formation,[10,33] well-known to be the key precursor in the formation of new bone. Currently, some 25 years after the introduction of these devices to help repair bone, they are still being actively prescribed.

Another medical problem, distinctly different from bone, is effectively treated using a device designed according to ICR principles. Chemotherapeutic depression, the ravaging effect commonly experienced by cancer patients following chemotherapy, is treated by means of the Seqex device. In this procedure ICR magnetic fields tuned to selected ions are simultaneously applied to the whole body. It is believed that one mechanism of action involves the reduction of reactive oxygen species, one of the debilitating consequences of chemotherapy. Figure 43.4 shows this effect[34] in a group of patients treated with Seqex. This device has also been used in treating a variety of other medical problems, with some positive results reported, in particular for multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). However there is a need for adequate replications of these studies.

Yet another aspect of the Seqex treatment is its apparent effect on pH, an observation that is somewhat consistent with laboratory results elsewhere[35] indicating that electromagnetic fields are able to alter pH in water. Some extra credibility can also be attached to this claim because part of the Seqex regimen involves first finding the group of ICR tuning frequencies that alter the specific bioimpedance of the whole body, implying, quite remarkably, that these ICR applications are specifically altering the physical properties of biological water.

One very important application of ICR in medicine with great potential surrounds its use in regenerative medicine. Calcium cyclotron resonance (at 7 Hz) has been deployed to stimulate embryonic stem cell differentiation into cardiomyocytes,[19] triggering the expression of specific cardiac lineage promoting genes. As with the protocols adopted in many other ICR studies, when the same experiments were repeated at other frequencies one failed to find the same effect, demonstrating that application of the correct ICR frequency is the critical factor. This demonstrated for the first time that differentiation of human adult cardiac stem cells is feasible, opening the possibility for eventually doing away with heart transplants as the sole recourse when dealing with heart failure. It has further been noted that ICR regenerative techniques likely extend well beyond cardiac tissue with applications in all phases of tissue engineering.

Judging by the results in a number of animal studies, it is very likely that many additional clinical applications utilizing ICR will eventually be developed. One such example is the decades long work by Prato[14] at the University of Western Ontario utilizing snails to investigate pain response. Although the model system appears very different from that which is human, the neurochemistry of the anesthesia reaction is quite similar. Based on this work it seems clear that ICR applications can greatly affect pain response, and might readily prove useful as an adjunct in current anesthesia procedures.

Another, completely different, animal study[36] conducted in Novikov's laboratory, irradiated mice infected with Ehrlich ascites carcinoma with a selected group of ICR frequencies. When compared to control animals, the exposed mice were practically free of tumors, with an outstandingly significant level of statistical confidence in the results.

Novikov has also led the way in extending the discovery by Zhadin, mentioned above, showing that ICR magnetic combinations can affect certain physical properties of amino acids. In particular, he found that ICR magnetic field combinations can affect proteins in a truly striking manner, hydrolyzing them into their constituent amino acid residues.[17] This represents something quite spectacular, considering that the thermal requirements for protein dissociation are orders of magnitude greater in energy than found in the ultraweak magnetic field combinations that were used. Directly as

a result of this discovery it was demonstrated by Bobkova et al.[37] that application of similar resonance fields to mice impacted with Alzheimer's resulted in dissolution of the β-amyloid plaque residues that many feel are the biochemical reason for Alzheimer's in humans.

There are many additional reports of this nature, showing that ICR magnetic field combinations are effective in dealing with various illnesses, with many unfortunately requiring further elaboration or human demonstration. For example, in one such case[12] it was demonstrated that ICR field combinations tuned to Ca^{2+} result in increased expression of insulin-like growth factor (IGF-II), a key factor in embryonic development. Properly extended, this work could potentially serve as a means of prophylactic prevention of Wilm's tumor in infants which is related to IGF-II expression in genetically impacted embryos.

DISCUSSION

It is ironic that so few applications of ICR to problems in the central nervous system have surfaced, considering that research in this general area was first stimulated by Adey's brain-related calcium efflux studies. Further there already is excellent experimental evidence that the nervous system makes great use of low-frequency electric signals, as in the endogenous generation of EEG signals. A number of laboratories[8,38,39] have found changes in rat behavior, with enhanced aggressiveness for one type of ionic stimulation (Mg^{2+}) and passiveness for another (Ca^{2+}), with responses to both types of stimulation significantly different from the behavior observed under ambient magnetic field conditions. Cell culture studies[11,40] also indicate that neuroblastoma cell proliferation is sensitive to ICR stimulation. For these and other reasons, one can readily anticipate there will be future approaches focused on using ICR to treat neurological problems ranging possibly from depression to neurodegeneracy.

It is not easy to explain the remarkable medicinal-like effects of ICR-tuned magnetic field combinations. Current thinking relates these effects to much older reports that there are magnetic field effects on water, a contentious area long tainted by dubious claims. However the theoretical advancement by Del Giudice,[29] following the discovery by Zhadin[16] of magnetic effects in weak amino acid solutions, makes it very likely that water is intimately involved in the ICR phenomenon. We advance the idea that the important target of ICR magnetic fields, as used therapeutically, is a biologically-specific water component that is structurally different from ordinary water. Although the physical characteristics attached to this second form of water are still in dispute,[41] one can nevertheless speculate that there is a need to maintain a sufficient fraction of this type of water in order to be in good health, and that ICR magnetic fields are effective because they act to increase its concentration in impacted areas. If there is indeed such a salubrious form of water, and its concentration is enhanced by application of appropriate ICR magnetic fields, then the curative properties of ICR stimulation are, in principle, very different from that of present medicine, in other words, more holistic than reductionist in flavor.

This observer has repeatedly championed[42] the idea that the utilization of electromagnetic principles by evolution represents a virtually unexplored aspect of biology. We should not be surprised at the ability of magnetic fields to enhance wellness, given the underlying electromagnetic nature of living things. It remains to be seen just how inclusive this feature is and to what extent it either adds to or supplants our traditional approach to medicine, presently dominated by molecular biology and biochemistry. There is general agreement that the central nervous system is designed essentially as an electrical arrangement to facilitate information transfer. The utilization of ICR in living things may merely be one additional evolutionary solution to the fundamental question of how best to regulate life, given the constraints of physical law.

DEDICATION

This work is dedicated to the memory of my good friend and colleague, Emilo Del Giudice, one of the important contributors to this area of research, who not only realized the significance of ICR in biology (early on, in Erice, in 1985!) but went on to later relate our observations to the general problem of water structure.

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Section IX

Electromagnetic Field Safety and Hazards

44 Electromagnetic Field Effects on Cells and Cancer Risks from Mobile Communication

*Igor Belyaev**

CONTENTS

COMPLEX EXPOSURE TO ELECTROMAGNETIC FIELDS

Both potentially detrimental and beneficial responses of living cells to weak, nonthermal (NT) electromagnetic fields (EMF) have been observed. So far, focus has been on biological effects of extremely low frequency (ELF, 1–300 Hz) EMF and EMF of microwave frequency range (MW, 300 MHz to 300 GHz). There is strong evidence that biological effects of EMF are dependent on many physical, physiological, and genetic parameters, which must be controlled in replication studies.[1,2] Source of funding may also affect the data.[3] While a significant body of published data shows biological effects of NT MW, studies supported by the mobile industry are less likely to report these effects.[3,4] Failure to control important parameters in replicated studies along with reduced funding for EMF research in economically developed countries may be the main cause of the lack of accepted mechanism for biological effects of NT EMF.

While funding for mechanistic EMF studies has been significantly reduced, the number of sources for ELF and MW exposure in everyday life is constantly growing. Moreover, some modern devices emit EMF in wide frequency ranges covering both ELF and MW. In particular, mobile phones not only expose the user to MW but also to ELF.[5–10] ITIS Foundation (The Foundation for Research on Information Technologies in Society) has performed detailed measurement of five mobile phones.[11] All five phones have shown the maximum B-field on the back side with extrapolated pulse heights between 35 and 75 μT. At this location, four out of the five tested phones exceeded the International Commission on Non-Ionizing Radiation Protection (ICNIRP) reference levels by several harmonics of 217 Hz. The maximum violation by a factor of two was detected at 650 Hz. The B-field on the front side of the phones tested is by a factor two to six times smaller and varies between 8 and 20 μT. The maximum DC fields were detected near the phone loudspeaker and reached levels up to 20 mT (half of the corresponding ICNIRP reference level of 40 mT).

Perentos et al. have recently measured and characterized the ELF magnetic field from several Global System for Mobile Communications (GSM) handsets using different probes which covered frequency range from static magnetic fields (0 Hz) to 2 GHz. Peak ELF fields at the front sides of five commercial GSM phones were assessed and a maximum of 22.4 μT was reported.[12] The main ELF component at 217 Hz was about 1 μT at a distance of 3 cm from the front side of the handset. The overall pulse peak was 4.2 times greater than the 217 Hz component. The 217 Hz magnetic field decreased with distance and reached 0.3 μT at approximately 5 cm from the front handset site. The overall ELF pulse peak produced by all ELF components was 4.2 times greater than the 217 Hz component.

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It has been known for a long time that weak ELF fields and NT MW produce similar effects with significant overlapping of molecular biological pathways.[13–15] In particular, stress response, molecular pathways for generation of reactive oxygen species (ROS), increased sensitivity of stem cells, and inhibition of melatonin production[16] linked effects of exposure at the cellular level with the observed increases in cancer risks.[17,18] ELF biological effects at intensities below the ICNIRP standards have been shown to manifest a complex dependence upon biological and physical variables similar to MW effects.[2,15,19–24] ELF and MW effects have been considered in the frames of the same physical models.[25–31]

In many cases similar to mobile telephony it is difficult to discriminate the effects of exposure to ELF and MW because of additional ELF fields created by the MW sources. Therefore, combined exposures should be considered in those cases for assessment of attendant biological effects including cancer risks.

ELF fields higher than 0.3 μT have consistently been shown to correlate with increased risks of childhood leukemia.[32,33] ELF has been classified by the International Agency for Research on Cancer (IARC) as a possible carcinogen, group 2B.[34] In 2011, the IARC Working Group classified MW as a possible carcinogen, 2B.[35] In this chapter, because of similarity between ELF and MW effects, only MW or combined MW/ELF effects on cells related to cancer risk assessment will be considered.

GENOTOXICITY

Genotoxic effects are the most direct cause of carcinogenicity. In 2011, the IARC Working Group evaluated genotoxicity of MW exposures considering studies with human and other cell types.[18] Diverse conclusions stemmed from these studies: in general, up to 50% of studies found some genotoxicity (positive reports) while the others did not (negative reports). This approximately similar number of positive and negative reports is in line with studies measuring other biological endpoints.[4,36,37] Both negative and positive reports collected for analysis by the IARC Working Group have had advantages and disadvantages. The typical disadvantage of negative reports is a lack of analysis of statistical power and positive controls, that is, data with known carcinogens which allow an estimate of the sensitivity of the applied methods. In other words, negative studies often did not answer the simple question: what value of eventual MW effect, 10% from control, two-fold control or whatever, is this particular study able to detect? The typical disadvantage of positive studies was a lack of specific absorption rate (SAR) measurements. However, SAR is not the uniquely important parameter describing the NT MW effects.[1] In addition, in many positive studies electric field and temperature were measured showing that the exposures were well below the thermal levels accepted by the ICNIRP as the criteria for safety standards.[38] In almost all negative studies, MW signals from generators were used which resemble only a very few real signals for mobile communication. The advantage of positive studies from the point of view of cancer risk estimation was the usage of mobile phones for exposure, which cover a wide range of real signals for mobile communication. Similar advantages and disadvantages persist for positive studies on genotoxicity published since 2011. Since 2011, the balance between negative[39,40] and positive[41–44] studies on MW genotoxicity has not changed much. This result is explained by dependence of NT MW effects on parameters which vary significantly between studies.[1] Taking into account this variability, it may be concluded that exposure to MW can induce DNA damage under specific conditions of exposure (type of cells, type of signal *etc*.[1]) while no effects are observed under others.

Blood Brain Barrier

The blood brain barrier (BBB) regulates exchanges between the blood and brain. The BBB is formed by the endothelial cells of the capillary blood vessels sealed together with tight junctions, connective tissue cells called pericytes and by the extracellular matrix of the basement membrane. Astrocytes form protrusions that wrap capillaries, and together with surrounding neurons form a complex and interdependent "neurovascular unit." An increase in the normally low BBB permeability for hydrophilic and charged molecules could potentially be detrimental. Thus, an increase in its permeability following exposure to MW enables the extravasation of substances that could induce brain tumors.

The experiments concerning effects of MW exposure on the BBB have been recently reviewed.[45,46] The review by Nittby et al. essentially concentrates on results from a Swedish group which cover, over more than 20 years repeatedly reported in more than 10 studies, the effects of NT MW on permeability of the BBB and nervous system tissue alterations (dark neurons) following exposure of Fisher 344 rats to low intensity continuous or GSM-modulated MW, at SAR down to 0.002 mW/kg.[45]

In the review by Stam, four additional studies with significant effects of MW exposure on the BBB and 24 studies without significant effects are reviewed.[46] Since that time, one new study on the effect of NT MW on the BBB has been published.[47] These authors investigated the effect of RF exposure on the permeability of the BBB in male and female Wistar albino rats. Right brain, left brain, cerebellum, and total brain were analyzed separately in the study. Rats were exposed to 0.9 and 1.8 GHz continuous-wave (CW) MW for 20 min (SAR of 4.26 mW/kg and 1.46 mW/kg, respectively). BBB integrity was analyzed using Evans-blue dye, which is known to be bound to serum albumin. In female rats, no albumin extravasation was induced by RF exposure while a significant increase in albumin was found in the brains of the RF-exposed male rats.

Only one available *in vitro* study analyzed the effect of MW in the BBB model system.[48] This model was a coculture of rat astrocytes and porcine brain capillary endothelial cells (BCEC). Samples were characterized morphologically by scanning electron microscopy and immunocytochemistry. The BBB phenotype of the BCEC was shown by the presence of zona occludens protein (ZO-1) as a marker for tight

junctions and the close contact of the cells together with the absence of intercellular clefts. Permeability measurements using C-14-sucrose indicated a physiological tightness which correlated with the morphological findings and verified the usefulness of this *in vitro* model. Samples were exposed to MW conforming to the GSM1800-standard used in mobile telephones (1.8 GHz). The permeability of the samples was monitored over four days. MW exposure significantly increased permeability for C-14-sucrose compared to unexposed samples.

While most BBB studies report negative data, other studies, including replicated studies from one Swedish group and supported by the *in vitro* model system data, suggest that MW exposure from mobile phones may affect the BBB under specific parameters of exposure.

MELATONIN, OXIDATIVE STRESS, ANTIOXIDANTS AND RADICAL SCAVENGERS

Free radicals are a group of highly reactive molecules consisting of unpaired electrons in the outer orbit. Free radicals that are derived from oxygen metabolism are known as reactive oxygen species (ROS). ROS are continuously neutralized by antioxidants present in body tissues. Whenever production of ROS exceeds the scavenging capacity of antioxidants, it leads to oxidative stress (OS). Production of radicals is a known pathway involved in development of cancer. OS caused by biological, chemical, and physical factors has been associated with increased risk of human cancer at various sites. Human cells induce and/or activate several oxidant generating enzymes that produce high concentrations of diverse free radicals and oxidants. These reactive species can damage DNA, RNA, lipids, and proteins, leading to increased mutations and altered function of enzymes and proteins, thus contributing to the multistage carcinogenesis process. Control of OS is being explored as an approach to chemoprevention of human cancers.

It is well known that endogenous ROS arise from mitochondrial oxidative metabolism and other reactions in cells.[49] The estimated average generation rate is ~10^9 ROS per cell per day,[50] which results in 10^6 oxidative DNA damage, 10^5 single-stranded breaks (SSB) and 0.1 double-stranded breaks (DSB) of DNA per cell per day.[49] It has been suggested that OS could be a key factor for MW-related cancer incidence.[51] Differences in the fundamental redox susceptibility of the cell lines employed in the analysis of MW-induced OS has been considered as a reason for the conflicting results reported due to its importance in mediating the pathological effects of NT MW.[51]

In many studies, MW exposure has been shown to cause OS-induced biological damage, manifested by a substantial increase of peroxidized lipids, oxidized proteins and fragmented/nicked DNA, see Georgiou for a review.[52] A substantial decrease has also been documented in the antioxidant defense mechanisms, that is, in the activity of crucial antioxidant enzymes and in the concentration of endogenous antioxidants. Exogenous antioxidants and inhibitors of certain ROS-producing enzymes reversed all these effects which is further evidence for the causative relation between OS and EMF exposure. MW-induced OS has also been shown in human cells *in vitro* by the increase of reactive oxygen/nitrogen species (ROS/RNS) indirectly assessed by nonspecific assays. A combined free radical pair/OS mechanism has been proposed in order to explain how EMF can cause disease in man.[52]

Substances which reduce the number of radicals such as melatonin (scavenger of •OH and other ROS), inhibit the incidence of tumors.[13] Melatonin has been shown to be protective against leukemia, breast cancer, prostate cancer, and melanoma.[53]

In their pioneering study, Lai and Singh described the effects of MW on rat brain cells as measured using a microgel electrophoresis assay.[54] These effects were significantly blocked by treatment of rats either with the spin-trap compound *N-tert*-butyl-α-phenylnitrone or with melatonin, both agents being free radical scavengers and antioxidants.[55] These data suggested that free radicals might be involved in the effects of MW.

The ability of scavengers and antioxidants to reduce NT MW effects has been tested by other research groups and this treatment inhibited the reported NT MW effects in most cases, as described below.

Oktem and colleagues exposed rats to MW from a GSM900 mobile phone with and without melatonin treatment.[56] Malondialdehyde (MDA), an index of lipid peroxidation, and urine *N*-acetyl-beta-D-glucosaminidase (NAG), a marker of renal tubular damage, were used as markers of OS-induced renal impairment. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate changes in antioxidant status. In the MW-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment inhibited these effects. The authors concluded that melatonin might exhibit a protective effect on mobile phone-induced renal impairment in rats.

Ozguner and colleagues exposed Wistar albino rats to MW from a GSM900 mobile phone with and without melatonin and analyzed histopathological changes in skin.[57] MW-induced increase in thickness of stratum corneum, atrophy of epidermis, papillomatosis, basal cell proliferation, granular cell layer (hypergranulosis) in the epidermis and capillary proliferation. Impairment in collagen tissue distribution and separation of collagen bundles in dermis were observed in exposed animals as compared to the control group. Most of these changes, except hypergranulosis, were prevented with melatonin treatment. The authors concluded that exposure to GSM900 MW caused mild skin changes and melatonin treatment could reduce these changes. In other studies of the same group, the ability of melatonin to reduce various MW-induced effects was confirmed and the inhibitory potential of the antioxidant caffeic acid phenethyl ester was reported.[58–61]

Ayata et al. analyzed the effects of 900 MHz MW with and without melatonin on fibrosis, lipid peroxidation, and

antioxidant enzymes in rat skin.[62] The levels of MDA and hydroxypyroline and the activities of SOD, GSH-Px, and CAT were studied. MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased significantly in the exposed group without melatonin and decreased significantly in the exposed group with melatonin. SOD activity was decreased significantly in the exposed group and this decrease was not prevented by the melatonin treatment. The authors assumed that the rats irradiated with MW suffer from increased fibrosis and lipid peroxidation and that melatonin can reduce the fibrosis and lipid peroxidation caused by MW.

Ilhan with coauthors investigated oxidative damage in brain tissue of rats exposed to GSM900 MW with and without pretreatment with *Ginkgo biloba* (Gb).[63] MW-induced oxidative damage measured as: (i) increase in MDA and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain SOD and GSH-Px activities, and (iii) increase in brain xanthine oxidase (XO) and adenosine deaminase activities. These MW effects were prevented by the Gb treatment. Furthermore, Gb prevented the MW-induced cellular injury in brain tissue revealed histopathologically. The authors concluded that ROS can play a role in the adverse effects of GSM900 MW and Gb prevents the MW-induced OS by affecting antioxidant enzyme activity in brain tissue.

Guney et al. examined 900 MHz mobile phone-induced OS that promotes production of ROS and investigated the role of vitamins E and C, which have antioxidant properties, on endometrial tissue against possible 900 MHz mobile phone-induced endometrial impairment in rats.[64] The animals were randomly grouped (eight each) as follows: (1) Control group (without stress and EMF, Group I), (2) sham-exposed rats (exposure device off, Group II), (3) rats exposed to 900 MHz EMF (EMF group, Group III), and (4) a 900 MHz EMF exposed + vitamin-treated group (EMF + Vit group, Group IV). A 900 MHz EMF was applied 30 min/day, for 30 days. Endometrial levels of nitric oxide (NO, an oxidant product) and MDA increased in EMF exposed rats while the combined vitamins E and C caused a significant reduction in the levels of NO and MDA. Likewise, endometrial SOD, CAT, and GSH-Px activities decreased in EMF-exposed animals while vitamins E and C caused a significant increase in the activities of these antioxidant enzymes. In the EMF group, histopathological changes in endometrium, diffuse and severe apoptosis were present in the endometrial surface epithelial and glandular cells and the stromal cells. Diffuse eosinophilic leucocyte and lymphocyte infiltration were observed in the endometrial stroma whereas the combination of vitamins E and C caused a significant decrease in these effects of EMF. It is concluded that oxidative endometrial damage plays an important role in the 900 MHz mobile phone-induced endometrial impairment and the modulation of OS with vitamins E and C reduces the 900 MHz mobile phone-induced endometrial damage both at biochemical and histological levels.

Koylu et al. studied the effects of MW on brain lipid peroxidation in rats, and the possible protective effects of melatonin on brain degeneration induced by MW.[65] The levels of lipid peroxidation in the brain cortex and hippocampus increased in the MW group compared with the control group, although the levels in the hippocampus were decreased by combined administration of MW and melatonin. Brain cortex lipid peroxidation levels were unaffected by melatonin treatment. The authors concluded that melatonin may prevent MW-induced OS in the hippocampus by strengthening the antioxidant defense system.

Balci et al. exposed albino Wistar rats to mobile-phone-emitted radiation and analyzed oxidant/antioxidant balance in corneal and lens tissues. The results of this study suggest that mobile telephone radiation leads to OS in corneal and lens tissues and that antioxidants such as vitamin C can help to prevent these effects.[66]

Sokolovic et al. evaluated the intensity of OS in the brain of Wistar rats chronically exposed to MW from mobile phones (SAR = 0.043 – 0.135 W/kg) during 20, 40, and 60 days.[67] A significant increase in brain tissue MDA and carbonyl group concentration was found. Decreased activity of CAT and increased activity of XO remained after 40 and 60 days of MW exposure. Melatonin treatment significantly prevented the increases in MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. The authors concluded that exposure to the mobile phone MW caused oxidative damage in the brain and that treatment with melatonin significantly prevented this oxidative damage.

Gajski and Garaj-Vrhovac investigated the radioprotective effect of bee venom against DNA damage induced by 915 MHz microwave radiation (SAR of 0.6 W/kg).[68] Whole blood lymphocytes of Wistar rats were treated with 1 mg/mL bee venom four hours prior to and immediately before irradiation. Standard and formamidopyrimidine-DNA glycosylase (Fpg)-modified comet assays were used to assess basal and oxidative DNA damage produced by ROS. Bee venom decreased basal and oxidative DNA damage induced by microwave radiation. The difference between the comet assay results in the presence and in the absence of Fpg-enzyme suggested that OS is responsible for the DNA damage induced by microwave radiation. Among other possible mechanisms, the antioxidant activity of bee venom may likely account for the radioprotective effect.

Mailankot et al. exposed adult Wistar rats to EMF from a GSM (0.9/1.8 GHz) mobile phone in active mode for one hour per day for 28 days, while control rats were sham-exposed to a mobile phone without battery.[69] Sperm counts in the epidermis showed no difference between exposed and control rats, however, a statistically significant 40% reduction in the proportion of motile sperm was observed in EMF-exposed rats. In addition, increased malondialdehyde levels were observed in testis (~8%) and epididymis (~12%) of EMF-exposed rats, together with a ~10% (testis) and ~24% (epididymis) significant decrease in intracellular reduced glutathione in EMF-exposed rats. Thus, the detrimental effects of EMF exposure may be accounted for by the impact on radical metabolism.

Tomruk et al. evaluated biological effects of whole-body 1800 MHz GSM-like MW exposure on liver oxidative DNA

damage and lipid peroxidation levels in nonpregnant, pregnant New Zealand White rabbits, and in their newborns.[70] Under controlled conditions of MW exposure, MDA levels significantly increased in nonpregnant and pregnant MW-exposed as compared to nonpregnant controls. But no difference was observed in MDA levels between pregnant controls and MW-exposed pregnant rabbits. Similarly, lipid peroxidation was found to be significantly increased in nonpregnant and pregnant MW-exposed as compared to nonpregnant controls. But no difference was found between pregnant controls and MW-exposed pregnant rabbits. No significant difference was found in amounts of 8-OHdGuanine in liver tissues of controls and MW-exposed nonpregnant and pregnant rabbits. No difference in MDA levels and 8-OHdG amounts in liver was observed between newborns of pregnant MW-exposed and newborns of pregnant controls. However, a significant reduction of ferrous oxidation in xylenol orange (FOX) levels in the liver of pregnant MW-exposed newborns was observed. These results indicate that exposure to 1800 MHz GSM signals may increase markers of OS.

Esmekaya et al. analyzed effects of 1.8 GHz GSM alone and in combination with Gb (EGb 761) pretreatment in human peripheral blood lymphocytes (PBL).[71] EMF exposure significantly increased frequency of sister chromatid exchanges (SCE) and inhibited cell viability. No temperature difference was observed between sham-control and EMF-exposed cells. Thus, the observed effects may be considered as NT. EGb 761 pretreatment significantly reduced both EMF effects. The authors concluded that EGb 761 had a protective role against EMF-induced mutagenesis.

Ozgur et al. investigated oxidative damage and antioxidant enzyme status in the liver of guinea pigs exposed to mobile phone-like EMF and the potential protective effects of *N*-acetyl cysteine (NAC) and epigallocatechin-gallate (EGCG) on the oxidative damage.[72] Nine groups of guinea pigs were used to study the effects of exposure to an 1800 MHz Global System for Mobile Communications (GSM)-modulated signal (average whole body SAR of 0.38 W/kg, 10 or 20 min per day for seven days) and treatment with antioxidants. Significant increases in MDA and total NO levels and decreases in activities of SOD, myeloperoxidase and GSH-Px were observed in the liver of guinea pigs after EMF exposure. NAC treatment induced an increase in hepatic GSH-Px activities, whereas EGCG treatment alone attenuated the MDA level. The extent of oxidative damage was found to be proportional to the duration of exposure. The authors concluded that the adverse effect of EMF may be related to the duration of mobile phone use. NAC and EGCG may protect the liver tissue against the EMF-induced oxidative damage and enhance antioxidant enzyme activities.

Female rats were either exposed to a mobile phone signal (900 MHz) or exposed to the mobile phone signal and treated orally with vitamin C.[73] MDA, antioxidant potential (AOP), SOD, CAT, GSH-Px, XO, adenosine deaminase (ADA) and 5′-nucleotidase (5′-NT) were analyzed in brain tissues. MW exposure caused an inhibition in 5′-NT and CAT activities. GSH-Px activity and the MDA level were also found to be reduced in the mobile phone group but not significantly. Vitamin C caused a significant increase in the activity of GSH-Px and nonsignificant increase in the activities of 5′-NT, ADA, and CAT enzymes. The results suggest that vitamin C may play a protective role against detrimental effects of mobile phone radiation in brain tissue.

Avci et al. studied the oxidative damage in Wistar rats induced by MW (1.8 GHz, SAR 0.4 W/kg) from mobile phones and the protective effect of garlic extract used as an antioxidant against this damage.[74] MW exposure increased the advanced oxidation protein product (AOPP) of brain tissue compared with the control group ($p < 0.001$). Garlic administration significantly reduced AOPP levels in brain tissue ($p < 0.001$). The serum NO levels significantly increased after MW exposure with and without garlic. Thus, MW exposure leads to protein oxidation in brain tissue and an increase in serum NO. Garlic administration reduced protein oxidation in brain tissue and did not have any effects on serum NO levels.

Kumar et al. investigated the effect of 10 GHz MW (two hours a day for 45 days) on male albino rats' reproductive system.[75] MW exposure reduced the level of melatonin and MDA. These results are indications of deleterious effects of MW on the reproductive pattern of male rats.

To conclude, most studies consistently show that supplementation with antioxidants and radical scavengers can reduce MW effects in cells of different origin. Studies have also demonstrated that antioxidants such as melatonin, caffeic acid phenyl ester, vitamin C, and vitamin E prevent OS or apoptosis caused by MW in animal tissues. Therefore, these studies indicate that induction of radicals is one of the key events in the bioeffects of NT MW. The level of radicals should be considered as an important parameter for the NT MW effects. Based on available data, a recent IARC monograph has admitted that biological systems are complex and factors such as metabolic activity, growth phase, cell density, and antioxidant level might alter the potential effects of MW.[18]

RADICALS, REACTIVE OXYGEN SPECIES AND INTRACELLULAR SIGNALING CASCADES

As a consequence of increased levels of free radicals, various cellular and physiological processes can be affected including gene expression, release of calcium from intracellular storage sites, cell growth, and apoptosis. Human spermatozoa are known to be particularly vulnerable to OS by virtue of the abundant availability of substrates for free radical attack and the lack of cytoplasmic space to accommodate antioxidant enzymes.[51] Moreover, the induction of OS in these cells not only perturbs their capacity for fertilization but also contributes to sperm DNA damage. The latter has, in turn, been linked with poor fertility, an increased incidence of miscarriage and morbidity in the offspring, including childhood cancer.

Purified human spermatozoa were exposed to EMF at 1.8 GHz and covering a range of SAR from 0.4 W/kg to

27.5 W/kg.[51] In parallel with increasing SAR, motility and vitality were significantly reduced after EMF exposure, while the mitochondrial generation of ROS and DNA fragmentation were significantly elevated. Furthermore, highly significant relationships between SAR, the oxidative DNA damage biomarker, 8-OHdG, and DNA fragmentation after EMF exposure were observed. The authors concluded that EMF in the power density and frequency range of mobile phones enhances mitochondrial ROS generation by human spermatozoa, decreasing the motility and vitality of these cells while stimulating DNA base adduct formation and, ultimately, DNA fragmentation. The data suggest that EMF from sources such as mobile phones might be one of the key environmental factors involved in the stimulation of sperm mitochondria to produce high levels of ROS. These findings have clear implications for the safety of extensive mobile phone use by males of reproductive age, potentially affecting both their fertility and the health and wellbeing of their offspring.[51]

Agarwal et al. evaluated effects of one hour exposure to MW during talk mode of a cellular phone on ejaculated human semen.[76,77] The results showed a significant increase in ROS production in exposed samples and a decrease in sperm motility, viability, and ROS-total antioxidant capacity score in exposed samples. A plausible explanation for the ROS production is that it is due to stimulation of the spermatozoa's plasma membrane redox system by EMF.

Friedman et al. reported the findings of a study to look at the potential of mobile phones to activate intracellular signaling cascades in human cells.[78] They found that MW at the frequency of 875 MHz commonly used in mobile communication are able to activate ERK1/2 (extracellular-signal-regulated kinases 1 and 2). This effect was observed even at intensities lower than those emitted by mobile phones that are unable to cause any measurable heating effects. This study provides evidence that MW induce ERK1/2 activation downstream of the EGF (epidermal growth factor) receptor, which is in turn activated by the release of ROS. These results also indicate that MW-induced phosphorylation of ERK is mediated by EGFR and ROS, and PI3K may have a partial effect downstream of the receptor in HeLa cells. It was still unclear whether this activation occurs by a direct ROS effect on membranal enzymes or is mediated via ROS-dependent cytoplasmic proteins. The authors therefore studied whether the release of Hb-EGF in response to mobile phone irradiation can be carried out in purified plasma membranes without the presence of cytoplasmic components. To examine this, plasma membranes were purified from serum-starved HeLa cells and treated with mobile phone irradiation at 875 MHz (0.300 mW/cm^2). It was found that Hb-EGF was released from these membranes at 15 and 30 min after irradiation, and this release was significantly reduced when the membranes were preincubated with the inhibitors NAC and GM-6001. These results indicate that ROS are activating matrix metalloproteinase (MMP) at the plasma membrane, a process that does not appear to require the involvement of cytoplasmic components. This pathway is mediated by MW-induced activation of NADH oxidase which generates ROS at the plasma membrane. ROS then directly activate MMP to cleave and release Hb-EGF, which binds to EGFR and activates the ERK cascade. It is unlikely that the MW intensity of 0.005 W/cm^2 for five minutes, which induces the phosphorylation of ERK, can change the temperature, and, indeed, no change in temperature could be detected in the medium, even at higher intensities. The fact that the stress-related cascades, which are known to be activated by heat or other related stresses, were not activated in the time course of experiments also indicates that the activation of ERK is induced by NT mechanisms. In summary, it was shown that ERK are rapidly activated in response to mobile phone irradiation. This activation is mediated by ROS that are produced by NADH oxidase upon irradiation, and directly activate MMP. In turn, the activated MMP cleave and release Hb-EGF, which then binds to EGFR, activating it, thereby stimulating the ERK cascade. This study demonstrated for the first time a detailed molecular mechanism for EMF-induced mitogen-activated protein kinase (MAPK) activation. Importantly, ERK1/2 has been strongly implicated in carcinogenesis, and inhibitors of the ERK1/2 pathway have attracted considerable interest as anticancer drugs.[79]

The ERK cascade is one of the four MAPK signaling cascades that regulate transcriptional activity in response to extracellular stimuli. The MAPK pathways have been characterized in several human cell types.[15] Exposure to NT ELF as well as MW affected the expression of many cellular proteins.[15]

In some studies, no effects of MW exposure on production of ROS were observed.[80] However, it is difficult to compare studies because they were either performed at parameters other than those where effects were observed or these parameters have not been described.

Lu et al. have demonstrated that ROS play an important role in the process of apoptosis in human peripheral blood mononuclear cells (PBMC), which can be induced by exposure to 900 MHz MW at the SAR of 0.4 W/kg when the exposure lasts longer than two hours.[81] The apoptosis is induced through the mitochondrial pathway and mediated by activating ROS and caspase-3, and decreasing the mitochondrial potential. The activation of ROS is triggered by the conformation disturbance of lipids, protein, and DNA induced by the exposure to 900 MHz MW.

During the last decade, the majority of relevant *in vitro* and *in vivo* studies have shown that ROS can develop in response to cell phone radiation at specific parameters of exposure. EMF was able to disturb ROS metabolism by increasing production of ROS or by decreasing antioxidant enzyme activity. Chronic exposure to EMF decreases the activity of CAT, SOD, and GSH-Px, and thus decreases the total antioxidant capacity. However, studies designed to measure MDA levels and SOD activity have shown conflicting results which may be dependent on different parameters of exposure in these studies. To conclude, a plausible biological mechanism to account for carcinogenesis is via free radical formation inside human cells.

GENE/PROTEIN EXPRESSION IN BRAIN CELLS

An important step in the cellular mechanism of carcinogenesis is a change in gene/protein expression. Several studies have recently analyzed NT MW effects on gene/protein expression in brain cells.

Paparini et al. analyzed effects of MW (1800 MHz signal for one hour at a whole body SAR of 1.1 W/kg) on gene expression in mice.[82] Gene expression was studied in the whole brain, where the average SAR was 0.2 W/kg, by expression microarrays containing over 22,600 probe sets. Comparison of data from sham and exposed animals showed no significant difference in gene expression. However, when less stringent constraints were adopted to analyze microarray results, 75 genes were found to be modulated following exposure. Forty-two probes showed fold changes ranging from 1.5 to 2.8, whereas 33 were downregulated from 0.67- to 0.29-fold changes, but these differences in gene expression were not confirmed by the reverse transcription-polymerase chain reaction (RT-PCR). Under these specific limited conditions, no consistent indication of gene expression modulation in whole mouse brain was found associated with 1800 MHz exposure.

In two studies,[83,84] expression of genes was examined in Fisher rat brain using Affymetrix gene chips covering the whole rat genome (about 30,000 gene probes). In the first study,[84] the two hour whole body exposure to 915 MHz GSM at SAR of 0.04 W/kg led to a statistically significant increase in expression of 11 genes and decline in one gene. The change in gene expression was considered when it increased 1.5 or two-fold or declined 0.5-fold. The induced genes cover functions such as activation and chemoattraction of microglia into the infarcted tissue (fractalkine), cell cycle regulation (Rgc32 protein), enzymatic hydroxylation (quinoid dihydropteridine reductase), regulation of neurotransmitter transport and thereby BBB function (Slc6a6). The expression of Nat1 genes was changed. The Nat1 gene encodes acetyltransferases (ATs) that can acetylate the endogenous arylalkylamines tryptamine, 5-hydroxytryptamine (serotonin), and 5-methoxytryptamine, the immediate precursor of melatonin. In the second study,[83] the changes in expression of numerous genes were reported in response to six hour exposure to 1800 MHz GSM at very low SAR of 0.013 W/kg. In this study a change in gene expression was considered when the expression had risen only by 1.05-fold or declined by 0.95-fold. The genes were not named in this study.

Two studies from the same research group[85,86] have examined effects on gene expression in rat brain and rat facial nerves. Using RT-PCR the authors found statistically significant changes in expression of several important genes such as calcium ATP-ase, endothelin, neural cell adhesion molecule, and neural growth factor. The exposure setup in this study consisted of a regular mobile phone and animals were exposed by its antenna.

In nine recent reports MW-induced changes in brain protein expression were studied in mice of different age and of different strains: C57BL/6N, C57BL/6NTac, hsp70.1 deficient, Balb/c, ICR, or nonspecified.[87–95] Detection of protein expression changes was done by immunocytochemistry using both monoclonal and polyclonal antibodies. Six of the published studies came from the same Australian research group. Most of them are based on the same biological material that was separately stained in order to detect different proteins. These studies have shown that mobile phone radiation has no effect on the expression of c-fos protein in adult and in fetal mice brains, stress proteins in the fetal brain (Hsp25, Hsp32, Hsp70) and on aquaporin-4 in adult brains and on the ionized calcium-binding adaptor molecule Iba1. However, numerical and statistical analysis is missing in a number of these studies and the conclusions are based on only a brief verbal description of the immunocytochemistry staining.

Lee et al. have determined that mobile phone radiation has no effect on the expression of stress proteins (HSP90, HSP70, HSP25) or phosphorylation of stress kinases (ERK, JNK, p38MAPK) in hsp70.1 deficient mice.[93] The same research group has also examined expression of proliferating cell nuclear antigen (PCNA), glial fibrillary acidic protein (GFAP) and NeuN proteins in C57BL/6N mice and found no effects of radiation exposure. However, only visual evaluation was performed in this second study and statistical analysis was not performed.[94]

Maskey et al. have shown that 835 MHz mobile phone radiation might affect expression of calbindin (CB) and calretinin (CR) in different areas of mouse brain.[95] Similar effects were further reported by the same authors.[96] Male mice were exposed at 835 MHz and different SAR values (1.6 [E1.6 group] and 4.0 [E4 group] W/kg) and distribution of CB D28-k, CR, and GFAP immunoreactivity (IR) was analyzed in the hippocampus. Compared with the sham-exposed group, decreased CB and CR IR, loss of CB and CR immunoreactive cells and increased GFAP IR exhibiting hypertrophic cytoplasmic processes were found in both exposed groups. The E4 group showed a more prominent decrement in CB and CR IR than the E1.6 group due to downregulation of CaBP proteins and neuronal loss. GFAP IR was more prominent in the E4 group than the E1.6 group. Decrement in the CaBPs can affect the calcium-buffering capacity leading to cell death, while increased GFAP IR and changes in astrocyte morphology, may mediate brain injury due to MW exposure.

Ammari et al. exposed Sprague-Dawley rats for 45 min/day at a brain-averaged SAR = 1.5 W/kg or 15 min/day at a SAR = 6 W/kg for five days per week during an eight-week period.[97] GFAP expression was measured by the immunocytochemistry method in the prefrontal cortex, cerebellar cortex, dentate gyrus of the hippocampus, lateral globus pallidus of the striatum, and the caudate putamen. Increases in GFAP levels in the different brain areas were seen three and 10 days after exposure. The results show that subchronic exposures to a 900 MHz signal for two months could adversely affect a rat brain and induce signs of a potential gliosis.

Fragopoulou et al. investigated the effects of mobile (SAR level range of 0.17–0.37 W/kg for three hours daily for eight months) and DECT (SAR range of 0.012–0.028 W/kg) phones for eight hours per day on the proteome of the

cerebellum, hippocampus, and frontal lobe in Balb/c mice following long-term whole body irradiation.[98] Three equally divided groups of animals (six animals/group) were used; the first group was exposed to a typical mobile phone, the second group was exposed to a wireless DECT base. Proteomics analysis revealed that long-term irradiation from both EMF sources significantly ($p < 0.05$) altered the expression of 143 proteins in total (as low as 0.003 fold downregulation up to 114 fold overexpression). Several neural function related proteins (i.e., GFAP, alpha-synuclein, glia maturation factor beta (GMF), and apolipoprotein E (apoE)), heat shock proteins, and cytoskeletal proteins (i.e., neurofilaments and tropomodulin) are included in this list as well as proteins of the brain metabolism (i.e., aspartate aminotransferase, Glutamate dehydrogenase) in nearly all brain regions studied. Western blot analysis of selected proteins confirmed the proteomics data. The observed protein expression changes may be related to brain plasticity alterations, indicative of OS in the nervous system or involved in apoptosis.

Karaca et al. evaluated gene expression and genotoxic effects of MW exposure (10.715 GHz, SAR 0.725 W/kg) for six hours in three days on brain cultured cells.[99] Micronuclei rate increased 11-fold. Eleven genes involved in apoptosis were investigated using the OligoGEArray Human Apoptosis microarray. MW exposure decreased STAT3 expression seven-fold. The data indicated that cell phone exposure may damage DNA and change gene expression in brain cells.

Dasdag et al. investigated long-term (two hours per day, seven days a week for 10 months) effects of 900 MHz radiofrequency radiation (electric field 16.26–29.43 V/m) on proteins in the rat brain.[100] A statistically significant increase of protein carbonyl in the brain of rats exposed to 900 MHz radiofrequency radiation was found ($p < 0.001$).

Celikozlu et al. studied the effects of EMF from cell phones (standby mode for the whole day and 30 min per day in talking mode) on the blood and brain of rats.[101] Rats were exposed during prenatal and postnatal periods until they were 80 days old. EMF exposure increased blood glucose and serum protein levels, decreased pyramidal neuron numbers and increased ischemic neuron numbers at the cortex region of the brain. While no effects were seen on hippocampal pyramidal cell numbers, EMF increased the amount of ischemic neurons three-fold compared to the control. Thus, EMF affected some biochemical parameters, especially the cortex region of the brain.

Sharma et al. exposed Swiss albino mice to MW (10 GHz, 0.25 mW/cm^2, 0.1790 W/kg) two hours per day for 30 days.[102] After exposure, mice were tested for spatial memory performance using the Morris water maze test (MWT). Brain proteins were measured 48 h after exposure and immediately after completion of the MWT. MW-exposed animals had statistically significant higher mean latency to reach the target quadrant compared to sham-exposed. A concurrent decrease in protein levels was estimated in whole brain of the exposed mice compared to sham-exposed mice. Thus, exposure to MW decreased the learning ability of mice in parallel with a simultaneous decrease in protein levels in the brain.

In some studies, no changes in gene/protein expression were found.[103] Noteworthy, it is difficult to compare the results from negative and positive studies because they often differed in important parameters for the NT MW effects or these parameters have not been described.

In conclusion, while comprehensive proof is still missing, the emerging data show that NT MW may affect gene/protein expression in brain cells implying functions that may be related to carcinogenesis.

CELL METABOLISM, TRANSMEMBRANE SIGNAL TRANSDUCTION

In multistage carcinogenesis, membrane-related events mediated through receptor mechanisms are involved in tumor promotion that is reversible and environmentally modulated.[53] Plausible biological mechanisms by which EMF may influence carcinogenesis include epigenetic events of tumor promotion such as transmembrane signal transduction and intercellular communication.[53] Disruption of communication between transformed cells and normal cells is believed to be involved in tumor promotion. Figueiredo et al. examined the possible clastogenic properties of MW exposure (2.5 and 10.5 GHz) on human blood lymphocytes.[104] There was no significant difference in the frequency of chromosomal aberrations between cells which had or had not been treated with MW. However, cell mortality increased markedly after exposure to microwaves. The results suggested that MW may target cell membranes.

A recent review identified the plasma membrane as a subcellular target of NT MW effects.[105] The effects of NT MW on plasma membrane structures (i.e., NADH oxidase, phosphatidylserine, ornithine decarboxylase) and voltage-gated calcium channels have been described. The authors explored the disturbance in ROS metabolism caused by NT MW and delineated NADH oxidase-mediated ROS formation as playing a central role in OS due to cell phone radiation.[105]

Volkow et al. evaluated whether cell phone exposure of the human head affects brain glucose metabolism, a marker of brain activity.[106] Metabolism in the region closest to the antenna (orbitofrontal cortex and temporal pole) was significantly higher for "cell phone on" than off conditions. The increases were significantly correlated with the estimated EMF amplitudes both for absolute metabolism and normalized metabolism. Thus, 50 minute cell phone exposure was associated with increased brain glucose metabolism in the region closest to the antenna in healthy participants compared with no exposure.

Sun et al. investigated the effects of 1.8 GHz MW exposure at different intensities on EGF receptor clustering and phosphorylation in human amniotic (FL) cells.[107] Exposure to MW at SAR of 0.5, 1.0, 2.0, or 4.0 W/kg for 15 min significantly induced EGF receptor clustering and enhanced phosphorylation on the tyrosine-1173 residue in FL cells. The authors conclude that membrane receptors could be one of the main targets for MW interaction with cells.

Aldad et al. observed that mice exposed *in utero* (800–1900 MHz cellular phones with a SAR of 1.6 W/kg) were

hyperactive and had impaired memory as determined using the object recognition, light/dark box, and step-down assays.[108] Whole cell patch clamp recordings of miniature excitatory postsynaptic currents (mEPSC) revealed that these behavioral changes were due to altered neuronal developmental programming. Exposed mice had dose-responsive impaired glutamatergic synaptic transmission onto layer V pyramidal neurons of the prefrontal cortex. This neuropathology depended on dose and duration of exposure, which varied from one to 24 h per day.

In conclusion, while not universally reported, emerging data show that exposure to mobile phones at specific conditions of exposure may affect signal transduction and metabolism in cells.

APOPTOSIS, CELL CYCLE PROGRESSION, MITOTIC SPINDLE, AND NEOPLASTIC TRANSFORMATION

Defects in apoptosis signaling pathways are common in cancer cells. Apoptosis could also be an important mechanism, which removes damaged cells and thus prevents the proliferation of potential cancer cells. Usually, genotoxic agents induce apoptosis. Thus, an increased level of apoptosis is often a sign of genotoxicity. On the other hand, a decreased apoptotic level may overlook the cells with unrepaired DNA damage stipulating neoplastic transformation.

Several studies indicated that MW might induce apoptosis in human cells by nongenotoxic mechanisms by affecting membrane properties and structures such as plasma membrane annexin receptors.[105]

Caraglia et al. have evaluated the *in vivo* effect of MW in human epidermoid cancer KB cells.[109] It was found that MW induces time-dependent apoptosis (45% after three hours) that is paralleled by an about 2.5-fold decrease of the expression of rat sarcoma protein (Ras) and murine leukemia viral oncogene homolog 1 (Raf-1) and of the activity of Ras and ERK1/2. Although the expression of Akt was also reduced, its activity was unchanged likely as a consequence of the increased expression of its upstream activator PI3K. In the same experimental conditions an about 2.5-fold increase of the ubiquitination of Ras and Raf-1 was also found and the addition for 12 h of proteasome inhibitor lactacystin at 10 μM caused an accumulation of the ubiquitinated isoforms of Ras and Raf-1 and counteracted the effects of MW on Ras and Raf-1 expression suggesting an increased proteasome-dependent degradation induced by MW. The exposure of KB cells to MW induced a differential activation of stress-dependent pathway with an increase of JNK-1 activity and HSP70 and 27 expressions and with a reduction of p38 kinase activity and HSP90 expression. The overexpression of HSP90 induced by transfection of KB cells with a plasmid encoding for the factor completely antagonized the apoptosis and the inactivation of the Ras → Erk-dependent survival signal induced by MW. Conversely, the inhibition of ERK activity induced by 12 h exposure to 10 mM Mek-1 inhibitor U0126 antagonized the effects induced by HSP90 transfection on apoptosis caused by MW. These results demonstrate that MW induce apoptosis through the inactivation of the Ras → ERK survival signaling due to enhanced degradation of Ras and Raf-1 determined by decreased expression of HSP90 and the consequent increase of proteasome-dependent degradation.

Czerska et al. exposed normal human lymphocytes for five days to CW or pulsed wave (PW) 2450 MHz radiation at nonheating (37°C) and various heating levels (temperature increases of 0.5, 1.0, 1.5, and 2°C).[110] The pulsed exposures involved one microsecond pulses at pulse repetition frequencies from 100 to 1000 pulses per second at the same average SAR levels as the CW exposures. At nonheating levels, CW exposure did not affect lymphoblastoid transformation. At heating levels both conventional and CW heating enhanced transformation to the same extent and correlate with the increases in incubation temperature. PW exposure significantly enhanced transformation at nonheating levels. At heating levels PW exposure enhanced transformation to a greater extent than did conventional or CW heating. The authors concluded that PW 2450 MHz radiation acts differently on the process of lymphoblastoid transformation *in vitro* compared with CW 2450 MHz radiation at the same average SAR.

Capri et al. evaluated the NT effects of both a 900 MHz GSM signal and a 900 MHz CW field at low SAR (70–76 mW/kg) on human PBMC *in vitro*.[111] Data obtained from cells exposed to a GSM-modulated field showed a slight decrease in cell proliferation when PBMC were stimulated with the lowest mitogen concentration and a slight increase in the number of cells with altered distribution of phosphatidylserine across the membrane. Data obtained from CW-exposed cultures showed no difference with respect to sham-exposed cultures in any of the end points studied.

Many environmental signals, including ionizing and UV radiations, induce activation of the Egr-1 gene, thus affecting cell growth and apoptosis. The effect of a modulated MW field at 900 MHz, generated by a wire patch cell (WPC) antenna exposure system on Egr-1 gene expression, was studied as a function of time in SH-SY5Y human neuroblastoma cells.[112] Short-term exposures induced a transient increase in Egr-1 mRNA level paralleled with activation of the MAPK subtypes ERK1/2 and SAPK/JNK. Exposure to MW had an antiproliferative activity in SH-SY5Y cells with a significant effect observed at 24 h. MW impaired cell cycle progression, reaching a significant G2-M arrest. In addition, the appearance of the sub-G1 peak, a hallmark of apoptosis, was highlighted after a 24 h exposure, together with a significant decrease in mRNA levels of Bcl-2 and survivin genes, both interfering with signaling between G2-M arrest and apoptosis. Survivin, a member of the IAP family, inhibits apoptosis directly; its expression is frequently high in cancer cells and shows a good correlation with resistance to chemotherapy.[113] The results provide evidence that exposure to a 900 MHz-modulated MW affect both Egr-1 gene expression and cell regulatory functions, involving apoptosis inhibitors like Bcl-2 and survivin, thus providing important insights

into a potentially broad mechanism for controlling *in vitro* cell viability.

The induction of apoptosis after exposure to 900 MHz EMF (GSM signal) was investigated by assessing caspase-3 activation in exponentially growing Jurkat cells and in quiescent and proliferating human PBL.[114] The exposure was carried out at an SAR of 1.35 W/kg in a dual wire patch cell exposure system where the temperature of cell cultures was accurately controlled. After one hour exposure to the EMF, a slight but statistically significant increase in caspase-3 activity, measured six hours after exposure, was observed in Jurkat cells (32.4%) and in proliferating human PBL (22%). In contrast, no effect was detected in quiescent human PBL. Under the same experimental conditions, apoptosis was evaluated in Jurkat cells by Western blot analysis and in both cell types by flow cytometry. To evaluate late effects due to caspase-3 activity, flow cytometry was also employed to assess apoptosis and viability 24 h after EMF exposure in both cell types. No effects were observed. Since in recent years it has been reported that caspases are also involved in processes other than apoptosis, further studies are warranted to investigate the biological significance of a dose-response increase in caspase-3 activity after EMF exposure.

Oral et al. studied apoptosis in the endometrium by exposing female rats to 900 MHz GSM EMF from a mobile phone, 30 min/day, for 30 days.[115] Increased MDA levels (indicative of lipid peroxidation) and apoptosis in endometrial tissue (stromal cells) of EMF exposed rats, partly reverted by vitamin treatment, were observed. However there was no actual dosimetry in the experiments, and the calculated SAR showed a wide range of variation (250 times). The same group,[64] using the same experimental protocol, observed an increase in oxidation products (NO, MDA), a decrease in activities of antioxidant enzymes (SOD, CAT, GSH-Px), and a diffuse and severe apoptosis in the endometrial surface epithelial and glandular cells and in stromal cells.

Odaci et al. examined paraffin embedded sections of the brain of four week old rats born from female rats exposed to 900 MHz GSM, 60 min/day, from the first gestation day to the end of gestation, at calculated SAR of 2 W/Kg (whole body), and performed cell counts in the dentate gyrus.[116] A slight but significant reduction in number of granule cells in dentate gyrus of pups from exposed rats (0.99×10^6 vs. 1.2×10^6) was observed.

Dasdag et al. exposed male Wistar rats to 900 MHz GSM, two hours per day, seven days a week for 10 months, at calculated SAR of 0.17–0.58 W/Kg, and studied the brain tissues.[117] They found no difference in OS indexes between the groups, while total antioxidant capacities was higher in the experimental group than in the sham group, and the apoptosis score of brains in the exposed group was significantly lower than in sham-exposed and control groups.

Bas et al. exposed pregnant rats to 900 MHz EMF during the first to nineteenth gestation days, 60 min/day, SAR of 2 W/kg, average power density of 1 ± 0.4 mW/cm^2, from the first to the last day of the gestation period.[118] Pyramidal cell number in rat cornu ammonis (CA) was estimated in offspring. MW exposure during the prenatal period significantly reduced the total pyramidal cell number in the CA. Therefore, prenatal exposure to MW plays a critical role in the neuronal formation in the hippocampus. The same research group investigated the number of pyramidal cells in the CA of the 16 week-old female rat hippocampus following postnatal exposure to 900 MHz, one hour per day for 28 days, SAR between 0.016 (whole body) and 2 W/kg (locally in the head). Histopathological evaluations were made on sections of the CA region of the hippocampus. Results showed that postnatal EMF exposure caused a significant decrease of the pyramidal cell number in the CA.

Sonmez et al. examined paraffin embedded sections of the cerebellum of 16 week-old female rats exposed to 900 MHz EMF, one hour per day for 28 days, at calculated average SAR of 0.016 (whole body) and 2 W/Kg (head).[119] A significant reduction of Purkinje cells was observed in the cerebellum of EMF exposed rats.

Jin et al. pre-exposed human promyelocytic leukemia HL-60 cells to 900 MHz EMF at 12 μW/cm^2 power density for one hour per day for three days and then treated with a chemotherapeutic drug, doxorubicin (DOX, 0.125 mg/L).[120] Treatment with DOX alone showed a significant decrease in viability, increased apoptosis, decreased MMP, increased Ca(2+) and decreased Ca(2+)–Mg(2+)ATPase activity. No significant differences were seen between unexposed, sham-exposed control cells and those exposed to EMF alone. The data showed increased cell proliferation, decreased apoptosis, increased MMP, decreased Ca(2+) and increased Ca(2+)–Mg(2+)-ATPase activity in EMF + DOX treated cells as compared to the DOX-treated cells. These observations were similar to the data of the same group which suggested that pre-exposure of mice to 900 MHz EMF at 120 μW/cm^2 power density for one hour per day for 14 days had a protective effect in hematopoietic tissue damage induced by subsequent gamma-irradiation.[121]

Trivino Pardo et al. cultured acute T-lymphoblastoid leukemia cells (CCRF-CEM) in the presence of 900 MHz EMF, 3 V/m, generated by a transverse electromagnetic (TEM) cell at short (two hour) and long (48 hour) exposure times.[122] The results showed a statistically significant decrease in the total CCRF-CEM cell number after 48 hours of exposure. No significant effect on cellular viability was observed at shorter exposure time (two hours). Fluorescence activated cell sorting (FACS) analysis has shown a statistically significant increase in the number of cells undergoing apoptosis after MW exposure both at two and 48 hours. Long-term exposure also affected the distribution of cells through the cell cycle decreasing the number of cells in G0/G1 phase and increasing the number of cells in S-phase. Expression of genes related to DNA repair and carcinogenesis was analyzed using a MWG Human Cancer Array (MWG Biotech AG). The authors found that the important genes which act as sensors of DNA damage (ATM, RAD17, RAD50, and PRKDC) are activated early (two hours) and their expressions remained high to 48 hours. This overexpression could produce a signal cascade that causes the activation of DNA repair signaling.

Some of the genes that were defined as essential in repair of DSB (BRCA1, LIG4, XRCC2) and SSB (XPC, MSH5) were found to overexpress at both times of exposure suggesting that 900 MHz EMF induces both SSB and DSB DNA breaks. On the other hand, some of the important genes essential for DNA repair of DSB (BRCA2, XRCC3, XRCC1, and XPA) and SSB (RFC1) were found downregulated, suggesting a possible deficiency in DNA repair cellular mechanisms. A number of other genes invoked on cell cycle control, differentiation, cytoskeleton regulation angiogenesis and apoptosis were down- or overregulated. To confirm the microarray data, the expression levels of some proteins, whose mRNAs are found up- or downexpressed after 900 MHz EMF, were analyzed by Western blot analysis. The protein expression levels of most of the EMF-affected genes were confirmed by the Western blot and were highly comparable to the microarray results. Although the fold changes observed by Western blot were larger than those observed with microarrays, there was a highly significant correlation between the two sets of data. Based on obtained data, the authors suggested functional pathways affected by the 900 MHz EMF exposure.

Ballardin et al. studied mitotic spindle disturbances and activation of the apoptosis pathway in V79 Chinese hamster cells upon 15 min exposure to continuous NT 2.45 GHz microwaves, 5 mW/cm^2 and 10 mW/cm^2 power density.[123] After MW exposure, the proportion of aberrant spindles and of apoptotic cells was significantly increased, while the mitotic index decreased in comparison to the untreated V79 cells. Additionally, V79 cells were also treated in a thermostatic bath mimicking the same temperature increase recorded during microwave emission. The effect of temperature on the correct assembly of mitotic spindles was negligible up to 41°C, while apoptosis was induced only when the medium temperature achieved 40°C, thus exceeding the maximum value registered during MW exposure. The authors concluded that short-time MW exposures cause reversible alterations of the mitotic spindle representing a proapoptotic signal in V79 cells.

Liu et al. investigated whether EMF would affect glial cells and act as a tumor-promoting agent.[124] Rat astrocytes and C6 glioma cells were exposed to 1950 MHz TD-SCDMA for 12, 24, and 48 h respectively. EMF exposure had differential effects on rat astrocytes and C6 glioma cells. A 48 h exposure damaged the mitochondria and induced significant apoptosis of astrocytes. Moreover, caspase-3, a hallmark of apoptosis, was highlighted in astrocytes after 48 h EMF exposure, accompanied by a significantly increased expression of Bax and reduced level of Bcl-2. The tumorigenicity assays demonstrated that astrocytes did not form tumors in both control and exposure groups. In contrast, the unexposed and exposed C6 glioma cells show no significant differences in both biological feature and tumor formation ability. The results implied that exposure to the EMF of 1950 MHz TD-SCDMA may not promote tumor formation, but continuous exposure damaged the mitochondria of astrocytes and induced apoptosis through a caspase-3-dependent pathway with the involvement of bax and Bcl-2.

Diversity in relation to micronuclei and specific chromosome aberrations (acentric fragments and dicentric chromosomes), found by Garaj-Vrhovac et al., indicates the aneugenic potential of microwave radiation.[125] Aneuploidy is often associated with tumors.[126] Aneuploidy may be caused by either genotoxic agents affecting DNA or agents which affect cell division and the mitotic spindle apparatus, resulting in the loss or gain of whole chromosomes. Effects of NT MW on the mitotic spindle and, related to this phenomenon, aneuploidy have also been found by other groups.

Fucic et al. used the micronucleus assay in combination with a new mathematical approach to separate clastogenic from aneugenic activity of three well-known mutagens (vinyl chloride monomer, x-rays and microwaves) on the genome of human somatic cells.[127] The comparison of frequencies of size distribution of micronuclei in the lymphocytes of humans exposed to each of these three mutagens showed that x-rays and microwaves were preferentially clastogens while vinyl chloride monomer showed aneugenic activity as well. Microwaves also possessed some mutagenic characteristics typical of chemical mutagens.[127]

Mazor et al. investigated the effects of 72 h *in vitro* exposure of 10 human lymphocyte samples to EMF (800 MHz, CW).[128] The lymphocytes were exposed in a specially designed waveguide resonator at SAR of 2.9 and 4.1 W/kg in a temperature range of 36–37°C. The induced aneuploidy of chromosomes 1, 10, 11, and 17 was determined by interphase fluorescent in-situ hybridization (FISH) using semiautomated image analysis. Increased levels of aneuploidy were observed depending on the chromosome studied as well as on the level of exposure. In chromosomes 1 and 10, there was increased aneuploidy at the higher SAR, while for chromosomes 11 and 17, the increases were observed only for the lower SAR. Multisomy (chromosomal gains) appeared to be the primary contributor to the increased aneuploidy. The effect of temperature on the level of aneuploidy was examined over the range of 33.5–40°C for 72 h with no statistically significant difference in the level of aneuploidy compared to 37°C. These findings suggest an athermal effect of EMF radiation that causes increased levels of aneuploidy.

Recent studies have reported that NT MW can induce mitotic spindle disturbances under specific conditions of exposure.[129–131] Moreover, the most recent study indicated that the E component of EMF is more significant than the H component in these effects.[130] While some other studies have not detected MW-induced aneuploidy[132] the authors noted that this discrepancy can result from difficulties in comparing studies because of the different physical and biological parameters analyzed, for example, the biological models used, the frequency of EMF studied, the SAR, and the duration of exposure.

Yang et al. investigated the cellular neoplastic transformation in response to 916 MHz continuous MW exposure for two hours per day with power density of 10, 50, and 90 W/m^2, in which 10 W/m^2 was close to the intensity near the antenna of a mobile phone.[133] NIH/3T3 cells were adopted in these experiment due to their sensitivity to carcinogens. NIH/3T3

cells changed in morphology and proliferation after five to eight weeks exposure and formed clones in soft agar culture after another three to four weeks depending on the exposure intensity. In the animal carcinogenesis study, lumps developed on the back of SCID mice after being inoculated into exposed NIH/3T3 cells for more than four weeks. The results indicate that microwave radiation can promote neoplastic transformation of NIH/3T3 cells.

In some studies, no MW effects were seen on mitotic spindle, cell cycle progression, neoplastic transformation, and apoptosis[134] which can depend on the differences in conditions of exposure including both physical and biological variables.[1] In particular, apparently controversial effects of MW on membranes, stress response and apoptosis in human cells[135–137] might depend upon the cell type as well as the type and duration of EMF exposure.[105]

In conclusion, while not universally, many studies provide evidence that exposure to microwaves, at specific conditions of exposure including intensities lower than that at which thermal effects may occur, may affect cell regulatory functions by pathways known to be involved in cell cycle control and apoptosis.

IMMUNE RESPONSE

Over the past decade, the manipulation of genes involved in functions of various immune cell types, together with pharmacological inhibitors of such cells or their functions, has shown them to play diverse and critical roles in fostering tumorogenesis.[138] The role of the immune system in development of cancer, as well as in modification of the course of neoplastic diseases is well established.[139]

Kolomytseva et al. studied the dynamics of leukocyte number and functional activity of peripheral blood neutrophils under whole-body exposure of healthy mice to low-intensity extremely high-frequency MW (42.0 GHz, 0.15 mW/cm^2, 20 min daily) and showed that exposure significantly affected the indices of nonspecific immunity.[140] It was shown that the phagocytic activity of peripheral blood neutrophils was suppressed by about 50% in two to three hours after the single exposure. The effect persisted for one day after the exposure, and then the phagocytic activity of neutrophils returned to normal within three days. A significant modification of the leukocyte blood profile in mice exposed to MW for five days was observed after the cessation of exposure: the number of leukocytes increased by 44%, mostly due to an increase in the lymphocyte content.

The modification of indices of the humoral immune response to thymus-dependent antigen (sheep erythrocytes) after a whole-body exposure of healthy mice to low-intensity extremely high-frequency MW was reported by Lushnikov et al.[141] Male NMRI mice were exposed in the far-field zone of a horn antenna at a frequency of 42.0 GHz and flux density of 0.15 mW/cm^2 under different regimes: once for 20 min, for 20 min daily during five and 20 successive days before immunization, and for 20 min daily during five successive days after immunization throughout the development of the humoral immune response. The humoral immune response was estimated on day five after immunization by the number of antibody-forming cells of the spleen and antibody titers. Changes in cellularity of the spleen, thymus, and red bone marrow were also assessed. The humoral immunity and cellularity of lymphoid organs changed insignificantly after acute exposure and a series of five exposures before and after immunization of the animals. However, after repeated exposures for 20 days before immunization, a statistically significant reduction of thymic cellularity by 17.5% and a decrease in cellularity of the spleen by 14.5% were revealed. The results show that a single low-intensity 42 GHz MW radiation exposure does not influence the humoral immune response intensity in healthy mice but influences immunogenesis under multiple repeated exposures.

Dabrowski et al. exposed mononuclear cells isolated from peripheral blood of healthy donors to 1300 MHz pulse-modulated MW at 330 pps with a pulse width of 5 μs at a power density of 10 W/m^2 (1 mW/cm^2) and SAR = 0.18 W/kg.[142] The exposed and control cells were assessed in the microculture system for several parameters characterizing their proliferative and immunoregulatory properties. Although the irradiation decreased the spontaneous incorporation of ^{3}H-thymidine, the proliferative response of lymphocytes to phytohemagglutinin (PHA) and to Con A as well as the T-cell suppressive activity (SAT index) and the saturation of IL-2 receptors did not change. Nevertheless, the lymphocyte production of interleukin (IL)-10 increased significantly and the concentration of interferon gamma remained unchanged or slightly decreased in the culture supernatants. Concomitantly, the microwave irradiation modulated the monokine production by monocytes. The production of IL-1beta increased significantly, the concentration of its antagonist (IL-1ra) dropped by half, while the tumor necrosis factor (TNF-alpha) concentration remained unchanged. These changes of monokine proportion (IL-1beta vs. IL-1ra) resulted in a statistically significant increase in the value of the LM index, which reflects the activation of the monocyte immunogenic function. The results indicate that pulse-modulated MW represent a potential for immunotropic influence, stimulating preferentially the immunogenic and proinflammatory activity of monocytes at relatively low levels of exposure.

To study MW effects on human lymphocyte activation, Capri et al. analyzed CD25, CD95, CD28 molecules in unstimulated and stimulated CD4+ and CD8+ T cells *in vitro*.[143] PBMC from young and elderly donors were exposed or sham-exposed to MW (1800 MHz, SAR 2 W/kg) with or without mitogenic stimulation. No significant changes in the percentage of these cell subsets were found between exposed and sham-exposed lymphocytes in both young and elderly donors. Nevertheless, MW exposure induced a slight, but significant, downregulation of CD95 expression in stimulated CD4+ T lymphocytes from elderly, but not from young donors. This age-related result is noteworthy given the importance of such molecules in regulation of the immune response.

Stankiewicz et al. investigated whether cultured immune cells induced into the active phases of the cell cycle (G1, S)

and then exposed to MW (900 MHz simulated GSM signal, 27 V/m, SAR 0.024 W/kg) will also be sensitive to the radiation.[144] The microcultures of PBMC exposed to MW demonstrated significantly higher response to mitogens and higher immunogenic activity of monocytes than control cultures. The results suggest that the immune activity of responding lymphocytes and monocytes can be changed by 900 MHz microwaves.

Some studies found no immune response to NT MW exposure[145–147] resulting in the conclusion[148] that studies of MW-exposed immune cells have shown no reproducible damage or change until the cells were heated, while others[149] report immunosuppressive or immunostimulatory phenomena in animals with long-term exposure to low-level MW fields. However, a recent replication study was able to support the positive findings of immune response to MW exposure.[150] In conclusion, studies on NT MW effects suggest that EMF at specific conditions of exposure can interact with immune cellular functions and their molecular pathways.

CHROMATIN, MODULATION OF DEOXYRIBONUCLEIC ACID DAMAGE AND REPAIR

Chromatin structure is important for processes involved in modulation of DNA damage and repair. A significant body of evidence shows the effects of chromatin compactness on radiation-induced DNA damage.

Electronic microscopy revealed that chromatin appears abnormally condensed, and occasionally some fibrous structures appear in response to NT MW exposure.[151] In relation to cancer risks, chromatin condensation can affect DNA repair. The method of anomalous time dependence (AVTD) is one of the most sensitive techniques to detect changes in chromatin conformation.[24,152] Using AVTD technique, Belyaev and coworkers consistently reported that exposure to NT MW affected chromatin conformation and DNA repair in *E. coli* cells.[30,153–165] Significant effects of NT MW exposure were also observed in normal human lymphocytes and human lymphoblastoid cell line.[134,166–168] Similar effects were observed for weak ELF.[19,24] While both condensation and decondensation of chromatin were seen in the exposed cells depending upon conditions of exposure and initial state of chromatin, chromatin condensation was a general response to MW. The data suggested that the MW effects differ at various GSM frequencies and vary between donors.

In concordance with AVTD data, chromatin condensation has been observed in MW-exposed human cells by other techniques.[169–171] Condensation of chromatin is a typical response to stress such as that induced by heat shock. Therefore, the data on MW-induced chromatin effects provide consistent evidence that NT MW stress human cells.

Hansteen et al. exposed lymphocytes from two smoking and four nonsmoking donors for 53 hours *in vitro* to 1.0 W/m^2 CW radiation at 18.0 GHz or 10 W/m^2 PW at 16.5 GHz, alone or in combination with MMC.[172] DNA synthesis and repair were inhibited *in vitro* in some cultures. For the 16.5 GHz pulsed exposure, a nonsignificant trend consisting of an increase in aberration frequencies with microwave radiation was shown for the DNA synthesis and repair inhibited cultures both with and without MMC. In another study of the same group, lymphocytes from six donors were exposed to 2.3 GHz, 10 W/m^2 CW, or 2.3 GHz, 10 W/m^2 PW (200 Hz pulse frequency, 50% duty cycle).[173] DNA synthesis and repair were inhibited in one experiment. These data are in line with a study in which individual variability in chromatin response to EMF was observed in replicated experiments with lymphocytes from the same donors.[19,24,168]

Chromatin condensation has been shown to affect DNA repair foci, which are formed at the locations of radiation-induced DNA DSB. In accordance with this mechanism and similar to heat shock, microwaves from mobile phones inhibited formation of endogenous DNA repair foci in human primary fibroblasts, human lymphocytes and mesenchymal stem cells.[134,166,167,174] In contrast to GSM exposure at the frequency of 915 MHz that consistently inhibited DNA repair foci in lymphocytes from 26 persons in total,[134,166,167] GSM exposure at 905 MHz did not inhibit DNA repair focus formation thereby providing further evidence that MW effects depend on carrier frequency.[1] Similar to MW, ELF exposure was also able to inhibit DNA repair in correlation with chromatin condensation.[134]

In conclusion, the available data show that EMF exposure is able to suppress DNA repair by a mechanism which involves chromatin condensation.

HUMAN STEM CELLS AND CANCER RISK

Stem/progenitor cells have for a long time been considered as a cellular target for the origination of cancer, both solid tumors and leukemia.[138,175,176] It is believed that gliomas originate from brain stem cells.[177]

It is widely accepted that DSB and their misrepair in stem cells are critical events in the multistage origination of various leukemias and tumors, including gliomas. Inhibition of DSB repair may lead to chromosomal aberrations by either illegitimate recombination events[179] or reduced functionality of nonhomologous end-joining.[180] To repair DSB, so-called DNA repair foci are formed at DSB locations.[181] Inability to form DNA repair foci has been correlated to radiosensitivity, genomic instability and other repair defects.[182–186]

It has recently been demonstrated that GSM and universal mobile telecommunications system (UMTS) MW from mobile phones inhibit formation of DNA repair foci in human stem cells at specific frequencies.[174] No heating was induced in the samples exposed to MW. The SAR values at different locations of the exposed samples were always well below thermal effects. Therefore, the MW effects could not be attributed to heating albeit a similar response was observed after heat shock. This similarity indicates that MW exposure at specific frequencies is a stress factor. In contrast to fibroblasts, stem cells did not adapt to MW from mobile phones during chronic exposure.[174] In other words, the inhibitory effect of MW on DNA repair in stem cells was irreversible

as also reported for human lymphocytes.[166] In addition, more MW frequencies were shown to affect stem cells as compared to differentiated cells. All together, these results show that stem cells are more sensitive to MW exposure than differentiated human primary cells. DSB and their misrepair are critical molecular events resulting in chromosomal aberrations (CA), which have often been associated with origination of leukemia and tumors including gliomas.[180] Inhibition of DSB repair may lead to chromosomal aberrations by either illegitimate recombination events[179] or reduced functionality of nonhomologous end-joining.[180] Therefore, inhibitory effects of MW exposure on DSB repair in stem cells may cause origination of cancer. These findings provide a direct mechanistic link to increased cancer risk. The finding that stem cells may react to more carrier frequencies as compared to differentiated cells may indicate that stem cells are the most relevant cellular model for validation of safe mobile communication signals. Because stem cells are more active in children,[187] children should represent the most sensitive age group for EMF-increased cancer risk.

Current models for radiation carcinogenesis have paid much attention to the stochastic process of energy deposition in cells, but accumulating evidence has shown that the nature of the target cells, that is, tissue stem cells and progenitor cells, needs to be taken into consideration.[188,189] Stem cell self-renewal and progenitor differentiation is regulated by the specialized microenvironment or "niche", in which these cells reside[190] and which regulate stem cells.[191–194] The importance of stem cells for carcinogenesis challenges the definition of volume for SAR determination in safety standards. Instead of random distribution of targets for carcinogenesis, localized distribution of SAR in stem cells and niches is needed. Because of the very small size of the niches in different tissues including the brain,[195] the SAR averaging should be performed at volumes much less than the currently accepted 10 g. Decreasing the sensitive volume to the stem cell niches, with sizes down to 10 μm,[189] may likely put almost all mobile phones out of the current safety standards, even given that they are only based on thermal effects and do not consider any other parameters except for SAR. From the point of view of stem cell organization, the volume of SAR determination may be especially important for setting the safety standards for children. During brain development, most stem cells and their niches are spatially ephemeral and temporally transient as the cellular and molecular "puzzle" behind neurogenesis and morphogenesis is "assembled" and "disassembled" at a dazzling pace. In contrast, in the adult, neural stem cells and their niches are retained in relevantly restricted regions with their local developmental processes occurring for life.[190]

It now appears that most, if not all, human tissues and organs including blood, skin, and brain contain stem/progenitor cells.[178] Therefore, stem cells in different organs are subjected to EMF exposure and attendant increased cancer risks may be anticipated.

To conclude, human stem cells represent a valuable cellular model for evaluation of safe EMF signals. It should be anticipated that some part of the human population, such as children, pregnant women, and groups of hypersensitive persons, could be especially sensitive to NT MW exposure.

CANCER RISK ASSESSMENT FROM A MECHANISTIC POINT OF VIEW

At present, a new situation has arisen when a significant part of the general population is chronically exposed (much longer than previously investigated durations of exposures) to EMF from multiple sources of mobile communication.[196–198] These exposures are characterized by low intensities, varieties and complexities of signals, and long-term durations of exposure that are comparable with a lifespan.

Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful for the evaluation of health risks from NT MW of mobile communication. The role of other exposure parameters such as frequency, modulation, polarization, duration, and intermittence of exposure should be taken into account.[1]

IARC has recently classified MW as a "Possible Human Carcinogen" (Class 2B).[35] Contrary to other panels, such as ICNIRP, whose members dismiss the NT MW effects based on their "nonreproducibility" and lack of generally accepted mechanism, the most representative so far international IARC panel was balanced and included scientists who argued for the complex dependence of NT effects on a variety of biological and physical parameters, which should be taken into consideration. IARC has noted that the reproducibility of reported effects may be influenced by exposure characteristics (including SAR or power density, duration of exposure, carrier frequency, type of modulation, polarization, continuous vs. intermittent exposures, pulsed-field variables, and background electromagnetic environment), biological parameters (including cell type, growth phase, cell density, sex, and age) and environmental conditions (including culture medium, aeration, and antioxidant levels).[18] IARC also admits that some of the discrepancies between EMF replication studies could be due to differences in species.[18] Physical factors that affect interpretation of study results, such as SAR, polarization, frequency, modulation, and background EMF, were considered in the IARC monograph.[18] IARC has admitted that, regardless of the type of exposure system, for a correct interpretation of the findings and replication of the experiments in other laboratories, it is important that all pertinent electromagnetic field exposure characteristics and biological parameters be fully addressed in the experimental design, and properly described in the study reports.[18]

By its classification, IARC has justified implementation of the precautionary principle, confirmed the existence of NT effects that can cause health risks, and indicated that the current safety standards are insufficient to protect health.

So far, most laboratory and epidemiologic studies did not control important features of the NT MW effects and thus they can significantly underestimate the health risks from mobile communication. The group of Hardell was the first epidemiologic group studying separately the MW signals from cordless phones, analogue phones, and digital phones.[199–202]

This approach is valid from the mechanistic point of view. Another important mechanistic challenge in epidemiologic studies is evaluation of dose instead of SAR, performed by Cardis et al.[203] and Li et al.[204] The "dose" approach is more mechanistically correct than the "SAR" approach in view of multiple studies showing that MW effects depend on dose and duration of exposure.[1]

Nowadays, it is rather difficult to enroll unexposed control groups for epidemiologic studies because almost the whole population in economically developed countries is exposed to a wide range of MW signals from various sources such as mobile phones, base stations/masts, WLAN, WPAN, DECT wireless phones and given that the duration of exposure (at least 10 years for cancer latency period) is important for the NT MW effects. Exposure from downlink sources (base stations etc.) may contribute up to 70% of total environmental outdoor-urban exposure in European countries while exposure to DECT phones is comparable to exposure to mobile phones. [205,206]

Substantial variation in the relative ratio of downlink and uplink signals between countries[196] can at least partially account for differences in epidemiologic data because of variation in exposure of control groups to downlink signals.

Importantly, because the signals are completely replaced by other signals faster than once per 10 years, the duration comparable with the latent period, epidemiologic studies cannot provide a basement for the assessment of cancer risks from upcoming new signals.

As far as different types of MW signals (carrier frequency, modulation, polarization, far and near field, intermittence, coherence, etc.) may produce different effects, cancer risks should ideally be estimated for each MW signal separately. In other words, one type of MW signal would correspond to one chemical compound. That means, for example, that each of the 124 signals involved in GSM uplink mobile communication should be separately evaluated to fit the situation accepted for estimation of cancer risks from chemical compounds.

In view of the available mechanistic studies it is clear that epidemiologic studies, which do not evaluate dose for control and exposed groups, should be considered either as inconclusive or significantly underestimating the possible cancer risks.

CONCLUSIONS

Recent data have provided evidence for molecular pathways and cellular mechanisms which may account for increased cancer risks related to exposure to NT EMF from various sources of mobile communication including cell phones.[18,207–209]

The current safety standards are insufficient to protect the public from NT EMF effects. Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful for the evaluation of health risks from NT MW of mobile communication. New standards should be developed based on knowledge of mechanisms for NT EMF effects. The precautionary principle should be implemented while new standards are in progress. It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons, could be especially sensitive to NT EMF exposure.

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45 Mobile and Cordless Phone Use and Brain Tumor Risk

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CONTENTS

INTRODUCTION

There has been a rapid increase in the use of both mobile phones and cordless phones during the last decade. The brain is the primary target organ during the use of the handheld phone. This has given concern of an increased risk for brain tumors, although other health effects are also discussed. Worldwide, an estimate of 6.8 billion mobile phone subscriptions was reported at the end of 2013 by the International Telecommunication Union (ITU; http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2013-e.pdf).

Many users are children and adolescents, which is of special concern regarding potential health effects.

The real increase in use and exposure to electromagnetic fields from wireless phones (mobile phones and cordless phones) in most countries has occurred since the end of the 1990s. When used they emit radiofrequency electromagnetic fields (RF-EMF)[1–3] and also extremely low frequency electromagnetic fields (ELF-EMF) from the battery.[4,5]

Since the use of this technology is widespread even a small effect on health would be of concern for the general population. In order to evaluate the carcinogenic effect of RF-EMF on humans, a meeting took place during 24 to 31 May 2011 at the International Agency for Research on Cancer (IARC) at WHO in Lyon, France. The Working Group consisted of 30 scientists representing four areas: "animal cancer studies," "epidemiology," "exposure" and "mechanistic and other relevant data" (http://monographs.iarc.fr/ENG/Meetings/vol102-participants.pdf). One of the authors, LH, was part of the epidemiology group. The four expert groups prepared first a written draft prior to the IARC meeting. Further work was done in the expert groups during the meeting and a final agreement, sentence by sentence, was obtained during plenary sessions with all experts participating.

On 31 May 2011, IARC categorized RF-EMFs from mobile phones, and from other devices that emit similar nonionizing electromagnetic fields, as a Group 2B, that is, a "possible," human carcinogen.[6,7] Nine years earlier IARC had also classified ELF-EMF as a Group 2B carcinogen.[8]

The IARC decision on mobile phones was based mainly on two sets of case-control human studies on brain tumor

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risk; our studies from Sweden (the Hardell group)[9–16] and the IARC Interphone study (also preprint studies available).[17–19] Both provided complementary and supportive results on positive associations between two types of brain tumors; glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones. There was "limited" evidence in experimental animals for the carcinogenicity of RF-EMF. The Working Group also reviewed studies with endpoints relevant to mechanisms of carcinogenesis, including genotoxicity, effects on immune function, gene and protein expression, cell signalling, oxidative stress, and apoptosis. Studies of the possible effects of RF-EMF on the blood–brain barrier and on a variety of effects in the brain were also considered. These results provided weak mechanistic evidence relevant to RF-EMF-induced cancer in humans.[6,7]

The final IARC decision was confirmed by voting of 27 present experts. A large majority of participants voted to classify RF-EMF radiation as "possibly carcinogenic" to humans, Group 2B. The decision was also based on occupational studies. One of the members of the epidemiology group, Peter Inskip from National Cancer Institute in USA, as well as Etienne Degrave from Belgian Ministry of Defence, were not present at the voting.[7] Maria Blettner, also a member of the Interphone study group, had the opinion that current evidence in humans was inadequate, therefore permitting no conclusion about a causal association. Jack Siemiatycki, the Chair of the epidemiology subgroup, did not vote at all although present. Thus, 25 of 27 present experts voted for Group 2B.

It should be noted that, initially, Anders Ahlbom, a Swedish participant of the Interphone Study Group, was invited to be a member of the expert group and also the subgroup chair in epidemiology. Before the meeting all experts had to declare any conflict of interest. Anders Ahlbom did not declare that he served on the Board of Directors of Gunnar Ahlbom AB, his brother's firm. This is a consulting firm in the domains of European Union affairs, especially within telecommunications. It was also revealed that the brother, Gunnar Ahlbom, had been a lobbyist in Brussels for the major Swedish telecom operator Telia Sonera for many years. This obvious conflict of interest was revealed by a Swedish journalist, Mona Nilsson, just a few days before the start of the meeting and reported to IARC on 18 May 2011. Anders Ahlbom was after that excluded from the Working Group at the IARC meeting.[7] He was instead invited as a specialist but without the opportunity to participate and vote for the final decision. After that Ahlbom decided not to come at all. He was replaced by Jack Siemiatycki as the epidemiology group Chair.

In this chapter an updated review of the evidence of an association between use of wireless phones and brain tumors is presented. Also some aspects on the IARC aftermath are given.

SOME TECHNICAL ASPECTS

The first generation of mobile phones was of the analogue type with an output power of 1 W at about 900 MHz followed by the 2nd generation GSM phones (2G) with either 900 or 1800 MHz frequency and with a pulsed output power. The mean output power was of the order of tens of mW. In the 3rd generation phones (3G, UMTS; Universal Mobile Telecommunication System) the output is more to be characterized as amplitude modulated than pulsed and the output power is of the order of tens of μW.

The Nordic countries were among the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981 but closed down on 31 December 2007, NMT 900 operated during 1986–2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1800 MHz, started to operate in 1991 and now dominates the market. The third generation of mobile phones, 3G or UMTS, using 1900/2100 MHz RF fields has been introduced worldwide in recent years, in Sweden in 2003. Currently the fourth generation, 4G (Terrestrial 3G), operating at 800/2600 MHz and Trunked Radio Communication (TETRA 380–400 MHz) are being established in Sweden and elsewhere. Nowadays mobile phones are used more than landline phones in Sweden *(*http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad--halvar-2011-pts-er-2011-21.pdf*)*. Currently the 5th (5G) generation is under development. One of the aims is for it to be possible to transmit large amounts of data in a short time.

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800–900 MHz RF fields, but since the early 1990s using a digital 1900 MHz system. The cordless phones are becoming more common than traditional telephones connected to landlines. Also these phones emit RF-EMF radiation similar to that of mobile phones. Thus, it is also necessary to consider the usage of cordless phones along with mobile phones, when human health risks are evaluated. It should be noted that the usual cordless base stations emit RF-EMF continuously. They are often installed in offices close to the person using a cordless phone handset or in homes, even in bedrooms next to the head of a sleeping person.

THE IARC AFTERMATH

It is interesting to see that different groups have interpreted the authoritative IARC evaluation very differently. No doubt the IARC decision started a worldwide spinning machine perhaps similar to the one launched by the tobacco industry when IARC was studying and evaluating passive smoking as a carcinogen in the 1990s.[20] Sowing confusion and "manufacturing doubt" is a well-known strategy used by the tobacco and other industries.[21–23]

A fact sheet from WHO issued in June 2011 shortly after the IARC decision stated that "*To date, no adverse health effects have been established as being caused by mobile phone use*," and furthermore that "*Tissue heating is the principal mechanism of interaction between radiofrequency energy and the human body*" (http://www.who.int/mediacentre/factsheets/fs193/en/). This statement contradicts the IARC

evaluation and was not based on evidence at that time on a carcinogenic effect from RF-EMF emissions. Furthermore WHO wrote that "*Currently, two international bodies have developed exposure guidelines for workers and for the general public, except patients undergoing medical diagnosis or treatment. These guidelines are based on a detailed assessment of the available scientific evidence*." These organizations were the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the Institute of Electrical and Electronics Engineers (IEEE).

ICNIRP is a private organization based in Germany that selects its own members. Their source of money is not declared. Furthermore their exposure guideline was established in 1998[24] based only on thermal (heating) effects from RF-EMF neglecting nonthermal biological effects. It was updated in 2009[25] and stated that: "*it is the opinion of ICNIRP that the scientific literature published since the 1998 guidelines has provided no evidence of any adverse effects below the basic restrictions and does not necessitate an immediate revision of its guidance on limiting exposure to high frequency electromagnetic fields. …Therefore, ICNIRP reconfirms the 1998 basic restrictions in the frequency range 100 kHz–300 GHz until further notice*." This guideline still provided by ICNIRP is 10 W/m^2. It should be noted that the ICNIRP guideline is used in most European countries as well as in many other countries. Unfortunately it is based on old data with no acknowledgment of cancer effects or nonthermal biological effects from RF-EMF exposure.

Certainly there are strong forces behind the scenes (http://www.nrk.no/programmer/tv/brennpunkt/1.6292981). IEEE is the world's most powerful federation of engineers. The members are or have been employed in companies or organizations that are producers or users of technologies that depend on radiation frequencies, such as power companies, the telecom industry, and military interests. IEEE has prioritized international lobbying efforts for decades specially aimed at the WHO. ICNIRP and WHO, both formally independent of the industry, have worked in close cooperation with the IEEE Committee on Man and Radiation (COMAR).

Interestingly the current project manager at the WHO, Emilie van Deventer, for the WHO EMF project has been a long time member of IEEE and is an electrical engineer. Her former position was at Toronto University in Canada where she held a position as adjunct professor that was financed by a telecom company and the Canadian Defense Department. She has no formal or earlier knowledge in medicine, epidemiology, or biology (http://www.waves.utoronto.ca/people_vandeventer.htm) (http://www.itu.int/ITU-T/worksem/emc-emf/201107/bios.html).

The WHO EMF project is supposed to

- Provide information on the management of EMF protection programs for national and other authorities, including monographs on EMF risk perception, communication and management.
- Provide advice to national authorities, other institutions, the general public, and workers about any hazards resulting from EMF exposure and any needed mitigation measures. (http://www.who.int/peh-emf/project/EMF_Project/en/index1.html)

In the WHO fact sheet it was also stated that "*WHO will conduct a formal risk assessment of all studied health outcomes from radiofrequency fields exposure by 2012*." The pertinent question is why WHO was so keen to make a new risk evaluation shortly after the IARC evaluation, an organization being part of WHO. In one year's time it would not be expected that new studies would be published changing the classification of RF-EMF as a possible, Group 2B, human carcinogen. The call by the WHO for another risk evaluation, together with its statement of "no adverse health effects," undermined the IARC decision and gave the telecom industry a "clean bill" of health, raising questions as to what agenda the WHO is pursuing in this matter. To date in February 2014 a "formal risk assessment" from WHO has not been presented.

The physicist Michael Repacholi from Australia seems to have started his career within this field with a study on lymphoma incidence in mice exposed to RF-EMF published in 1997.[26] The results showed that the lymphoma risk was statistically significantly higher in the exposed mice than in the controls with odds ratio (OR) = 2.4, 95% confidence interval (CI) = 1.3–4.5. He became the first chairman of ICNIRP in 1992 and during 1996 to 2006 the leader of the WHO department of electromagnetic radiation, called the WHO EMF project. He is still the Chairman emeritus at ICNIRP (https://www.icnirp.org/cv.htm) and has propagated worldwide, during almost 20 years, the thermal paradigm of health risks from RF-EMF exposure without acknowledging the nonthermal paradigm or any cancer risks. In 1995 he suggested that WHO should start the EMF project. This was adopted by WHO, see WHO Press office: WHO launches new international project to assess health effects of electric and magnetic fields; 4 June 1996 (http://legacy.library.ucsf.edu/documentStore/t/t/x/ttx22d00/Sttx22d00.pdf).

Repacholi started immediately a close colloboration with ICNIRP (his own organization) inviting the electric, telecom and military industries to meetings. He recruited the engineer Emelie van Deventer to WHO after his own resignation in 2006. A large part of the WHO EMF project has been financed by the industry (see Leloup D. Téléphonie mobile: Trafic d'influence à l'OMS? Mediaattitudes. 2007: http://www.mediattitudes.info/2006/12/trafic-dinfluence-loms.html and World Health Organization. The International EMF Project. Progress Report June 2005–2006: http://www.who.int/peh-emf/publications/reports/IAC_Progress_Report_2005–2006.pdf). The influence of the telecom industry over the WHO EMF project has raised concern (http://microwavenews.com/news/time-stop-who-charade).

Shortly after the IARC decision on RF-EMF in May 2011, Swerdlow et al. (online 1 July 2011) on behalf of ICNIRP published their view on mobile phones and brain tumors, mainly relating to the Interphone study.[27] Their conclusion was that "*Nevertheless, although one can not be certain, the*

trend in the accumulating evidence is increasingly against the hypothesis that mobile phone use causes brain tumors." However this conclusion was based on selective reporting of studies and results biased towards the null hypothesis. Thus several items were not discussed in the article such as the omission of cordless phone use in the Interphone study published in 2010,[17] thereby neglecting an important source of RF-EMF exposure. This resulted in a conservative risk estimate for mobile phone use. One important aspect is that our research group included cases aged 20–80 years,[13,14] whereas Interphone published results for the age group 30–59 years at diagnosis. This difference is important since the highest incidence of astrocytoma WHO grade IV (glioblastoma multiforme) is found in the age group 45–75 years with mean age 61 years and 80% older than 50 years.[28] Limiting the age to 59 years in Interphone diminishes the possibility of finding an increased risk taking a reasonable tumor induction period. Excluding the age group 20–29 years, as in Interphone, also makes an evaluation of young users more difficult.

Swerdlow et al.[27] write "*We have discussed elsewhere why the Hardell et al. results are problematic (Ahlbom et al. 2009*[29])." Thereby they neglect to describe the different methods used in these studies as we had explored previously.[30] In fact, excluding cordless phone use and limiting the study to the age group 30–59 years produced similar results in both study groups as we have published previously.[31]

Swerdlow et al. do not discuss in more detail the results in Interphone,[17] published in Appendix 2, with a statistically significant increased risk for glioma seen in the group two to four years for regular use, with one to 1.9 years used as reference category, OR = 1.68, 95% CI = 1.16–2.41. The highest OR was found in the 10+ years category for regular use, OR = 2.18, 95% CI = 1.43–3.31. Results were not presented according to type of mobile phone used. Overall, cumulative use ≥1640 h in the shortest latency group of one to four years before the reference date resulted in an increased risk, OR = 3.77, 95% CI = 1.25–11.4.

The highest absorption of RF-EMF emissions from a handheld phone is on the same side of the brain (ipsilateral) as the phone is used.[1] Highest dose is absorbed in the temporal lobe of the brain. In Interphone, cumulative call time of mobile phones ≥1640 h resulted in glioma in the temporal lobe with an OR = 1.87, 95% CI = 1.09–3.22, and for ipsilateral mobile phone use, an OR = 1.96, 95% CI = 1.22–3.16.[17] Likewise, in our studies, the OR was higher for ipsilateral use of mobile or cordless phones, and for malignant brain tumors in the temporal lobe.[13,14] These facts were neglected in the Swerdlow et al. commentary.[27]

Furthermore, regarding glioma risk in relation to anatomical location of the tumor, Swerdlow et al.[27] cite results from part of Interphone published by Larjavaara et al.[32] That study used unclear methods and concluded that no clear relationship existed. However, the study by Cardis et al. (online June 9, 2011, also presented at the IARC meeting in May 2011)[19] published the same year as Larjavaara et al. was not included in the Swerdlow et al. review. In the publication, based on another part of Interphone data, the estimated RF dose from mobile phone use in the tumor area was associated with an increased risk of glioma. The OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumor center for more than seven years before diagnosis with an OR of 1.91 (95% CI = 1.05–3.47) in the highest quintile of exposure. These results were based on sound methods.

Regarding incidence of brain tumors, Swerdlow et al.[27] refer to de Vocht et al.[33] with data from England. However, they omit the increasing incidence of brain tumors, the majority glioma, in the temporal lobe during 1998–2007 for men and women ($p < 0.01$). That is the tumor area of most interest in relation to wireless phone use. Our research group had published increasing incidence of astrocytoma, the most common type of glioma, for the time period 2000–2007,[34] but that was not mentioned by Swerdlow et al.

Repacholi et al.[35] made a review on wireless phone use and cancer risks. However, the article was not balanced with omission of facts and results and with conclusions not based on published findings. For example, the authors used the Hill viewpoints from 1965,[36] based on smoking and lung cancer risk, and concluded that, "*In summary, none of the Hill criteria support a causal relationship between wireless phone use and brain cancer or other tumors in the areas of the head that most absorb the RF energy from wireless phones*." This conclusion goes far beyond what the authors studied using less reliable methods and is not based on published data. The Hill viewpoints are discussed in more detail below.

FURTHER STUDIES AND META-ANALYSES

In the following, further studies after the IARC evaluation in May 2011 are discussed. Our new study with brain tumor cases diagnosed during 2007 to 2009 give results for longer latency periods (time from first use until tumor diagnoses) than in previous studies for wireless phone use. We have published results for acoustic neuroma,[37] meningioma,[38] and malignant brain tumors,[39] and these are summarized in Table 45.1. First we present results for the most common malignant brain tumor, glioma, and use of mobile and cordless phones. As mentioned, we also considered use of cordless phones in the assessment of exposure to RF-EMF from wireless phones in our studies. This is in contrast to Interphone that included only mobile phone use, thereby omitting a large part of RF-EMF exposure which biased the risk estimates towards unity.

GLIOMA

Glioma is the most common malignant brain tumor and represents about 60% of all central nervous system tumors. The most common glioma subtype is astrocytoma. Astrocytic tumors are divided in two groups depending on the malignant potential; low-grade (WHO grades I–II) and high-grade (WHO grades III–IV). Low-grade astrocytoma has a relatively favourable prognosis, whereas survival is shorter for patients with high-grade glioma. Glioblastoma multiforme

TABLE 45.1
OR and CI for Glioma (n = 1380), Meningioma (n = 1625) and Acoustic Neuroma (n = 316) for Use of Mobile and Cordless Phones in Different Latency Groups

	Mobile Phone		Cordless Phone		Wireless Phone	
Latency	**Ca/Co**	**OR, 95% CI**	**Ca/Co**	**OR, 95% CI**	**Ca/Co**	**OR, 95% CI**
Glioma (n = 1380)						
Total, >1 year	945/2148	1.3 (1.1–1.6)	752/1724	1.4 (1.1–1.7)	1074/2472	1.3 (1.1–1.6)
>1–10 years	563/1362	1.3 (1.1–1.6)	565/1308	1.4 (1.1–1.7)	622/1515	1.3 (1.1–1.5)
>10–20 years	303/672	1.4 (1.1–1.8)	181/403	1.5 (1.1–1.9)	369/831	1.4 (1.1–1.8)
>20 years	79/114	2.2 (1.5–3.1)	6/13	1.4 (0.5–3.7)	83/126	2.0 (1.4–2.9)
p, trend		*0.01*		*0.79*		*0.03*
Meningioma (n = 1625)						
Total, >1 years	956/2148	1.0 (0.9–1.2)	817/1724	1.1 (0.9–1.3)	1117/2472	1.0 (0.9–1.2)
>1–10 years	610/1362	1.0 (0.8–1.2)	598/1308	1.1 (0.9–1.3)	669/1515	1.0 (0.8–1.2)
>10–20 years	299/672	1.1 (0.8–1.3)	212/403	1.2 (0.9–1.5)	394/831	1.1 (0.9–1.3)
>20 years	47/114	1.0 (0.7–1.6)	7/13	1.3 (0.5–3.3)	54/126	1.0 (0.7–1.5)
p, trend		*0.89*		*0.55*		*0.70*
Acoustic neuroma (n = 316)						
Total, >1 year	200/2148	1.6 (1.2–2.2)	156/1724	1.5 (1.1–2.1)	227/2472	1.5 (1.1–2.0)
>1–10 years	142/1362	1.6 (1.2–2.2)	132/1308	1.5 (1.1–2.1)	156/1515	1.4 (1.1–1.9)
>10–20 years	46/672	1.8 (1.1–2.9)	21/403	1.2 (0.7–2.1)	57/831	1.8 (1.1–2.7)
>20 years	12/114	3.7 (1.7–7.7)	3/13	6.5 (1.6–25)	14/126	3.9 (1.9–7.9)
p, trend		*0.06*		*0.049*		*0.01*

Regarding acoustic neuroma see Hardell et al.[37]; glioma and meningioma results to be published. Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age at diagnosis, gender, socioeconomic (SEI)-code and year for diagnosis.

(WHO grade IV) accounts for 60%–75% of all astrocytoma. The peak incidence is between 45–75 years of age with median survival less than one year.[40]

Our case-control studies covered patients diagnosed with brain tumor during 1997 to 2003 or 2007 to 2009. These results have been published.[13,14,37–39] We have now made a pooled analysis of the two study periods. Use of mobile phone gave OR = 1.3, 95% CI = 1.1–1.6 in total, increasing to OR = 2.2, 95% CI = 1.5–3.1 (p trend = 0.01) in the latency group >20 years, Table 45.1. The longest latency time >25 years gave OR 3.0, 95% CI = 1.7–5.2 (data not in table). Also use of cordless phones increased the risk, producing OR = 1.4, 95% CI = 1.1–1.7 in total. However, there was no clear trend with increasing latency. In the article to be published[41] we analyzed latency in five-year intervals. The highest risk was found in the latency group >15–20 years, OR = 1.7, 95% CI = 1.1–2.5. Few subjects were included in the latency group >20 years. Wireless phone use (mobile and cordless phones in total) gave highest risk in the >20 years latency group with OR = 2.0, 95% CI = 1.4–2.9 (p trend = 0.03).

The only published results for use of mobile phones and >10 years latency come from our research group and Interphone (≥10 years in Interphone). We have now made a meta-analysis of the results in these studies using ≥10 years latency, Table 45.2. Furthermore we adopted in our studies the same cut-off for highest cumulative use, ≥1640 h, as in Interphone. This meta-analysis gave for ipsilateral mobile phone use, that is the same side as the tumor appeared, in the ≥10 years latency group OR = 1.55, 95% CI = 0.99–2.42. Regarding anatomical localization the highest exposure is in the temporal lobe. The risk was statistically significant for glioma in the temporal lobe with OR = 1.45, 95% CI = 1.07–1.97. Cumulative mobile phone use ≥1640 h gave statistically significant increased risk for ipsilateral glioma in total and also glioma located in the temporal lobe. These results clearly show that use of mobile phones increases the risk of glioma. We have shown that use of cordless phones also increases the risk. Excluding such use, as in Interphone, would bias risk estimated towards unity, as we have shown in one publication.[31] Since Interphone did not assess such use, our meta-analysis could only be made for mobile phone use. Excluding cordless phones did thus give conservative risk estimates. The results indicate an early effect in the genesis of glioma (initiator) and for digital phones also a late effect (promoter). For further discussion see our recent publication.[39]

HAZARD RATIO (HR) FOR SURVIVAL OF PATIENTS WITH GLIOMA

A carcinogenic effect of RF-EMF emissions would be strengthened if exposure correlates with survival of glioma patients. To further elucidate that possibility we analyzed survival of all cases with malignant brain tumor (n = 1251) in our case-control studies for the time period 1997–2003.[42]

TABLE 45.2
Use of Mobile Phones and Glioma Risk, Meta-Analysis of Hardell et al.[41] and Interphone[17]

	Hardell et al.		Interphone		Meta-Analysis	
	Ca/Co	OR, 95% CI	Ca/Co	OR, 95% CI	Ca/Co	OR, 95% CI
Latency ≥10 years						
All	382/786	1.55 (1.21–1.99)	252/232	0.98 (0.76–1.26)	634/1018	1.23 (0.79–1.93)
Ipsilateral	238/360	1.91 (1.40–2.60)	108/82	1.21 (0.82–1.80)	346/442	1.55 (0.99–2.42)
Contralateral	130/257	1.34 (0.93–1.94)	49/56	0.70 (0.42–1.15)	179/313	0.99 (0.53–1.87)
Temporal lobe	113/786	1.54 (1.01–2.35)	94/69	1.36 (0.88–2.11)	207/855	1.45 (1.07–1.97)
Cumulative use ≥1640 h						
All	211/301	2.13 (1.61–2.82)	210/154	1.40 (1.03–1.89)	421/455	1.73 (1.15–2.62)
Ipsilateral	138/133	3.11 (2.18–4.44)	100/62	1.96 (1.22–3.16)	238/195	2.54 (1.62–3.98)
Contralateral	66/105	1.56 (1.01–2.40)	39/31	1.25 (0.64–2.42)	105/136	1.46 (1.02–2.10)
Temporal lobe	59/301	2.01 (1.25–3.21)	78/47	1.87 (1.09–3.22)	137/348	1.95 (1.37–2.78)

Numbers of exposed cases (Ca) and controls (Co) are given. Glioma: Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1640 hours) groups.

Hazard ratio (HR) for survival was close to unity for all glioma cases for use of wireless phones, HR = 1.1, 95% CI = 0.9–1.2. However, latency >10 years increased HR to 1.2, 95% CI = 1.002–1.5. Increased ratio was found for both mobile phone use, HR = 1.3, 95% CI = 1.0005–1.6, and cordless phone use, HR = 1.3, 95% CI = 0.9–1.9. HR also increased with cumulative number of hours of use of mobile phone and cordless phone with a statistically significant trend for tertiles ($p = 0.01$) of use of both phone types. This study showed elevated HR, indicating decreased survival of all glioma cases with long-term and high cumulative use of wireless phones. Clearly these effects show a biological effect from RF-EMF exposure leading to a more aggressive tumor.

MENINGIOMA

Meningioma is the most common benign brain tumor and accounts for about 30% of intracranial tumors.[43] It develops from the pia and arachnoid membrane that cover the central nervous system. Meningioma is an encapsulated, well-demarked, and rarely malignant tumor. It is slow growing and gives neurological symptoms by compression of adjacent structures. Headaches and seizures are common symptoms. This tumor type is most common among middle-aged and elderly persons. There are more women than men that develop meningioma with the incidence about two-fold higher in women than men.[44] Ionizing radiation is a well-established risk factor with time interval to tumor development of decades.[45]

The pooled analysis of our two study periods 1997–2003 and 2007–2009 gave for mobile phone use OR = 1.0, 95% CI = 0.9–1.2 and for cordless phone use OR = 1.1, 95% CI = 0.9–1.3 in total using >1 year latency time (Table 45.1, data to be published). In the latency group >20 years wireless phone use gave OR = 1.0, 95% CI = 0.7–1.5.

The meta-analysis of our studies and Interphone gave in the ≥10 years latency group OR = 0.97, 95% CI = 0.80–1.18, see Table 45.3. Similar results were found in that latency group for ipsilateral and contralateral mobile phone use. With cumulative mobile phone use ≥1640 h ipsilateral mobile phone use gave OR = 1.46, 95% CI = 1.05–2.03. However, since there was no statistically significant increased risks for ipsilateral use or localization in the temporal lobe in the >10 years latency group the results do not show a clear pattern of an association. These results show no pattern of a consistent association between use of wireless phones and meningioma.

ACOUSTIC NEUROMA

Acoustic neuroma or vestibular schwannoma is a benign tumor that is located in the eighth cranial nerve that leads from the inner ear to the brain. This tumor type does not undergo malignant transformation. It tends to be encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It is a slow growing tumor in the auditory

TABLE 45.3
Use of Mobile Phones and Meningioma Risk, Meta-Analysis of Hardell et al. [to be published] and Interphone[17]

	Hardell et al.		Interphone		Meta-Analysis	
	Ca/Co	OR, 95% CI	Ca/Co	OR, 95% CI	Ca/Co	OR, 95% CI
Latency ≥10 years						
All	346/786	1.07 (0.84–1.36)	110/112	0.83 (0.61–1.14)	456/898	0.97 (0.80–1.18)
Ipsilateral	161/360	1.05 (0.76–1.44)	40/42	0.88 (0.52–1.47)	201/402	1.00 (0.76–1.31)
Contralateral	126/257	1.20 (0.84–1.71)	20/25	0.58 (0.29–1.16)	146/282	1.03 (0.75–1.42)
Temporal lobe	82/786	1.25 (0.81–1.95)	12/12	0.60 (0.22–1.62)	94/798	1.11 (0.74–1.66)
Cumulative use ≥1640 h						
All	141/301	1.24 (0.93–1.66)	130/107	1.15 (0.81–1.62)	271/408	1.20 (0.96–1.50)
Ipsilateral	67/133	1.46 (0.98–2.17)	46/35	1.45 (0.80–2.61)	113/168	1.46 (1.05–2.03)
Contralateral	51/105	1.11 (0.71–1.73)	28/28	0.62 (0.31–1.25)	79/133	0.94 (0.64–1.37)
Temporal lobe	32/301	1.37 (0.80–2.34)	21/14	0.94 (0.31–2.86)	53/315	1.28 (0.79–2.07)

Numbers of exposed cases (Ca) and controls (Co) are given. Fixed-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1640 hours) groups.

canal but grows gradually out into the cerebellopontine angle with potential compression of vital brain stem centers. Tinnitus and hearing problems are usual first symptoms of acoustic neuroma. Although acoustic neuroma is a benign tumor it causes persistent disabling symptoms after treatment such as loss of hearing and tinnitus that severely affect the daily life. The eighth cranial nerve is located close to the handheld wireless phone when used, so there is particular concern of an increased risk for neuroma development due to exposure to RF-EMF emissions during use of these devices. In fact, acoustic neuroma might be the "signal tumor" for the carcinogenic effect from RF-EMF emissions.

In the pooled analysis of our case-control studies on acoustic neuroma diagnosed 1997–2003 and 2007–2009 use of mobile phone gave OR = 1.6, 95% CI = 1.2–2.2 in the >1 year latency group.[37] The risk increased to OR = 3.7, 95% CI = 1.7–7.7 using >20 years latency, Table 45.1. The corresponding results for use of cordless phone were OR = 1.5, 95% CI = 1.1–2.1 and OR = 6.5, 95% CI = 1.6–25. Wireless phone use in total gave in the >20 years latency group OR = 3.9, 95% CI = 1.9–7.9 (p trend = 0.01).

In the meta-analysis of our results and Interphone, ipsilateral mobile phone use increased the risk for acoustic neuroma, see Table 45.4. Cumulative use ≥1640 h gave OR = 2.71, 95% CI = 1.72–4.28 in the ipsilateral group whereas contralateral use gave OR = 0.99, 95% CI = 0.56–1.75. We conclude that these findings are consistent with an increased risk for acoustic neuroma associated with use of wireless phones.

OTHER RECENT STUDIES

There are after the IARC evaluation in May 2011 some additional studies on acoustic neuroma other than our recent publication.[37]

In the U.S. study by Han et al.,[46] regular mobile phone use was statistically significantly more common among the cases (p = 0.006). The adjusted OR for ≥10 years' mobile phone use was 1.29, 95% CI = 0.69–2.43 (crude OR = 2.20, 95% CI = 1.43–3.39). Regarding cordless phone use, the adjusted OR for ≥10 years use was 1.07, 95% CI = 0.51–2.24 (crude OR = 1.40, 95% CI = 0.84–2.35). However, not all statistically significant confounders were included in the adjusted model (residency excluded) and no results were given for wireless phone use in total. The authors noted that they had insufficient information on mobile phone use. The results for cordless phones were not discussed in detail.

An increased risk for acoustic neuroma associated with reported use of mobile phone was found in a study from the UK.[47] Use in the 10+ years group gave rate ratio (RR) = 2.46, 95% CI = 1.07–5.64 with increasing risk with duration of use (p trend = 0.03). The study was limited by, for example, mobile phone use only at baseline, no details on handedness use, no information on tumor laterality and no assessment of use of cordless phones, and is further discussed below.

Another Swedish study group published results recently on acoustic neuroma diagnosed during 2002 to 2007. Regular mobile phone use produced OR = 1.18, 95% CI = 0.88–1.59

TABLE 45.4
Use of Mobile Phones and Acoustic Neuroma Risk, Meta-Analysis of Hardell et al.[37] and Interphone[18]

	Hardell et al.		Interphone		Meta-Analysis	
	Ca/Co	OR, 95% CI	Ca/Co	OR, 95% CI	Ca/Co	OR, 95% CI
Latency ≥10 years						
All	58/786	2.26 (1.43–3.58)	68/141	0.76 (0.52–1.11)	126/927	1.30 (0.45–3.78)
Ipsilateral	34/360	2.10 (1.20–3.67)	44/52	1.18 (0.69–2.04)	78/412	1.57 (0.89–2.76)
Contralateral	22/257	2.41 (1.20–4.84)	17/30	0.69 (0.33–1.42)	39/287	1.30 (0.38–4.41)
Cumulative use ≥1640 h						
All	27/301	2.40 (1.39–4.16)	77/107	1.32 (0.88–1.97)	98/408	1.63 (1.18–2.25)
Ipsilateral	19/133	3.18 (1.65–6.12)	47/46	2.33 (1.23–4.40)	66/179	2.71 (1.72–4.28)
Contralateral	8/105	1.54 (0.63–3.76)	16/26	0.72 (0.34–1.53)	24/131	0.99 (0.56–1.75)

Numbers of exposed cases (Ca) and controls (Co) are given. Acoustic neuroma: Random-effects model used for all meta-analyses of latency ≥10 years and fixed-effects model used for all meta-analyses of cumulative use ≥1640 hours, based on test for heterogeneity in the overall (≥10 years and ≥1640 hours) groups.

increasing to OR = 1.51, 95% CI = 0.92–2.49 in the highest cumulative exposure group ≥1640 h.[48] Higher risk estimates were found for latency <10 years than for longer time; latency ≥13 years the longest time period. Regarding analogue phones, highest risk was seen in the less than five years latency group, OR = 2.85, 95% CI = 0.70–11.6. Use of digital mobile phone gave highest risk in the five to nine years latency group with OR = 1.53, 95% CI = 1.02–2.32. No clear pattern of an association was found in the laterality analysis. Contralateral use yielded, in general, higher risks than ipsilateral casting doubts on the methods used. Deficient or loss of hearing is an early sign of acoustic neuroma and, of course, an outcome after surgery. Use of cordless phone gave overall OR = 1.41, 95% CI = 1.07–1.86 increasing to OR = 1.74, 95% CI = 1.22–2.46 in the five to nine years latency group. No laterality analysis was published for cordless phone use. In contrast to our studies no category of "wireless phone use" was presented. That means that when analysing mobile phone use some individuals in the "unexposed" group might have used a cordless phone and in the analysis of use of cordless phones, users of mobile phone could have been included in the "unexposed" group. There was no overlap of cases with our studies.

TUMOR VOLUME

Associations between the estimated amount of mobile phone use and acoustic neuroma and between the laterality of phone use and tumor location were analyzed in a case-control study from South Korea.[49] No increased risk was found for acoustic neuroma but the methods used seem to be less reliable, for example, time at diagnosis for cases but time at interview of controls were used as cutoff for exposure. In the case-case part of the study, tumor volume and estimated cumulative hours showed a strong correlation ($r^2 = 0.144$, $p = 0.002$), and regular mobile phone users showed tumors of a markedly larger volume than those of nonregular users ($p < 0.001$). When the analysis was limited to regular users who had serviceable hearing, laterality showed a strong correlation with tumor side (OR = 4.5, 95% CI = 0.585–34.608). The authors concluded that acoustic neuroma tumors may coincide with the more frequently used ear of mobile phones and that tumor volume showed strong correlation with amount of mobile phone use.[49]

Previously the Danish part of Interphone reported the mean size of acoustic neuroma for regular mobile phone users as 1.66 cm^3 and 1.39 cm^3 for nonusers (Wilcoxon test: $p = 0.03$). The risk of developing a larger acoustic neuroma with a volume of ≥1.51 cm^3 was 1.87, 95% CI = 0.75–4.64 for regular mobile phone users in comparison with nonusers or rare users.[50]

In our recent pooled analysis on acoustic neuroma,[37] tumor volume increased per year of latency and per 100 h of cumulative use of wireless phones. The result was statistically significant for analogue mobile phones, in accordance with overall findings of higher risk for use of that phone type. It should be noted that the increase in tumor volume was higher for ipsilateral use of mobile phones and for cordless phones than for contralateral use of the respective type. The percent change in volume per 100 h for ipsilateral mobile phone use was +2.4%; 95% CI −0.1 to +4.9%; $p = 0.06$, and for contralateral +1.1%; 95% CI −1.5 to +3.8%; $p = 0.41$. The corresponding results for cordless phone were for ipsilateral

use +2.1%; 95% CI −2.4 to +6.8%; $p = 0.36$, and for contralateral: +0.7%; 95% CI −2.2 to +3.7%; $p = 0.62$.

Three studies that have reported increased acoustic neuroma volume in relation to mobile phone use and cordless phone use (only assessed by our research group) show that RF-EMF exposure affects tumor growth.

RISKS TO CHILDREN AND ADOLESCENTS

Children have smaller heads and thinner skull bones than adults. Their brain tissue also has higher conductivity and these circumstances give higher absorption from RF-EMF than for adults.[1–3] The developing brain is more sensitive to toxins[51] and it is still developing until about 20 years of age.[52] Use of wireless phones was widespread among children and adolescents in Swedish studies,[53,54] but also in most other investigated countries (http://www.gsma.com/publicpolicy/wp-content/uploads/2012/03/GSMA_ChildrensMobilePhones2012WEB.pdf). The greater absorption of RF energy per unit of time, the greater sensitivity of their brains, and their longer lifetimes with the risk to develop a brain tumor leaves children at a higher risk than adults from mobile phone radiation.

We already analyzed, in our previous studies, three age groups for first use of a wireless phone: <20 years, 20–49 years and 50–80 years.[34] We have now made the analyses in our pooled studies for the time periods 1997–2003 and 2007–2009. Highest risk for glioma was found for first use of mobile phone or cordless phone before the age of 20 years, Table 45.5. Thus, mobile phones yielded OR = 1.8, 95% CI = 1.2–2.8 for glioma increasing to OR = 2.3. 95% CI = 1.3–4.2 for ipsilateral use. The corresponding results for cordless phone use were OR = 2.3, 95% CI = 1.4–3.9 and OR = 3.1, 95% CI = 1.6–6.3, respectively. Thus, highest risk was found for first use of the wireless phone before the age of 20. Also for acoustic neuroma the risk was highest in the youngest age group with OR = 2.2, 95% CI = 0.9–5.3 for use of mobile phone increasing to OR = 2.4, 95% CI = 0.8–7.5 for ipsilateral use. Only two cases reported first use of a cordless phone before the age of 20, so no conclusions could be drawn for cordless phones.

Regarding meningioma, we found no risk difference between the three age groups for first use of mobile or cordless phone use, Table 45.5. The risk was not statistically increased or decreased in any age group. Similar results were found for ipsilateral and contralateral use. Thus, first mobile phone use before the age of 20 gave in total OR = 0.8, 95% CI = 0.5–1.4 and for ipsilateral use OR = 1.1, 95% CI = 0.5–2.3.

There are few other studies on brain tumor risk for children from use of wireless phones. Mobikids is one study that is ongoing. A multi-center case-control study was conducted in Denmark, Sweden, Norway, and Switzerland, CEFALO.[55] It included children and adolescents aged 7–19 years and has been commented by us elsewhere in detail since serious methodological problems exist in the study design and interpretation of the results.[56]

In CEFALO a statistically nonsignificant increased risk for brain tumors among regular users (one call per week for at least six months) of mobile phones was found; OR = 1.36, 95% CI = 0.92–2.02. This OR increased somewhat with cumulative duration of subscriptions and duration of calls.[55] No data for long-term use were given; the longest latency period was five years. Interestingly, further support of a true association was found in the results based on operator-recorded use for 62 cases and 101 controls, which for time since first subscription >2.8 years yielded a statistically significant OR of 2.15, 95% CI = 1.07–4.29, with a statistically significant trend ($p = 0.001$).

Use of cordless phones was not well assessed. The authors stated that such use was covered only in the first three years of use. No explanation was given for this most peculiar definition. Wireless phone use was not considered, that is use of both mobile phones and cordless phones as the relevant exposure category, as used by our research group and adopted by IARC.[6,7] Instead Aydin et al.[55] included use of cordless phones in the "unexposed" category when risk estimates were calculated for mobile phone use. Similarly, when use of cordless phones was analyzed mobile phone use was regarded as "no exposure." Thus, an increased risk was potentially concealed.

The authors summarized that they "*did not observe that regular use of a mobile phone increased the risk for brain tumors in children and adolescents*." An editorial in the same journal accompanied that conclusion by stating that the study showed "*no increased risk of brain tumors in children and adolescents who are regular cell phone users*."[57] This was echoed by a news release from the Karolinska Institute in Stockholm claiming that the results of no increased risk were "reassuring" (http://ki.se/ki/jsp/polopoly.jsp?d=130&a=125250&l=en&newsdep=130).

However, these statements go far beyond what the study really showed. In fact, the results indicate a moderately increased risk, in spite of low exposure, short latency period, and limitations in study design and analyses.

DANISH COHORT STUDY

Ideally a cohort study on wireless phone users would be of substantial value. However, several problems exist to establish a cohort with high quality assessed exposure. Use of both mobile phones and cordless phones need to be included. Such use varies over time and exposure to RF-EMF emissions depends also on several physical characteristics for different phone types. The types of mobile phones are changing and operator data on use of cordless phones is impossible to get.

An attempt to establish a cohort of mobile phone users was made in Denmark in cooperation between the Danish Cancer Society and the International Epidemiology Institute (IEI), Rockville, MD, USA. It was financed by grants from two Danish telecom operation companies (TeleDenmark Mobil and Sonafon), IEI, and the Danish Cancer Society. The source of money for IEI has not been disclosed.

TABLE 45.5
OR and CI for Glioma, Meningioma and Acoustic Neuroma in Different Age Groups for First Use of the Wireless Phone

	Glioma (n = 1380)			Meningioma (n = 1625)			Acoustic Neuroma (n = 316)		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Wireless phone, total	1074/2472	1.3	1.1–1.6	1117/2472	1.0	0.9–1.2	227/2472	1.5	1.1–2.0
<20 years old	81/108	1.8	1.2–2.7	27/108	0.8	0.5–1.3	9/108	1.6	0.7–3.7
20–49 years old	678/1540	1.3	1.1–1.6	678/1540	1.1	0.9–1.3	153/1540	1.7	1.2–2.3
≥ 50 years old	315/824	1.3	1.1–1.6	412/824	0.9	0.8–1.1	65/824	1.3	0.9–1.8
Mobile phone, total	945/2148	1.3	1.1–1.6	956/2148	1.0	0.9–1.2	200/2148	1.6	1.2–2.2
<20 years old	69/93	1.8	1.2–2.8	24/93	0.8	0.5–1.4	9/93	2.2	0.9–5.3
20–49 years old	605/1337	1.3	1.1–1.6	575/1337	1.1	0.9–1.3	131/1337	1.8	1.3–2.6
≥ 50 years old	271/718	1.3	1.1–1.6	357/718	1.0	0.8–1.2	60/718	1.5	1.03–2.1
Cordless phone, total	752/1724	1.4	1.1–1.7	817/1724	1.1	0.9–1.3	156/1724	1.5	1.1–2.1
<20 years old	46/48	2.3	1.4–3.9	7/48	0.5	0.2–1.1	2/48	0.6	0.1–2.6
20–49 years old	436/1022	1.3	1.02–1.6	459/1022	1.1	0.9–1.4	103/1022	1.6	1.1–2.4
≥ 50 years old	270/654	1.4	1.2–1.8	351/654	1.0	0.8–1.3	51/654	1.5	0.98–2.2

Regarding acoustic neuroma see Hardell et al.;[37] glioma and meningioma results to be published. Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis.

The first results from the Danish study on brain tumor risk among mobile phone subscribers were published in 2001.[58] It included subjects from January 1, 1982 until December 31, 1995 identified from the computerized files of the two Danish operating companies, TeleDenmark Mobil and Sonafon. A total of 723,421 subscribers were initially identified but the final cohort consisted of only 58% of these subjects. Due to lack of names of individual users 200,507 corporate users were excluded. They were expected to be the heaviest users and such exclusion would underestimate any risk estimates.

The first update of the Danish study gave follow-up data until 2002.[59] The median time since first subscription was this time 8.0 years. It was now stated that the cohort members were excluded from the reference population, which seems not to have been the case in the first publication. The Standardized Incidence Ratio (SIR) for glioma was close to unity, SIR = 1.01, 95% CI = 0.89–1.14. The highest SIR was found for glioma in the temporal lobe where RF-EMF exposure from a mobile phone would be highest, SIR = 1.21, 95% CI = 0.91–1.58 (n = 54 cases).

After the outcome of the IARC-evaluation was made public in June 2011,[6] two additional reports on the Danish cohort were soon published. Both were new updates of mobile phone subscribers and included more information on risk related to longer follow-up. One focused on acoustic neuroma[60] while the other gave results both for all cancers and separately for glioma and meningioma.[61]

Approximately 2.9 million of the Danish population of 5.5 million in total was included in the record linkage study on acoustic neuroma.[60] Of the 2.9 million subjects 420,095 were mobile phone subscribers that started their subscription 1987–1995 and in accordance with the aim of the study had lasted for ≥11 years, that is, 1998–2006 during which period the tumor cases were ascertained. No evidence of an increased risk was found for ≥11 years of subscription; adjusted Incidence Rate Ratio (IRR) was 0.87, 95% CI = 0.52–1.46. The analysis of long-term exposure (≥11 years) was based on only 15 "exposed" cases with acoustic neuroma all of which were men.

The fourth report on the Danish mobile phone cohort on tumors of the central nervous system showed no overall increased risk.[61] This was true also when restricted to the individuals with the longest mobile phone use, ≥13 years of assumed subscription. This time the number of the cohort was reduced to 358,403 (49.5%) of the initially identified subscribers (n = 723,421). This number was also used in the study on acoustic neuroma,[60] see above. The major additional exclusion (n = 54,350) was due to record linkage with the Danish so-called CANULI cohort on socioeconomic factors.[62] That register started 1990 and included subjects from the age of 30. Subscription holders aged 18–29 years were excluded from the mobile phone cohort; this was also the case for the third publication (acoustic neuroma). Follow-up of cancer started at January 1, 1990, or at the age of 30 if occurred later, and ended December 31, 2007. The study period was 1990–2007[61] but the cohort was established during 1982–1995. Cancer cases before 1990 were disregarded since the CANULI cohort started in 1990. The authors did not discuss the impact of the exclusion of these subscribers on the results. This exclusion would include the early users of analogue phones, which had higher emissions of RF-EMF than the later digital system. Moreover, the exclusion of young subscribers (18–29 years) could be of importance since, as discussed above, studies have shown highest risk in subjects that started the use of a mobile or cordless phone before the age of 20.[34]

Some of the many shortcomings of the Danish cohort study include:

1. Corporate subscribers of mobile phones (200,507 people), who are likely to have been heavy users, were classified as "unexposed."
2. Mobile phone subscription holders not using the phone were classified as "exposed."
3. Users of cordless phones not using a mobile phone were classified as "unexposed."
4. Nonsubscribers using the mobile phone were classified as "unexposed."
5. Persons with a mobile phone subscription later than 1995 were classified as "unexposed."
6. No individual exposure data (e.g., on cumulative exposure or side of head mostly used).
7. No operator-verified data on years of subscription assessed.

These limitations are likely to have led to an underestimate of any risk in this study. One would expect considerable misclassification of mobile phone use both among subscribers and the reference population since no new subscribers were included in the exposed cohort after 1995.

The publication of the latest update of the Danish study[61] was accompanied by an editorial by Anders Ahlbom and Maria Feychting from the Karolinska Institute in Sweden.[63] It began with the statement: *"Evidence is reassuring, but continued monitoring of health registers and prospective cohorts is still warranted*." They did, however, forget to mention that less than 50% of the initial cohort remained for analysis. Although more long-term data were now available and adjustment for socioeconomic factors could be made, the update by Frei et al.[61] suffers from basically the same methodological limitations—mainly related to exposure assessment—as the first one did. Instead of addressing the limitations of the Danish cohort study in full, Ahlbom and Feychting[63] used their space to selectively report on results in the Hardell group studies choosing the time period 2000–2003[64,65] although the whole investigation period was 1997–2003.[13,14] They discussed incidence data on brain tumors in Sweden instead of Denmark, which would have been more appropriate regarding a Danish cohort study.

It is clear from these limitations that the authors' conclusion that: "*In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association*" is not soundly based.[61] We concluded in our review that its many limitations—embedded in the study design from the very beginning and mainly related to poor exposure assessment—cloud the findings of the four reports to such an extent that render them uninformative, at best.[66]

UK COHORT STUDY

As shortly discussed above, in 2013 Benson et al.[47] published a study on UK mobile phone users. Use of mobile phones was assessed in about 65% of a cohort of women established for another purpose during 1996 to 2001. Only baseline data collected at one time between 1999 and 2005 were used with the questions: "*About how often do you use a mobile phone?*" (never, less than once a day, every day); and "*For how long have you used one?*" (total years of use). In 2009, the participants were asked how much they did talk on a mobile phone and how many years they had used the phone. However, these later data were not used in the analysis. Of those reporting no use of a mobile phone at baseline, 49% reported such use in 2009. The incidence of brain tumors was assessed in 2005 and the average follow-up was only seven years. No increased incidence of glioma was found ($n = 571$ cases). For acoustic neuroma ($n = 96$ cases), there was an increase in risk with long term use *versus* never use (10+ years: RR = 2.46, 95% CI = 1.07–5.64, $p = 0.03$), the risk increasing with duration of use (trend among users, $p = 0.03$). No data were available on handedness for mobile phone use or tumor localization in the brain. Use of cordless phones was ignored. This study has poorly assessed exposure and has the same shortcomings as the Danish cohort study.[61]

In a letter to the Editor, Benson et al. gave updated follow-up data to 2011.[67] They no longer found a statistically significant increased risk for acoustic neuroma. However, these results were based on the same baseline data as previously and similarly lack scientific precision in the assessment of exposure.

Similarly to the Danish cohort study, this study is uninformative regarding use of mobile phones and the risk of cancer due to serious limitations in the assessment of long-term lifetime use. Cordless phone use was not assessed thus underestimating any risk increase.

IARC CONTROVERSY

A remarkable commentary on mobile phones and cancer, addressing next steps after the 2011 IARC review, was published by Jonathan Samet together with three persons at IARC.[68] Samet was the Overall Chair of the IARC evaluation on RF-EMF in May 2011 and the three other persons, Kurt Straif, Joachim Schüz and Rodolfo Saracci, were staff members at IARC present at the meeting.

The authors discuss *pros* and *cons* for the classification at the IARC classification of exposure to RF-EMFs as "possibly carcinogenic to humans," Group 2B. Special emphasis is said to be given to articles published after the IARC decision. However, several peer-reviewed more recently published articles are either misinterpreted or omitted from their presentation. One such example is the three papers published by our research group with free Internet access on meningioma (July 19, 2013),[38] acoustic neuroma (July 22, 2013),[37] and malignant brain tumors (September 24, 2013).[39]

In their commentary Samet et al. are not so careful when they compare methods used in the Hardell group and Interphone studies. For example, there were large differences in recruitment of cases and controls, participation rates, and assessment of exposure that we have explored in detail elsewhere.[39,69,70]

In fact, using the same age group as in Interphone and omitting the use of cordless phones as in Interphone, gives similar results from both study groups.[30,31] These circumstances have in reviews given rise to the conclusion that the Hardell group studies are of greater precision in epidemiological terms than Interphone.[71,72]

In fact, remarks can be made on the Samet et al. presentation of the Interphone results with several omissions of results. For example, one result in the Cardis et al.[19] study on the estimation of cumulative energy absorbed by brain tissue from mobile phone use was: "*The ORs for glioma in the highest exposed area were higher in long-term users than in short-term users (OR 2.80, 95% CI 1.13 to 6.94 for 10 years or more of use).*" This was not mentioned by Samet et al.

The authors claim regarding the CEFALO study on brain tumors in children[55] that "*Almost all odds ratios were slightly elevated…. although not statistically significant in any of the analyses relating various measures of exposure to brain tumor risk*." However, the results, based on operator-recorded use yielded for time since first subscription >2.8 years, a statistically significant increased odds ratio with trend $p = 0.001$, see above.

The Danish cohort study on mobile phone users[61] is discussed by the authors. It was included in the IARC evaluation of RF-EMF[6,7] but the conclusion was that "*phone provider, as a surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment*." Samet et al. write that this was "*a study considered by the IARC Working Group,*" but they fail to report the conclusion by the Working Group. They also make reference to the UK mobile phone study by Benson et al.[47] but fail to discuss the shortcomings of the study. The many limitations in the Danish and UK studies are discussed in this chapter above.

The authors discuss incidence data on brain tumors, but have omitted critical viewpoints on those studies too, such as limited latency period for full evaluation of time trends, shortcomings of cancer register data, and doubtful methods used by for example, Little et al.[73] We have discussed such shortcomings in more detail elsewhere.[69] We have also discussed elsewhere the increasing incidence of brain tumors in several countries including Denmark,[69] the latter not mentioned by Little et al.[73] and certainly well-known to Joachim Schüz, a former employee at the Danish Cancer Society (http://microwavenews.com/news-center/joachim-sch%C3%BCz-moves-iarc-interphone-analysis-continue). In fact, there was a sharp increase in the incidence of brain tumors during 2003 to 2012. This increase also clouds the results by Deltour et al.[74] on glioma incidence in the Nordic countries during 1997–2008. Furthermore, these results cast further doubt on the methods and findings in the Danish cohort study on mobile phone users.[61]

Samet et al. choose to present the evidence regarding mobile phones and cancer in a selective "no risk" way. Their article ends with "Keeping people well-informed" but it would have been wise for them to follow that rule in their own commentary.

The controversial activities regarding cancer risks, based on epidemiology, by IARC employees seem not to be an isolated occasion by Straif, Schüz and Saracci. As published in The Epidemiology Monitor (http://www.epimonitor.net/PrintVersion/Jan14/Jan-Feb_2014_The_Epidemiology_Monitor.pdf) the Italian epidemiologist Paolo Boffetta was found to have serious conflicts of interest in an asbestos case in Italy. He published an article in *European Journal of Cancer Prevention* downgrading short-term cancer risks from exposure without disclosing that he at the same time was a paid expert for the industry in a court case. This was a joint publication with Carlo La Vecchia, a coeditor of the very journal, and likewise without disclosing his own conflicts of interest. Paolo Boffetta was a former employee at IARC; "Chief of the Unit of Environmental Cancer Epidemiology" 1995–2003 and "Group Head and the first Coordinator of the Genetics and Epidemiology Cluster" 2004–2009 (http://en.wikipedia.org/wiki/Paolo_Boffetta). After terminating his position at IARC, Boffetta was a founder and vice-president of the International Prevention Research Institute, a consulting company which has done work for industry. The whole story was brought to attention by an investigation published by the French newspaper *Le Monde* (http://www.lemonde.fr/sciences/article/2013/12/16/les-troubles-liaisons-d-un-epidemiologiste-italien_4335239_1650684.html). Asbestos is not the only agent with toxic effects that has been questioned by Boffetta to be a health problem.

The aforementioned IARC employee, Joachim Schüz, was, together with Professor Anssi Auvinen from Finland, responsible for the evaluation of epidemiological studies on cancer risks from RF-EMF exposure (Kjell Hansson Mild, personal communication, see also letter from Kjell Hansson Mild to Mr John F. Ryan, Acting Director, Public Health Directorate, European Commission, dated 24 April, 2014) in the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). The preliminary opinion approved 12 December, 2013 is available and has been open public comments (http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_041.pdf). The committee's conclusion is that "*Epidemiological studies on RF EMF exposure do not unequivocally indicate an increased risk of brain tumours, and do not indicate an increased risk for other cancers of the head and neck region, or other malignant diseases including childhood cancer. Earlier studies raised open questions regarding an increased risk of glioma and acoustic neuroma in heavy users of mobile phones. Based on the most recent cohort and incidence time trend studies, it appears that the evidence for an increased risk of glioma became weaker while the possibility of an association of RF EMF exposure with acoustic neuroma remains open*."

This conclusion is based on wishful thinking and not scientific evidence. Schüz and Auvinen thereby make reference to the Danish cohort study.[61]

The cohort study by Benson et al.,[47] published in 2013, is also included as reference. The study by Deltour et al.[74] is taken as evidence against an increased risk for brain tumors. It should be noticed that Schüz is coauthor of these studies, which have many shortcomings and cannot be taken as evidence against cancer risks from wireless phone use. All the more remarkable

is that only one of our studies is included: *Use of mobile and cordless phones and survival of patients with glioma*.[42] All the rest, that is all case-control studies on brain tumor risk, are missing in spite of being well-known to Schüz and Auvinen.

Thus, a similar attitude as in the article by Samet et al.[68] with selective inclusion of published scientific evidence and not to include our recent articles also occurred in SCENHIR. Most revealing is that a paper by Poulsen et al. published a few days (Epub 20 Jun 2013; http://aje.oxfordjournals.org/content/178/2/190.abstract) before our recent articles for the study period 2007–2009 was included in SCENIHR while our studies, published a few days later, were not. Schüz was one of the authors of the Poulsen et al. paper.

Schüz was fully aware of our articles already, before the date of the publication, at the proof stage. The exclusion of our articles cannot be defended since they were sent to IARC as soon as they were published. The articles were also presented in the SCENIHR update working group by one person in our research group, Professor Kjell Hansson Mild, already at the proof stage. According to personal communication from Kjell Hansson Mild and a letter from him (see above), the Chair of the epidemiology group Joachim Schüz refused to include these studies in SCENIHR. He claimed that he makes the decision, being in charge of the epidemiology part in SCENIHR. Obviously, he may have contributed to the same decision in the Samet et al. article[68] as in SCENIHR. This is a most remarkable attitude for a person also acting as Head of the Section of Environment and Radiation at IARC (http://www.iarc.fr/en/staffdirectory/displaystaff.php?id = 40294).

This attitude is all the more striking since these are the first studies with long term data on brain tumor risk with latency more than 20 years (time since first use until tumor diagnosis).

The above-cited conclusion in SCENIHR is not based on scientific evidence. The conclusion would of course have been different if all scientific evidence had been included in the evaluation. It is a serious danger for epidemiology when scientific and ethical integrity are not considered to be necessary qualifications for participation in scientific committees. Certainly selective inclusion of studies violates standards for academic integrity and distorts scientific evidence. At the final end it is not within the realm of public health. The scientific community should take this matter extremely seriously.

INCIDENCE OF BRAIN TUMORS

It has been suggested that overall incidence data on brain tumors for countries may be used to qualify or disqualify the association between mobile phones and brain tumors observed in the case-control studies. As mentioned above, in support of the cohort findings that Frei et al.[61] presented for Denmark, Ahlbom and Feychting[63] refer to data on overall brain tumor incidence from the Swedish Cancer Registry rather than from the Danish Cancer Registry, which would have been more relevant.

The age-standardized incidence of brain tumors increased in Denmark with +41.2% among men and +46.1% among women during 2003 to 2012 (http://www.ssi.dk/Aktuelt/Nyheder/2013/~/media/Indhold/DK-dansk/Sundhedsdataogit/NSF/Registre/Cancerregisteret/Cancerregisteret2012.ashx). A news release based on the Danish Cancer Register states that during the last 10 years there has been an almost two-fold increase in the incidence of the most malignant glioma type, glioblastoma multiforme (https://web.archive.org/web/20121128153253/http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjernesvulster.htm). So far these incidence data are not generally available.

Also in the CEFALO study, including Denmark, Sweden, Norway, and Switzerland,[55] only data from the Swedish Cancer Registry were used in time trends for brain tumor incidence. As we have displayed elsewhere,[56] annual change in incidence in the age group 5–19 years differs between the Nordic countries. Thus, for the time period 1990–2008 in Norway a yearly increase in incidence with +3.3%, 95% CI +0.8 to +5.9% in boys and +2.5%, 95% CI +0.2 to +4.9% in girls was seen, whereas in Sweden there was a decline in boys and a slight increase in girls. Thus, it would have been more appropriate in CEFALO to discuss trends in all included countries.

The quality of the Swedish Cancer Registry for reporting central nervous system tumors, particularly high-grade glioma, has been seriously questioned.[75] In the Deltour et al.[74] article on cancer incidence in the Nordic countries, Sweden accounted for about 40% of the population. Thus, under-reporting of brain tumor cases to the Swedish Cancer Register would make the conclusions of the Deltour et al. study less valid.

Little et al.[73] studied the incidence rates of glioma during 1992 to 2008 in the United States and compared with ORs for glioma associated with mobile phone use in the 2010 Interphone publication[17] and our pooled results published in 2011.[16] Since our results are discussed and questioned by Little et al., their study needs to be reviewed in more detail. Our response to the journal (*BMJ*) was never accepted for publication in a paper version and cannot be found via PubMed, only on the web (http://www.bmj.com/content/344/bmj.e1147/rr/578564).

First, one important methodological issue that was not stated in the abstract or in Figures 2 through 4 in the article by Little et al.,[73] but can be found in the web appendix, is that observed rates were based on men aged 60–64 years from the Los Angeles SEER registry as the baseline category. These data were used to estimate rates in the entire dataset, men and women aged ≥18 years and all 12 SEER registries. Thereby numerous assumptions were made.

Using only men, as Little et al.[73] did, ignores the fact that women had less frequent use of mobile phones than men in our studies. Overall 31% of women reported such use versus 57% of men. Furthermore, use varies with age group with a large difference according to age, as we have explored in our publications.[16,34] Thus, the age group 60–64 year old men is not valid to use for all of these calculations.

Little et al.[73] do not explain how they obtained different results on incidence trends based on the Hardell group

results and Interphone on the risk for mobile phone use. They ignored that the Hardell group also assessed use of cordless desktop phones in contrast to Interphone and had another age group. We have discussed these aspects above.

There are several other points that may be added. One example is that the results for anatomical localizations and tumor grade [in Table 5 in the article] by Little et al. are based on numerous assumptions from SEER data, Interphone and the Hardell group studies. The authors seem not to have paid attention to the fact that the fraction of mobile phone users differs for gender and age groups. Furthermore, in the final Interphone Study Group[17] publication only results for the whole glioma group were presented in contrast to our published results for both low-grade and high-grade astrocytoma,[13] results that are ignored by Little et al. We found a higher risk for high-grade glioma in our studies.[76] This is of interest considering the statistically significant yearly increasing incidence of high-grade glioma in the SEER data for 1992–2008, +0.64%, 95% CI +0.33 to +0.95% published by Little et al.[73] without any further comments. On the contrary, the incidence of low-grade glioma decreased with –3.02%, 95% CI –3.49 to –2.54%. They also reported increasing yearly trend for glioma in the temporal lobe, +0.73%, 95% CI +0.23 to +1.23%, as would be expected based on anatomical distribution of RF-EMF emissions from the handheld wireless phone. Certainly these findings should have been explored in more detail.

In summary, the conclusion by Little et al. that "*Raised risk of glioma with mobile phone use, as reported by one (Swedish) study…are not consistent with observed incidence trends in the U.S. population data…"* goes far beyond scientific evidence and what would be possible to show with the faulty methods used in the study.

One should be careful about using data on the incidence of brain tumors, like in Aydin et al.[55] and Deltour et al.,[74] to dismiss results in analytical epidemiology. There might be other factors that influence the incidence rate like changes in exposure to other risk factors for brain tumors that are not assessed in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease.[77] The mechanism for RF-EMF carcinogenesis is unclear which adds to the view that descriptive data on brain tumor incidence are of limited value.

There are in fact other studies that show an increasing incidence of brain tumors. In Australia the incidence of primary brain tumors was studied in two areas, the state of New South Wales and Australian Capital Territory, with about seven million inhabitants.[78] The study covered the time period 2000–2008 and all diagnoses had a histopathological verification. It included 13 pathology databases servicing 24 neurosurgical centers. Adults aged ≥65 years recorded the largest proportion of malignant brain tumors, 52%. The annual percentage change (APC) for malignant tumors increased statistically significantly +3.9%, 95% CI +2.4 to +5.4%. An increase was seen among both men and women. The APC for benign tumors increased with +1.7%, 95% CI –1.4 to +4.9%, thus not statistically significant.

From urban Shanghai an increasing incidence of brain and nervous system tumors for the time period 1983–2007 was reported with APC +1.2%, 95% +0.4 to +1.9% in males and APC +2.8%, 95% CI +2.1 to +3.4% in females.[79] No results were given for different tumor types, for example, malignant and benign brain tumors, or anatomical site. The authors concluded that "*The study did not support an association between cellular telephone use and increased risk of brain and nervous tumours.*" However, that statement goes far beyond what is scientifically justified from this register-based study and what was actually investigated.

Certainly it is more informative to analyze incidence trends by anatomical site and histology of the tumor. de Vocht et al.[33] reported, in England for the time period 1998–2007, a statistically significant increasing incidence of brain tumors, the majority glioma, in the temporal lobe for men ($p < 0.01$) and women ($p < 0.01$), and frontal lobe for men ($p < 0.01$). The incidence also increased for women in the frontal lobe, although not statistically significantly ($p = 0.07$). The incidence decreased in other parts of the brain.

Zada et al.[80] studied incidence trends of primary malignant brain tumors in the Los Angeles area during 1992 to 2006. APC was calculated for microscopically confirmed histological subtypes and anatomic sub sites. The overall incidence of primary malignant brain tumors decreased over the time period with the exception of glioblastoma multiforme (astrocytoma grade IV). The annual age adjusted incidence rate of that tumor type showed a statistically significant increase in the frontal lobe with APC +2.4% to +3.0% ($p \leq 0.001$) and temporal lobe APC +1.3% to +2.3% ($p \leq 0.027$) across all registries. In the California Cancer Registry the incidence of glioblastoma multiforme also increased in cerebellum, APC +11.9% ($p < 0.001$). In the parietal and occipital lobes or in overlapping lobes no statistically significant changes in incidence were seen. For lower grade astrocytoma decreases of annual age adjusted incidence rates were observed. The authors concluded that there was a real increase in the incidence of glioblastoma multiforme in frontal and temporal lobes and cerebellum. These results by Zada et al.[80] are of interest since the highest absorbed dose of RF-EMF emissions from mobile phones has been calculated to occur in these parts of the brain.[1]

It should also be noted that Deltour et al.[74] reported increasing glioma incidence rates in Denmark, Finland, Norway, and Sweden for the time period 1979–2008. APC increased for men with +0.4%, 95% CI +0.1 to +0.6% and for women with +0.3%, 95% CI +0.1 to +0.5%. Unfortunately no data were given for subtypes of glioma and anatomical sites of the tumors, which would certainly have been informative. The authors did not consider these and other limitations when they conclude that "*Our data indicate that, so far, no risk associated with mobile phone use has manifested in adult glioma incidence trends…many increased or decreased risks reported in case-control studies are implausible, implying that biases and errors in the self-reported use of mobile phone have likely distorted the findings."* It should be noted that, regarding Sweden, we reported increasing incidence of

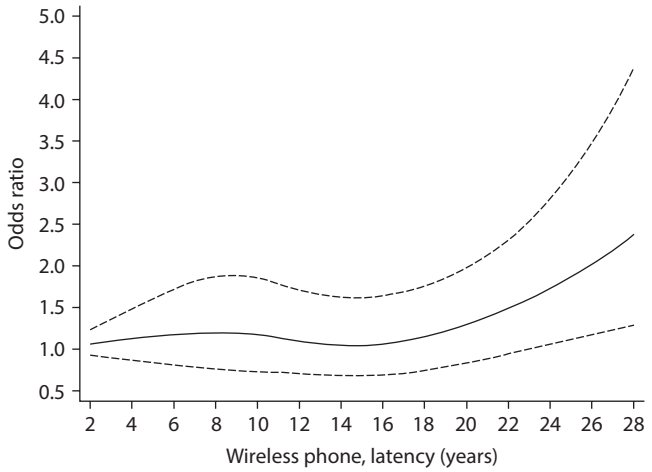

FIGURE 45.1 Restricted cubic spline plot of the relationship between latency of wireless phones and malignant brain tumors. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

astrocytoma WHO grades I–IV during 1970 to 2007. In the age group >19 years the annual change was +2.16%, 95% CI +0.25%–4.10% during 2000 to 2007.

In England the age-standardized incidence rates for malignant brain tumors in the frontal and temporal lobes rose at an average annual percentage change (AAPC) of +3.7% per annum, 95% CI +2.9 to +4.6% ($p < 0.0001$). Overall rates for all malignant tumors increased slightly. The results show that the pattern of change in incidence over time is statistically significantly different for frontal and temporal lobe tumors compared with all other brain tumors. (Alasdair Philips, Powerwatch, UK, personal communication, to be published.)

de Vocht et al.[81] used ecological data to generate hypotheses on environmental risk factors for cancers of the brain and nervous tissue. National age-adjusted cancer incidence rates were obtained from the GLOBOCAN 2008 resource and combined with data from the United Nations Development Report and the World Bank list of development indicators. Cancer rates, potential confounders, and environmental risk factors were available for 165 of 208 countries. National incidences of brain and nervous system cancers were associated with continent, gross national income in 2008, and Human Development Index Score. The only exogenous risk factor consistently associated with higher incidence was the penetration rate of mobile/cellular telecommunications subscriptions. According to these ecological results the latency period is at least 11–12 years, but probably more than 20 years. These results are in agreement with the latency period for malignant brain tumors that we have recently published; see Figure 45.1.[39]

BIOLOGICAL EFFECTS

There is no generally accepted mechanism by which RF-EMF exposure produces changes in DNA. The energy level associated with exposure is too low to cause direct DNA strand breaks and DNA crosslinks. However, DNA damage can be caused by cellular biochemical activities such as free radicals. Several studies indicate that RF-EMFs increase free radical activity in cells.[82,83] This process is probably mediated via the Fenton reaction. Hydrogen peroxide is converted into hydroxyl free radicals that are potent cytotoxic molecules. This reaction is catalyzed by iron. High levels of iron are found in metabolically active cells such as cancer cells as well as in cells undergoing abnormal proliferation, but also in brain cells. Glia cells might turn cancerous from DNA damage.

There are by now a vast majority of scientific studies published in peer-reviewed scientific journals showing nonthermal effects. The brain tumor risk as discussed above is one nonthermal risk.

We used serum transthyretin (TTR) as a marker of cerebrospinal fluid and blood–brain barrier damage in a cross-sectional study on 313 subjects.[84] We found a statistically significant positive β coefficient for TTR for time since first use of mobile phones and desktop cordless phones combined ($p = 0.03$), that is, increased serum concentrations of TTR. The electromagnetic field parameters were similar for the phone types. In a provocation study on 41 persons exposed for 30 min to an 890 MHz GSM signal with specific absorption rate of 1.0 W/kg to the temporal area of the brain, we found statistically significant increased serum TTR 60 min after exposure.[85]

In the BioInitiative Report 2012 leading researchers in this area, Dr. Leif Salford, Dr. Henrietta Nittby and Dr. Bertil Persson in Sweden concluded regarding blood–brain barrier damage: "*The intense use of mobile phones, not least by youngsters, is a serious memento…We cannot exclude that after some decades of (often), daily use, a whole generation of users, may suffer negative effects such as autoimmune and neuro-degenerative diseases maybe already in their middle age.*" (http://www.bioinitiative.org/report/wp-content/uploads/pdfs/sec10_2012_Effects_Electromagnetic_Fields_Wireless_Communication.pdf).

They continue with

> *One remarkable observation, which we have made in our studies throughout the years, is that exposure with whole-body average power densities below 10 mW/kg gives rise to a more pronounced albumin leakage than higher power densities, all at nonthermal levels. These very low SAR-values, such as 1 mW/kg, exist at a distance of more than one meter away from the mobile phone antenna and at a distance of about 150–200 m from a base station.*
>
> *Further, when a mobile phone operating at 915 MHz (and its antenna) is held 1.4 cm from the human head, the very low SAR levels of 10 mW/kg exist in deep-lying parts of the human brain such as the basal ganglia, and the power density of 1 mW/kg and less is absorbed in thalamus bilaterally.*
>
> *With this information as a background, it is difficult to recommend safety limits as the function of existing mobile systems might not allow for limits that produce SAR levels below 1 or 0.1 mW/kg in the human brain, which are reported to cause a pathological leakage of the BBB and [lead] to neuronal damage.*

Our research group studied the lipocalin type of prostaglandin D synthase or ß-trace protein (BTP) synthesized in the choroid plexus, leptomeninges and oligodendrocytes of the central nervous system. It is secreted into the cerebrospinal fluid. BTP is the key enzyme in the synthesis of prostaglandin D2, an endogenous sleep-promoting neurohormone in the brain. Exposure to RF-EMF has, in some studies, been associated with disturbed sleep. We studied the concentration of BTP in blood in relation to emissions from wireless phones.[86,87] The concentration of BTP decreased in the youngest age group in the study, 18–30 years, with increasing number of years of use of a wireless phones. Also, cumulative use in hours decreased the concentration of BTP. EMF emissions may downregulate the synthesis of BTP in the brain. This mechanism might be involved in sleep disturbances reported in persons exposed to RF-EMF fields.

Another example of a nonthermal effect is the finding that exposure to RF-EMF induces significant sperm DNA damage[88] and subsequent sperm apoptosis.[89] Studies have shown a positive association between mobile phone use and impaired male reproduction.[90]

Specifically, the postmeiotic phase during DNA synthesis is the most vulnerable phase to environmental toxins, because during that phase the cells have lost part of their cytoplasm containing the abundant antioxidant enzymes that protect from reactive oxygen species (ROS) oxidation.[91] Studies have shown that RF-EMF may stimulate ROS generation both *in vivo*[92] and *in vitro*.[93] Increased generation of ROS is considered to be one of the primary mechanisms that are involved in the bioeffects that are mediated by RF-EMF exposure.[94]

In a recently published study, it was demonstrated that RF-EMF exposure induced the formation of oxidative base damage in a mouse spermatocyte-derived cell line.[95] This was mediated by ROS production. These results suggest that RF-EMF radiation emitted during mobile phone use may produce genotoxicity in the form of DNA base damage. To further elucidate the central role of ROS in RF-EMF exposure-induced DNA base damage, the authors used α-tocopherol pretreatment to antagonize the oxidation of ROS; α-tocopherol is an important lipophilic antioxidant that can inactivate harmful ROS. The protective role of α-tocopherol pretreatment confirmed that ROS are involved in RF exposure-induced DNA base damage.[95] The mode of action for RF-EMF-induced genotoxicity involved the induction of oxidative DNA base damage. These findings support the idea that low energy RF-EMF that is insufficient to directly induce DNA strand breaks may nonetheless produce genotoxic effects in the form of DNA base damage.

Another recently published study showed that 2.45 GHz low-level RF-EMF radiation induced oxidative stress and suppressed implantation or pregnancy in mice. It was also concluded that it might lead to deformity of the embryo in case pregnancy continues. Furthermore, the oxidative stress may lead to DNA strand breakage in the brain according to the authors and thus be a mechanism for causation of brain tumors. The effects were nonthermal at power density = 0.033549 mW/cm^2, and specific absorption rate (SAR) = 0.023023 W/kg.[96] Another report concluded that oxidative stress from RF-EMF exposure is a significant mechanism affecting female and male reproductive systems.[97] This notion is supported in a study where semen samples were exposed to RF-EMF radiation, 850 MHz, SAR 1.46 W/kg at 10 cm distance. There was a statistically significant decrease in sperm motility and velocity and increase in DNA fragmentation in exposed semen samples.[98]

Antioxidants such as melatonin, vitamin C and vitamin E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model.[99–101]

The results in the study by Liu et al.[95] and Shahin et al.[96] are important findings to further elucidate the mechanisms for RF-EMF genotoxicity. These effects are clearly nonthermal. In summary these and other studies show that oxidative stress is an important mechanism for adverse health effects from RF-EMF emissions. Nonthermal effects of electromagnetic fields on living systems have been further discussed in a monograph from the Ramazzini Institute[102] (http://www.icems.eu/papers/ramazzini_library5_part1.pdf).

DISCUSSION

We know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in a large series of tumors of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma.[103] Thus, since the natural history of most glioma cases, from earliest events to clinical manifestation, is unknown but most likely requires several decades, the exposure duration has in most studies been incompatible with a tumor-initiating effect. Our latest study is the first with long-term use of wireless phones.[39] Interestingly, the most elevated OR was found in the latency group >25 years use. We also found results indicating a late effect on tumor development (promotion).

Initiation and promotion have different effects on the incidence of brain tumors. An initiating effect would have the most direct effect on the incidence. Our results indicate that such an effect would be apparent after more than 20 years use of mobile phones, and thus be too early to be found in cancer registries. On the other hand, if the exposure acts as a promoter, this would decrease latency time for already existing tumors, giving a temporary, but not a continuous, increase in incidence. In addition, it must be noted that any such effect on tumor development is limited by the magnitude of the shift of the age-incidence function and its slope for the respective tumor type.[104]

Of special interest in relation to the 3rd generation of mobile phones (3G; UMTS) is that chronic exposure to GSM and UMTS signals resulted in significant inhibition of double-strand breaks (DSB) repair in human stem cells. Statistical analysis revealed that UMTS exposure affected human stem cells more strongly than did the GSM exposures. Inhibitory effects of RF-EMF exposure on DSB repair in stem cells may result in formation of chromosomal aberrations and therefore origination of cancer. Alternatively, RF-EMF exposures may induce a stress response. Both possible interpretations

provided a mechanistic link to increased cancer risk because stem cells are considered as the most relevant targets for origination of tumors of different types, including glioma.[105]

Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 on association or causation that provides a helpful framework for evaluation of the brain tumor risk from RF-EMF.[36] We used his viewpoints to evaluate association versus causation on RF-EMF and brain tumor risk.[70] All nine issues on causation according to Hill were evaluated. Regarding wireless phones only studies with long-term use were included. Also laboratory studies and data on the incidence of brain tumors were considered. The criteria on *strength, consistency, specificity, temporality*, and *biological gradient* for evidence of increased risk for glioma and acoustic neuroma were fulfilled. Additional evidence came from *plausibility* and *analogy* based on laboratory studies. Regarding *coherence* several studies show increasing incidence of brain tumors, especially in the most exposed area. Support for *experiment* came from antioxidants that can alleviate the generation of ROS involved in biological effects, although a direct mechanism for brain tumor carcinogenesis has not been shown. Also the finding of no increased risk for brain tumors in subjects using the mobile phone only in a car with an external antenna is supportive evidence. Hill did not consider that all nine viewpoints needed to be essential requirements. For more information see our publication.[70]

CONCLUSION

Based on current literature, supported by the Hill criteria, glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions from wireless phones and regarded as carcinogenic to humans. Current guidelines for exposure need to be urgently revised.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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46 Dirty Electricity

*Samuel Milham**

CONTENTS

Since the 1979 Wertheimer and Leeper study[1] there has been concern that exposure to power frequency (50/60 Hz) electromagnetic fields (EMFs), especially magnetic fields, may contribute to adverse health effects including cancer. Until now, the most commonly used exposure metric has been the time-weighted average of the power frequency magnetic field. However, the low risk ratios in most studies suggest that magnetic fields might be a surrogate for a more important metric. I present evidence that a new exposure metric, high frequency voltage transients (dirty electricity) existing on electrical power wiring, is an important predictor of morbidity and mortality in electrically exposed populations. The new metric is measured with a Graham/Stetzer meter (G/S meter), also known as a Microsurge II meter (MS II meter), which is plugged into electric outlets.[2] This meter displays the average rate of change of these high frequency voltage transients (dV/dT) that exist everywhere on electric power wiring and gives a numerical output in G/S units. High frequency voltage transients found on electrical wiring both inside and outside of buildings are caused by an interruption of electrical current flow and by arcing and sparking. The electrical utility industry has referred to these transients as "dirty electricity."

There are many sources of dirty electricity in today's electrical equipment. Examples of electrical equipment designed to operate with interrupted current flow are light dimmer switches that interrupt the current twice per cycle (120 times/s), power saving compact fluorescent lights that interrupt the current at least 20,000 times/s, halogen lamps with switching power supplies, electronic transformers, and most electronic equipment manufactured since the mid-1980s that use switching power supplies. This includes computers, copy machines, furnace fans, air conditioners, and all transmitters including cell towers. Dirty electricity generated by electrical equipment in a building is distributed throughout the building on the electric wiring. Dirty electricity generated outside the building enters the building on electric wiring and through ground rods and conductive plumbing, while within buildings, it is usually the result of interrupted current generated by electrical appliances and equipment. Each interruption of current flow results in a voltage spike described by the equation V¼L_di/dt, where V is the voltage, L is the inductance of the electrical wiring circuit, and di/dt is the rate of change of the interrupted current. The voltage spike decays in an oscillatory manner. The oscillation frequency is the resonant frequency of the electrical circuit. The G/S meter measures the average magnitude of the rate of change of voltage as a function of time (dV/dT). This preferentially measures the higher frequency transients. The measurements of dV/dT read by the meter are defined as G/S units. The bandwidth of the G/S meter is in the frequency range of these decaying oscillations. Figure 46.1 shows a two-channel oscilloscope display. One channel displays the 60 Hz voltage in an electrical outlet while the other channel with a 10 kHz high-pass filter between the oscilloscope and the electrical outlet, displays the high frequency voltage transients on the same electrical outlet.[3]

DIRTY ELECTRICITY AND CANCER IN SCHOOLS

Although no other published studies have measured high frequency voltage transients and risk of cancer, one study of electric utility workers exposed to transients from pulsed electromagnetic fields found an increased incidence of lung cancer among exposed workers with very high relative risks.[4] In 2001, Ossiander and I[5] presented evidence that the childhood leukemia mortality peak at ages two to four which emerged in the U.S. in the 1930s was correlated with the spread of residential electrification in the first half of the twentieth century in the U.S. While doing the childhood leukemia study, I noticed a strong positive correlation between level of residential electrification and the death rate by state due to some adult cancers in 1930 and 1940 vital statistics. At the time, a plausible electrical exposure agent and a method for its delivery within residences was lacking. However, in 2008 I coauthored a study of a cancer cluster in school teachers at a La Quinta, California middle school[6] which indicated that high frequency voltage transients (also known as dirty electricity) were a potent universal carcinogen with cancer risks over 10.0 and significant dose–response for a number of cancers. They have frequencies between 2 and 100 kHz. These findings are supported by a large cancer incidence study in 200,000 California school employees which showed that the same cancers and others were in excess in California teachers statewide.[7] Power

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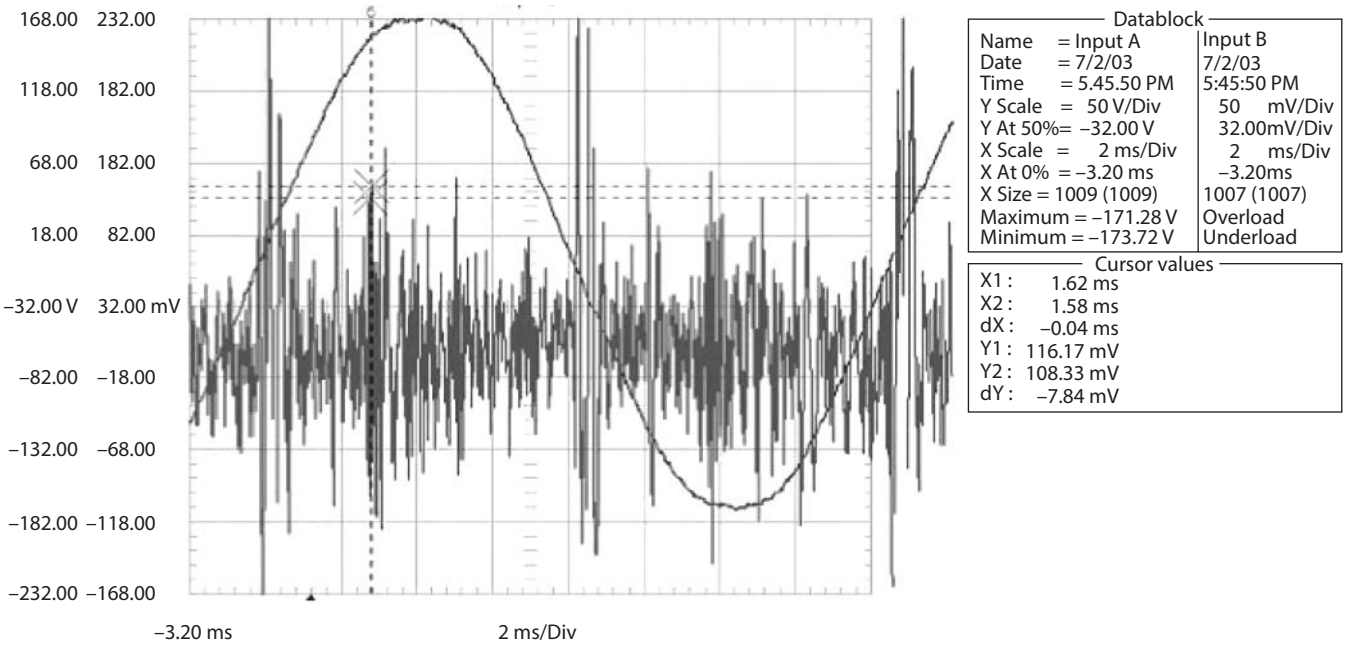

FIGURE 46.1 Oscilloscope display of dirty electricity: 60 Hz electrical power (channel 1) with concurrent high frequency voltage transients (channel 2). A 10 kHz high-pass filter was used on channel 2 in order to filter out the 60 Hz voltage and its harmonics.

frequency magnetic fields (60 Hz) measured at the school were low and not related to cancer incidence, while classroom levels of high frequency voltage transients measured at the electrical outlets in the classrooms accurately predicted a teacher's cancer risk. These fields are potentially present in all wires carrying electricity and are an important component of ground currents returning to substations especially in rural areas. This helped explain the fact that professional and office workers, like the school teachers, have high cancer incidence rates. It also explained why indoor workers had higher malignant melanoma rates, why melanoma occurred on parts of the body which never are exposed to sunlight, and why melanoma rates are increasing while the amount of sunshine reaching earth is stable or decreasing due to air pollution. A number of very different types of cancer had elevated risk in the La Quinta school study, in the California school employees study, and in other teacher studies. The only other carcinogenic agent which acts like this is ionizing radiation.

The health and mortality effects of electrification happened so gradually, and on such a wide scale, that they went virtually unnoticed, and the major illnesses that can be attributed to them came to be considered "normal" diseases of modern civilization. Although major cities had electricity at the turn of the last century, it took until the mid-1950s for the last farms in the United States to be electrified. By 1940, more than 90% of all the residences in the Northeastern United States and California were electrified. By 1940, almost all urban residences in the United States were electrified and urban residents were, therefore, exposed to EMFs in their residences and at work, while rural residents were exposed to varying levels of EMFs, depending on the progress of rural electrification in their states. In 1940, only 28% of residences in Mississippi were electrified, while five Southern states had less than 50% of residences electrified. Eleven states, mostly in the Northeast, had residential electrification rates above 90%. In the highly electrified Northeastern states and in California, urban and rural residents could have similar levels of EMF exposure, while in states with low levels of residential electrification, there were potentially great differences in EMF exposure between urban and rural residents. It wasn't until 1956 that these differences finally disappeared. What was already known by then, but not appreciated, was that urban death rates were much higher than rural rates for cardiovascular diseases, malignant neoplasms, diabetes, and suicide in the 1930 and 1940 United States mortality data. In 1930, urban cancer death rates were 58.8% higher than rural cancer death rates. Rural death rates were significantly correlated with the level of residential electric service by state for most of the causes examined. It is difficult to believe that mortality differences of this magnitude could go unexplained for more than 70 years after first being reported, and 40 years after they had actually been noticed and commented upon. I suspect that, in the early part of the twentieth century, nobody was looking for answers or knew how to properly frame the appropriate broad epidemiologic questions. By the time EMF epidemiology began in earnest in 1979, the entire population was exposed to EMFs. There was then simply no way to find an unexposed control group; therefore, all studies were potentially biased. Cohort studies, which follow groups of people forward in time, were by then using EMF-exposed population statistics to compute expected values, and case-control studies were comparing more exposed cases to less exposed controls. By way of analogy, the mortality from lung cancer in two-pack-a-day smokers is more than 20 times that

of nonsmokers, but only three times that of one-pack-a-day smokers. Extending that analogy to EMFs, after 1956, the EMF equivalent of a nonsmoker ceased to exist in the United States, with the exception of the small Amish population. The inescapable conclusion of these findings is that the twentieth century epidemic of the so-called diseases of civilization, including cardiovascular disease, cancer, diabetes, and also suicide, was caused by electrification and the unique biological responses we have to it. A large proportion of these diseases may therefore be preventable.

We are electrochemical soup at the cellular and organ level. Think of ECG (electrocardiogram), EEG (electroencephalogram), and EMG (electromyogram). We evolved in a complex EMF environment with an interplay of natural terrestrial and extraterrestrial EMF sources from solar activity, cosmic rays, and geomagnetic activity. I believe that our evolutionary balance, developed over the millennia, has been severely disturbed and disrupted by man-made EMFs. I believe that man-made EMFs, especially dirty electricity, are chronic stressors and are responsible for many of the disease patterns of electrified populations. The dramatic differences in mortality in 1940 U.S. data between electrified urban areas and nonelectrified rural areas are reported in detail in a 2010 paper[8] (see Figure 46.2).

The 2008 study at the La Quinta, California middle school was followed by a study at Vista del Monte elementary school in North Palm Springs, California. This school, like many others, had a cell phone tower on campus within 40 feet of a classroom wing. The teachers at this school reported a cancer cluster in the office and teaching staff, and hyperactivity in students in certain classrooms. The entire school had very high dirty electricity readings. Their dirty electricity levels were higher than those at the La Quinta school. The Vista del Monte G/S readings averaged 1300 compared to 750 at La Quinta. The cancers (12 cancers, including six female breast cancers among 75 personnel employed at the school since 1990) were over-represented in the wing of the school closest to the cell tower, and the G/S readings were highest in the classrooms closest to the cell tower base. At the same stage of the investigation, La Quinta school had 11 cancers in 137 teachers. A fourth grade teacher complained that her students were hyperactive and unteachable. The outlets in her room measured over 5000 G/S units. On a Friday afternoon after school, I reduced the measured dirty electricity in the wiring from over 5000 to less than 50 G/S units with five plug-in capacitive filters from Stetzer Electric. With no change in either cell tower radiation or the lighting, the teacher reported an immediate dramatic improvement in student behavior in the following week. They were calmer, paid more attention, and were teachable all week except for Wednesday when they spent part of the day in the library. Later, the teacher told me that she could change the behavior of the children by removing and reinserting the filters. The change took between 30 and 45 min. This young teacher also became the thirteenth cancer case in this small teachers' cohort. On January 25, 2011, I presented my findings to the Palm Springs Unified School District Board of Education. I sent the Powerpoint of my presentation in advance. I was surprised to learn at the last minute that the board had hired Leeka Kheifets to contest my findings and had provided her with a copy of my presentation. Of course, I had not been given a copy of her presentation. I offered to filter the school at no cost to the district, guaranteeing an improvement in student test scores and attendance. My offer was refused.

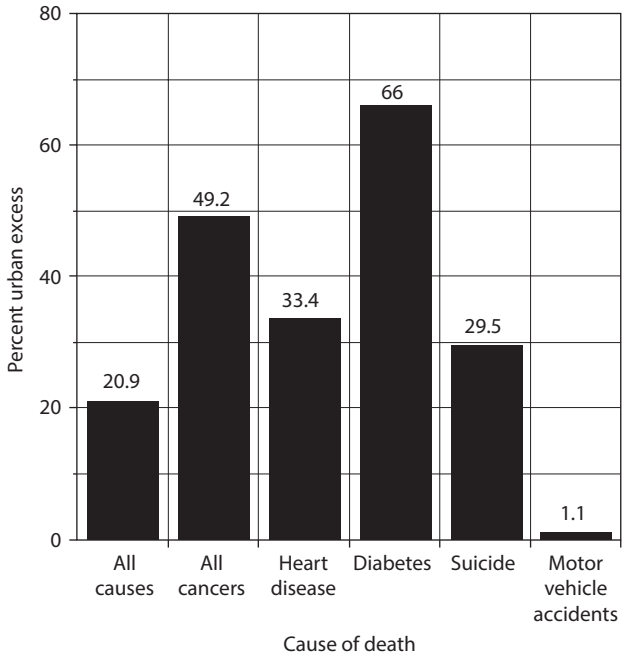

FIGURE 46.2 1940 U.S. white resident crude death rates: percent urban excess.

CELL TOWER TRANSMITTER TOXICITY

Cell tower transmitters, like all transmitters, operate on direct current (DC). They also use the DC to charge their backup batteries. The utility 60 Hz AC is changed to DC by a switching power supply which generates dirty electricity which contaminates the grid. People who are concerned about health issues regarding cell towers focus on the radio frequency (RF) emissions, but dirty electricity is another unrecognized important exposure. A Brazilian study[9] showed higher cancer rates within 500 m of the cell tower base. Since the transmitted RF intensity decays as the square of the distance from the tower, the dirty electricity is the more likely cause of cancer out to 500 m.

Chronic urinary neurotransmitter changes in residents near a new cell tower erected in Rimbach, Austria, were recently reported.[10] Microwave radiation from the tower was presumed to be the active agent. The urinary catecholamine neurotransmitters were studied in volunteers over a period of a year and a half. Epinephrine, norepinephrine, dopamine, and phenylethylamine (PEA) all had significant changes in level, indicating chronic dysregulation of the stress system. Dopamine levels dropped significantly during the first year of study. PEA levels were unchanged for six months and then dropped significantly over the next year. The authors

postulated that cell tower radiation generated a chronic stress response in the residents, accounting for the great variety of morbidity and mortality that has been reported in residents near cell towers. I believe that dirty electricity and other EMF exposures are chronic stressors of electrically exposed populations, and this response is responsible for EMF associated morbidity and mortality. After reducing dirty electricity levels in an Olympia Washington public library, the urinary dopamine levels in the library staff increased.[11]

For over 80 years, economists have noted a paradoxical improvement in health indices (declining mortality rates and increasing life expectancy) during economic recessions. Mortality rates increase and life expectancy decreases during economic expansions. The title of a paper "The reversal of the relation between economic growth and health progress: Sweden in the nineteenth and twentieth centuries,"[12] sent me into historical electrification and mortality data again. The expected decline of health indicators with economic recessions and improvement with economic growth in the nineteenth century Sweden was reversed in the twentieth century, giving the counterintuitive pattern of higher mortality and lower life expectancy in economic expansions and improvement of these indices in recessions. The change or "tipping point" occurred at the end of the nineteenth century or early in the twentieth century when electrification was introduced into Sweden. All five of the reversals of annual industrial electric energy use in the U.S. between 1912 and 1970 were accompanied by recessions with lowered GDP, increased unemployment, decreased mortality, and increased life expectancy. The mortality improvement between 1931 and 1932 by state in the U.S. strongly favored urban (electrified) areas over rural areas. Rural unemployment was positively correlated with residential electrification percentage by state in 1930. The health effects of economic change are mediated by electrical exposure.[13] The improvement of health indices in Nazi occupied Europe in WWII and in Cuba during their recent economic collapse were not due to caloric restriction, but to lowered EMF exposure.

Edison's nine "Jumbo" generators had serious brush arcing problems and commutator wear. This means that from the very beginning of electrification in the U.S. in 1892 and the rest of the world, dirty electricity was being sent out into the grid. In an attempt to control the arcing, he added metallic mercury to the commutators, but this caused illness in his workers. Brushed generators and motors have the same problem today. At my request, David Stetzer captured wave forms and measured the dirty electricity from three large commercial generators. All had dirty electricity levels above 200 Microsurge meter units and dirty sine waves.

ELECTRIFICATION, DIABETES, OBESITY, ASTHMA, POST-TRAUMATIC STRESS DISORDER, AND OTHER "DISEASES OF CIVILIZATION"

In 2011 the *Lancet* published a paper listing fasting plasma glucose (FPG) and diabetes prevalence in 199 countries and territories around the world.[14] Islands are over-represented in places with high blood glucose and diabetes prevalence.[15] Seven of 10 of the places with highest FPG in males are small islands, while only one of the 10 places with the lowest FPG are. In 2011, the same group, Global Burden of Metabolic Risk Factors in Chronic Diseases Collaborating Group, also published a similar analysis of body mass index (obesity) with nearly identical results.[16] I believe that the worldwide epidemics of diabetes and obesity are both due to exposure to dirty electricity on electric utility wiring coming from ground currents, generator brush arcing, bad wiring connections, cell tower switching power supplies, computers, and electrical appliances with switching power supplies. Islands without fuel supplies are likely to import diesel oil to fuel generator sets which generate dirty electricity which rides along on the 50 and 60 Hz transmission frequencies.

De-Kun Li has published two important prospective studies showing that magnetic field exposure during pregnancy increases the risk of asthma and obesity in offspring.[17,18] If the islands of Oceania are cleaned up, it may take a generation to see the effects. I think I also know the etiology of the excess suicides, post-traumatic stress disorders, and a number of other Gulf War illnesses. About 85% of the fuel oil imported into Afghanistan and Iraq is used for air conditioning at a cost of $20.2 billion per year (2011 report). The portable diesel-fueled generator sets which power the air conditioners generate dirty electricity. The wiring also can't be very good, because of the reports of increased accidental electrocution in military personnel in Iraq and Afghanistan. Interestingly, Navy and Air Force personnel don't share the recent suicide increase seen in the Army and Marine Corps.

The highest asthma prevalence rate reported is in the population of Tristan da Cunha, a small Atlantic island with six diesel generator sets for electrical power.

The trend to "green" energy sources like wind and photovoltaic solar generating facilities will increase exposures to dirty electricity. They use grid intertie inverters and controllers to convert the power they generate into utility-grade electricity that can be sent out on the grid. I expect that commercial fuel cell generating facilities will have the same problem. The devices that do the conversion inject transients onto the grid. The dirty electricity in homes with a rooftop photovoltaic system was 60 G/S units with the inverter turned off and 600–1400 G/S units with it on. Every residential and commercial photovoltaic solar generating facility I've examined generates high levels of dirty electricity. The oscilloscope wave form has a characteristic beads on a chain appearance and is usually at 20 kHz. The high-pass filter wave form flattens out when the inverter is turned off. The wave form in Figure 46.3 was taken in a home with operating grid intertied roof-top photovoltaic solar collectors.

Wind turbine farms create two serious health problems: low frequency sound pressure waves (infrasound) caused by the turbine blades and dirty electricity caused by their inverters. Dr. Nina Peirpont has written a book called *Wind Turbine Syndrome,* and Magda Havas and David Colling have a paper describing wind farm dirty electricity.[19] At two southern California wind farms, the grid, air and earth are

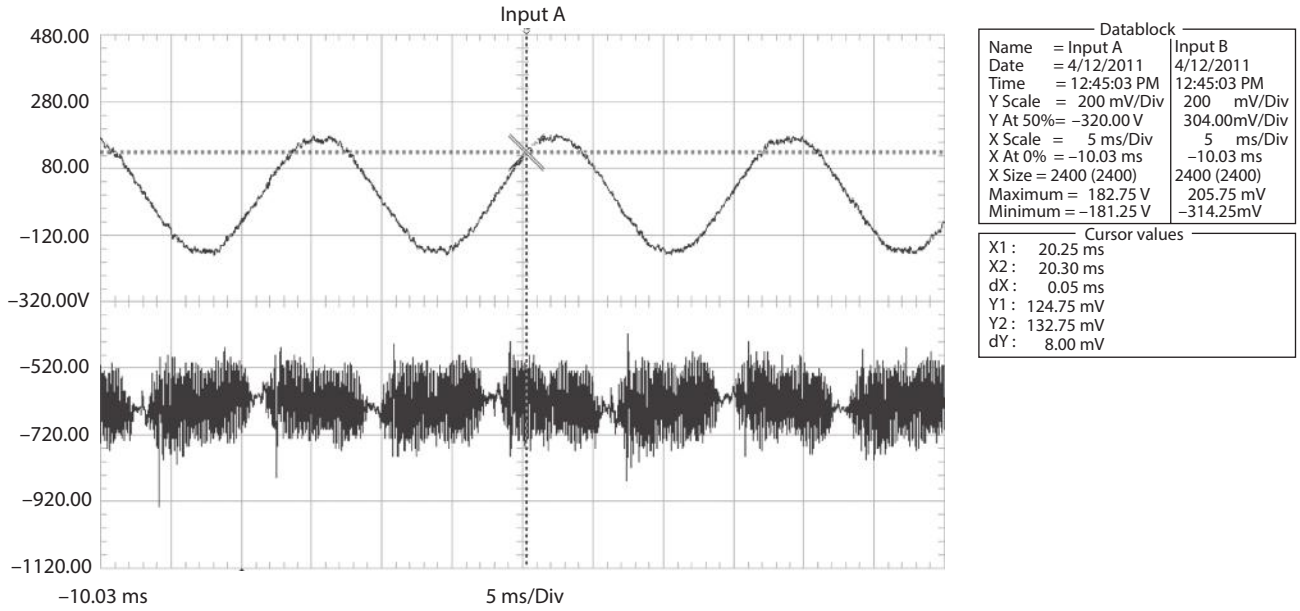

FIGURE 46.3 Santa Barbara CA home dining room outlet. Top line: input A = AC; bottom line: input B = high pass filter; 20 kHz.

heavily contaminated with dirty electricity, with 7 V in the ground and 3 V in the air at the Campo wind farm in San Diego county near Boulevard, California. The wave forms in air and the ground match peak for peak (see Figure 46.4).

The Old Order Amish (OOA) in North America live without electricity. They have less than half the cancer incidence of the U.S. population[20] and about half the type 2 diabetes prevalence as other U.S. citizens despite having the same body mass index.[21] Cardiovascular disease,[22] Alzheimer's disease[23] and suicide[24] are reported to be less common in the OOA. A pediatric group practice in Jasper, Indiana, that cares for 800 Amish families has not diagnosed a single child with ADHD, and childhood obesity is almost unseen in this population.[25] Remarkably, the life expectancy of the OOA has been about 72 years for the past 300 years for both men and women. In 1900, the life expectancy of U.S. males was 46.3 and 48.3 years for females (http://gerontology.umaryland.edu/, fall 2003. V6, No. 2). If the rest of the U.S. population had the disease incidence and prevalence of the OOA, the U.S. medical care and pharmaceutical industries would collapse.

Unfortunately, funding sources for EMF research have almost completely dried up in the United States, unlike in Europe and other countries. We have also lost a whole generation of young investigators in university, private, and government labs who were forced into other research areas by the lack of money to support this important research. Industry and cell phone money has corrupted the research process, politicians, the media, and government. After my generation of investigators has moved on, there will be nobody to take our place in the United States. Ultimately, to get a real handle on the problem, we will have to rethink how we distribute electricity and communicate. Getting rid of wireless forms of communication is a logical first step. I predict that when the latency periods (time between first exposure and diagnosis) for brain tumors have been achieved, we are in for a calamitous epidemic of cell phone-induced brain tumors. With rare exceptions, such as Lennart Hardell's work in Europe, most of the cell phone brain tumor epidemiology is of such low quality that it doesn't merit publication. With nonparticipation rates among controls around 50%, it is impossible to have any confidence in study results. I suspect that cell phone money has compromised both the investigators and the journals.

Today, homes are being built without wiring for landline telephones. The large telecommunication companies are in a race to force consumers to go all wireless. They plan to saturate urban and rural areas with Wi-Fi and Wi-Max systems, and the Federal Communications Commission (FCC) is assisting this with recommendations for private/public (taxpayer) cooperative funding. Most airlines now offer in-flight Wi-Fi. Transmitting microwaves in a metal cylinder will expose passengers and crew to reflected hot-spots. In addition, broadband internet connections transmitted over power lines (BPL) have been deployed in certain areas and are spreading quickly. This technology delivers high frequencies to every outlet in the grid. Many jurisdictions are unfortunately outlawing incandescent light bulbs in favor of the compact fluorescent bulbs (CFLs), which generate RF and high frequency voltage transients in addition to containing mercury. This, too, is a mistake. CFLs will prove more dangerous to the environment and to people than any energy savings they promise. Light emitting diode (LED) bulbs will probably be the best power saving light bulb alternative.

The electric grid should be rebuilt with wiring adequate enough to return currents to the substation without using the ground. Over 70% of delivered current returns to the utility

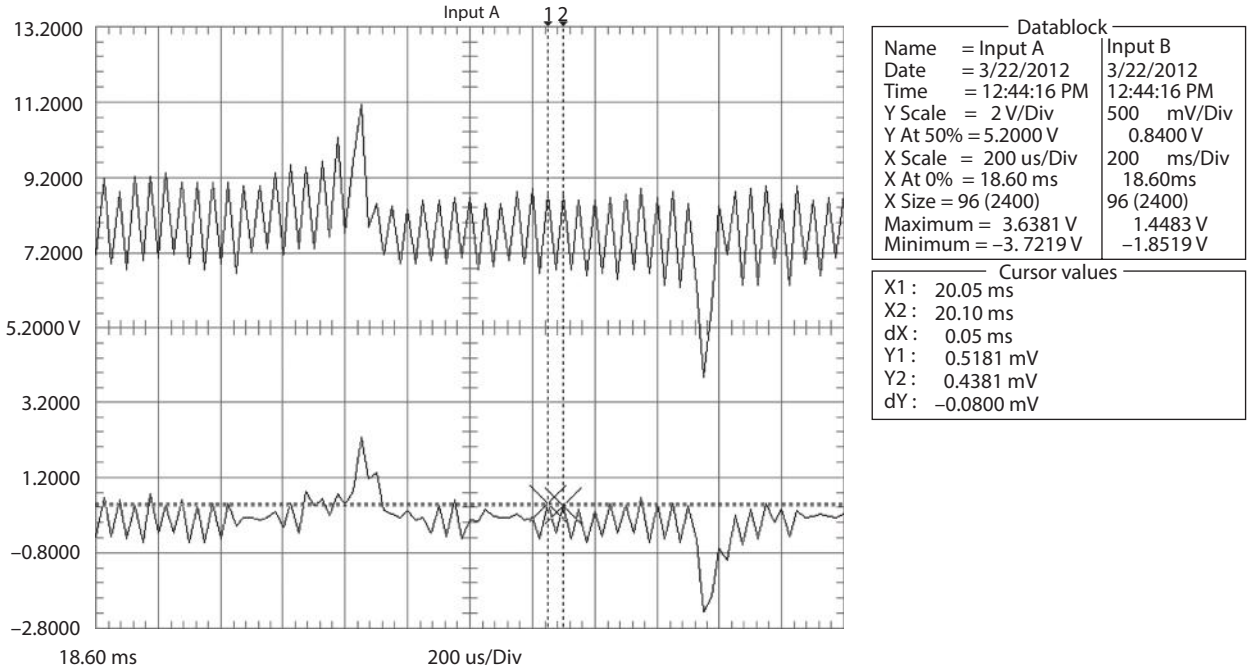

FIGURE 46.4 Manzanita Tribal Headquarters, San Diego County CA. Top line: input A= antenna in air; Bottom line: input B = ground voltage in 40 feet of wire; 20 kHz in ground and air.

substations via the earth. The grid was originally built for return currents to travel over wires. It should also be possible to reduce the high frequency voltage transients from the electricity delivered to our homes and offices. Similarly, since the electronic equipment of cell towers and terrestrial RF transmitters (AM, FM, TV) operates on direct current, the inverters and switching power supplies that change the AC line voltage to DC, interrupt the current flow, and inject dirty electricity into the grid that powers them. I'm sure it is possible to build inverters that won't generate dirty electricity, but until rules and regulations force this, power quality will be sacrificed for profit.

Recent deployment of "smart meters" for residential electricity, water, and gas billing at homes and businesses emit RF and dirty electricity, since the smart meter transmitter operates on DC, using a switching power supply to convert the grid AC to DC. The billing information could be sent over existing phone lines, or over fiber optic lines. Other "smart grid" schemes for self-regulating appliances will also increase residential RF exposure. Most new appliances have microwave transmitters built into them which communicate constantly with the smart meter.

Since most of the electricity that is generated is literally used to turn the wheels of industry with electric motors, it is important that they be made as clean as possible. There is a recent trend toward variable speed motors that generate a lot of dirty electricity. Most new furnace fan and air conditioner motors use variable speed motors to minimize electricity use.

The explosive recent increase in RF radiation and high frequency voltage transient sources, especially in urban areas from cell phones and towers, terrestrial antennas, Wi-Fi and Wi-Max systems, broadband internet over power lines, and personal electronic equipment, suggests that like the twentieth century EMF epidemic, we may already have a twenty-first century epidemic of morbidity and mortality underway, caused by high frequency electromagnetic fields. The good news is that many of these EMF diseases may be preventable by simple environmental manipulation, if society chooses to pay attention. Unless public outrage intervenes, I'm afraid that our "diseases of civilization" will only get worse.

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47 Electrosensitivity
Sources, Symptoms, and Solutions

Andrew Tresidder and Michael Bevington*

CONTENTS

CONCEPTUAL CONTEXT AND DESCRIPTION OF TERMS

"*Electrosensitivity doesn't exist because it can't!*" This was heard recently from an eminent authority, writer of many peer-reviewed papers on a number of health subjects. "*If it doesn't heat tissue, it can't cause damage!*" Two hundred years ago, eminent authorities might have denied the existence of electricity itself—as a mere fairy story told to amuse them—whilst some 300 years before that everybody *knew* that the sun revolved around the earth (that is until Copernicus published his *De Revolutionibus Orbium Coelestium*, just before his death in 1543). "*Electrosensitivity doesn't exist because it can't!" is merely an evolutionary position of (mis)understanding, held at a point where a person does not yet comprehend the mechanism.* Personally, though I learnt physics at medical school, the concept of electrons moving along a wire is as good as a fairy story to me—I've never seen an electron!—but I am happy to take the explanation on trust, and turn the switch and accept that the lights will come on!

Electrosensitivity (ES), Electromagnetic Sensitivity, Electromagnetic Hypersensitivity (EHS) or Idiopathic Environmental Intolerance is the phenomenon where the human organism experiences symptoms from exposure to the stimulus of electromagnetic (EM) fields of certain strengths and frequencies (including radiofrequency (RF) microwave transmissions), which symptoms then abate and disappear after the stimulus ceases. "Idiopathic" is a term coined from the Greek, used frequently with authority (as is much medical descriptive terminology) and which means "suffering" (pathic) "from itself" (idio)—thus a term which actually says "it's true, but I don't understand the mechanism"—as in Essential, or Idiopathic Hypertension, a medical state which afflicts millions of patients in the world.

Failure to understand the mechanism does not invalidate the state that the patient is suffering—although it does make it less easy to heal rather than palliate a disease process—because if the mechanism is not understood, then it is less convincing to some people to approach healing resolution by the time honored medical approach of "Tolle Causam" (Latin for "Take Away the Cause"), that is, to recognize that biological organisms are designed to be healthy self-repairing devices with a default setting of restoring self to health, given the presence of the right (supportive) internal and external conditions and the absence of the wrong conditions (such as noxious stimuli). This may lead (as in the case of essential hypertension) to treatment of certain parameters to restore "normality" without healing resolution back to the design default of health—which is not the same as allowing the organism to be healthy again within a healthy environment. Remember that Pasteur, father of the "germ theory" of external causation by a single agent, said on his death-bed "*Bernard avait raison. Le germe n'est rien, c'est le terrain qui est tout." [Bernard was right. The microbe is nothing, the soil is everything]. Pasteur, L., quoted in Selye.*[1] Thus even the great Pasteur was big enough to admit that his own understanding had only been part of the truth.

It is inappropriate to criticize those who do not yet understand, but to try to share current understanding—for society's understanding is the product of our education and the

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sum and overview of our (often super-specialized) learning to date. As the Chinese proverbs say:

> Man who looks at sky from bottom of well sees only small part of sky.
>
> Man trained to use hammer sees many things as a nail.

In these days of the specialization of learning from early years, there is not always the cross-discipline understanding that there could be. For instance, most of biomedicine still ignores the insights from quantum mechanics and relativity, whilst within a single discipline there is often the danger of the development of "intradisciplinary group-think." Of course such group-think may be right, or it may be wrong—but it will certainly always be the product of prevailing fashions, influenced by the prejudices of the times, and also by vested interests.

A wise professor at medical school told students that today's heresy would be tomorrow's dogma and then be held to be redundant knowledge in only a few years. For it is easier for all of us to cling to the security of what we believed yesterday, than to change our minds, as Copernicus found out—and wisely avoided excommunication and possible execution for heresy by delaying publication until he could avoid the consequences of a world hierarchy made angry by what he asserted. By the way, what did *De Revolutionibus Orbium Coelestium* do?—it turned on its head the prevailing world belief that the sun circled the earth (and not the other way around).

So this paper has been put together by a Classicist trained in cross-discipline thinking and a GP with a holistic view of health, led to the subject by personal experience and by experience which has helped a number of patients, affording unique insights and a motivation to look clearly at a subject with a desire to illuminate the area. The same authority quoted above as saying "Electrosensitivity can't exist" also commented on the World Health Authority's 2011 classification of RF transmissions as Class 2b (possible) carcinogens as being "Well it's only Class 2b, it's pretty weak and not important." The same comments were probably uttered by eminent authorities about the "merely hypothetical and unproven" dangers from tobacco, asbestos and lead in petrol just a few short years ago.

When society faces important truths which are inconvenient (especially to vested interests) and require courageous action and leadership, there is a great tendency to denial on many levels, and a great temptation to "shoot the messenger," pretend that the issue is either psychological, a placebo or nocebo response, a media driven psychosis, or discredit the patients' honest stories, or threaten legal or other action. And some vested interests have powerful lobbies. However, though everybody is guided by best intention, they may not always see the whole picture. Throughout history, early (and unwelcome) messengers have been criticized, dismissed, vilified, or sometimes executed…

Technological advances usually benefit society and may move forwards rapidly—witness the Industrial Revolution, the spread of steam power and rail transport. Later we see the spread of electricity, personal road transport (cars etc.), electronic communication and air travel. Safety considerations *always* lag the technological advances—and are often resisted vociferously by the industry concerned. The highest rate of road deaths per miles travelled by car was in the 1920s—in small part due to driver inexperience, but in large part due to little or evolving safety considerations. For example, until enough people died or were injured, the importance of adequate tread on tires was unknown—and then ignored—only finally being dealt with by legislation many years later. Another example is the resistance by car manufacturers to factory fitting of front and rear safety belts—presumably on the basis of human choice (to exit the vehicle through the windshield) but in reality on cost grounds.

Considering electrosensitivity, it is interesting that product liability insurance for health issues for mobile phones and other such transmitting technology is avoided by many of the major insurers who understand the potential risks. Perhaps they suspect something that the rest of us are not being told?

What is the biological basis for ES? We will approach this after noting the current classifications used worldwide—but not as yet in common usage in most countries.

Current Classification of Electromagnetic Hypersensitivity

Nordic Council of Ministers (2000): ICD-10.R68.8: "Electromagnetic intolerance" or "el-allergy" is a multisymptomatic idiopathic environmental intolerance[2] (or ICD-10.Y68.8 for occupational cases). Symptoms disappear in a nonelectrical environment.

WHO (2005): EHS is characterized by a range of nonspecific symptoms. A more general term for sensitivity to environmental factors is Idiopathic Environmental Intolerance: IEI-EMF.[3]

WHO publication (2007) ES is "not a known psychological disorder."

Austrian Medical Association (2012): ES as ICD-10.Z58.4

BIOLOGICAL CONTEXT

Biological organisms are intrinsically electromagnetic. The trillions of humming cells in a human being each contain electrical DC current flows, and these currents coordinate together in synergy throughout the body. One example of a synergistic coordination detectable by gross electrical measuring devices is the electrical effect of billions of specialized cardiac cells—readable by all doctors as an ECG.

Our bodies were developed over millions of years against a background radiation level of minimal signal apart from solar flares. Current man-made signal levels are in places many trillions of times this level. Our bodies have developed organs of special sense which are exquisitely sensitive to certain frequencies of the electromagnetic (EM) spectrum—such as down to a photon or two of visible light, or a billionth of a

watt of sound. Amplification systems include cellular calcium and other mechanisms. It seems entirely possible that cells are sensitive to other RF as well. Animals across a wide range of species detect the tiniest of changes in magnetic fields for navigation and have been doing this for over 100 million years. This is a detection and response to EM fields of minute signal strength—not thermal power effects. There is growing evidence that man-made EM fields are disrupting this ability to navigate using the earth's magnetic field.[4]

Case Study 1

Case 1 is Mr P, aged 62, who presented with a two year history of regular headaches since moving house. A retired headmaster and IT teacher, he had no previous history of headaches despite a busy job. The headaches were frontal and occipital, and varied over time. The current house had the telephone socket in the bedroom, and the WiFi router adjacent. A signal detector confirmed a high field strength in the room and near the bed, of up to 3 V/m and over 1000 μW/m^2 (the normal background field strength in the environment is <0.02 V/m and <1 μW/m^2). The router, as per its technical design, generated signal 24 hours a day, and with up to a 50 m radius. He was advised to remove the router from the bedroom and switch it off whenever not in use, with the effect that he changed his exposure from 168 hours a week in close proximity to 10–20 hours at a distance. He was advised that it could take up to a week for his body to become symptom free, due to the phenomenon of Adaptation/Resistance (Selye) and the time taken for a healing resolution.

Blood tests were organized, and a brain scan considered. Two weeks after first presentation, he was able to confirm that four days after making the changes he had become headache free, and had remained so ever since. His words at the time were "I now feel as though I have been inside a microwave oven for some time—my headaches have gone and the itching of my head has settled." Blood tests showed no abnormalities in Full Blood Picture (FBP), erythrocyte sedimentation rate (ESR), urea and electrolytes (UEs), or liver function tests (LFTs). The planned scan was deferred (and the cost saved). One year later he remains headache free, although prolonged exposure to transmitting technology can bring back his headaches.

Sensitivity is the response of the organism to a stimulus. Sensitivity is characterized by the appearance of symptoms or signs in response to a stimulus, and the disappearance after removal of the stimulus. It is part of the body's design responses that enable discrimination between Self and non-Self, the monitoring of the environment and the organism's response to environmental pressures.

Most biological organisms are not only electromagnetic, but also inherently magneto-sensitive, with genes known as cryptochromes responsible for this ability.

The power effect of an EM RF field is measured in safety terms, according to the International Committee on Non-Ionizing Radiation Protection (ICNIRP), relevant to the thermal (heating) effects on tissue over six minutes. The signal effect of an EM RF field is the nonthermal effect on biology—and of course EM signaling is used widely by the body, in special sense organs, and throughout other tissues. All cells use very low potentials of DC current across membranes, so the body is already electrically sensitive. So to pretend that these nonthermal effects do not exist is to ignore elementary biology and physics; however it is an interesting line of thought for some to be diverted by, and no doubt convenient to certain vested interests.

It is not the purpose of this chapter to argue the merits of various safety limits, but we note that those of ICNIRP are being superseded around the world by far more stringent limits. There are always leaders and slow adopters; the UK has the unenviable record of being one of the late nations to severely restrict the use of x-rays in obstetric practice—up to 50 years behind some nations—when the incidence of childhood cancer was already suspected and proven to be a result of exposure *in utero*.

Specialized animal organs of sense include the eyes (sensitive in an adapted state down to a single photon), the ears (sensitive to environmental vibrations of minute amounts), the nose (sensitive down to a single molecule of some scents), and vibration (sensitive to minute movements, such as in the earthworm and others). There are other senses than the big five of sight, hearing, taste, smell and touch—some birds are known to navigate by a magnetic compass developed over 90 million years ago, whilst magnetotactic bacteria stem from ancestors from two billion years ago. In pigeons, the inclination sensitivity of the magnetite receptors in the beak is between 0.02 and 0.17 degrees, down to 0.01 μT (10 nT) (incredibly sensitive!). (By comparison, the earth's magnetic field is 50 μT (50,000 nT), whilst current ICNIRP safety limits for magnetic field exposure are 100,000 nT, and the recent Bioinitiative report proposes a limit for chronic exposure of 100 nT.)

Human cryptochromes are shown to be magnetosensitive.[5] The human brain also contains magnetite, particles synthesized within the body (for what purpose?) of 10–70 nm, of 90–200 nm and some of 600 nm size.[6] In the pia and the dura, there are over 100 million crystals per gram—and the larger particles could transduce a 50 Hz field at 0.4 μT (as well as mobile phone frequencies).

Hypersensitivity, whether due to allergens such as pollen and house dust mite giving respiratory symptoms, due to food components giving rise to urticaria, or other allergens, is considered to be the result of antigen/antibody complexes. It results in type 1, 2, 3, or 4 hypersensitivity reactions. Although electrical fields have physical mass, everybody thinks that they cannot be antigens that fit into a receptor on the cell's surface (because they are "too small to be physical antigens")—so it requires a small conceptual step to remember that the symptoms of sensitivity reactions are generated by inter cell signaling, and that inter cell signaling occurs as

a result of individual cell reaction, again modulated by signaling. What is the nature of this inter- and intracellular signaling? We know that neurotransmitters diffuse at a speed of a few cm/s, and nerves transmit electrical impulses at speeds of up to 6 m/s—both of which are painfully slow compared to the speed of thought or of reactions from the cerebellar system as we walk over rough ground. However, it is the cell membrane that acts as a physical and insulating barrier (with protein molecules in the walls which may act as semiconductors), with different concentrations of ions between inside and out—and different electrical potentials. In fact, there are continuous minute DC currents in action both inside and outside cells, with changes in function mediated by switching (like a transistor semiconductor in electronics) in response to changes in potential due to ion gradient changes. For instance, as a response to injury, a cell membrane allows an influx of Ca^{++} ions down a huge concentration gradient, with major resultant changes in function and behavior. Initially a cell may respond to this stimulus by repair, but continued noxious stimuli in excess of the capacity of the repair mechanism result in ongoing damage and production of free radicals with resultant disordered function and, at a cellular level, ill health. Study of the field of calcium metabolism in living organisms has been led at Imperial College, London by Andrew Goldsworthy.

Nerve cells send off signals that are assumed to reflect activity from the organ they innervate—just as a telephone wire carries a clear signal from one person to another. However, if the wire itself is damaged, bent, broken, or wobbled, then the signal becomes distorted. Skin cells repair themselves, and carry out normal functions—however if irritated or damaged, histamine and other responses can result, with rashes or irritation being the body reaction.

It is entirely possible that sensitivity symptoms can originate either from irritation of the tissues which send a distress message, or from disruption of the nerve cell function or other signaling mechanism, or from an inherent sensitivity to the signal effects.

Human beings, in common with other mammals, have a design default of "health"—and a physiology designed to restore health after noxious insults. However, there is a "bucket effect." The organism can cope with only so much insult at a time, and only so much in total, before vitality is eroded. The bucket can process insults A, B, C, D, E, and F perfectly adequately—one at a time and in isolation. However, put ABCDE and F all together at the same time, the bucket overflows, and the organism becomes overwhelmed. Health then degenerates into a disease state—preceded by symptoms of sensitivity as the organism seeks to restore balance.

Many humans feel headaches before a thunderstorm, arising from an increased electrical tension in the atmosphere (irrespective of barometric pressure changes). The headaches resolve when the storm has broken. This is a normal phenomenon of electrosensitivity, known personally to many people.

Geomagnetic storms arise from charged particles from the sun. Those of interest last one to five days at around 100 nT. Acute health effects in humans observed include an increase in depressive illnesses, melatonin disruption, heart rate variability, and blood pressure changes,[7] whereas in bees a magnetic storm day resulted in a change in nest-exiting directions.[8]

Ants lose their ability to forage,[9] with changes in linear and angular locomotion, when exposed to RF signal such as that from wireless equipment like mobile phones, smartphones, digital enhanced cordless telephone (DECT) phones, WiFi routers—and can die.[10] The authors wryly note "One very elegant feature of using ants as experimental animals is—as for other animal species, plants and bacteria—that they do not lend themselves to psychological explanatory models, such as mass media driven psychoses. If they react to artificial electromagnetic fields, it is not because they have listened to radio broadcasts, watched the TV news or read columns in tabloids. No, then they do react to the actual adverse environmental exposure."

Fruit flies are also particularly sensitive to RF signals.[11] All EMF sources used created statistically significant effects regarding fecundity and cell death-apoptosis induction, even at very low intensity levels (0.3 V/m bluetooth radiation), well below ICNIRP's guidelines, suggesting that *Drosophila* oogenesis system is suitable to be used as a biomarker for exploring potential EMF bioactivity.

Human health is a delicate balance. It can be adversely affected by interfering factors including chemical pollution, smoke, pollens, molds, the food we eat, what we drink, lack of sleep, lack of fresh air, lack of sunlight, lack of fresh water and so on.

Observed effects and possible mechanisms of EM fields and RF transmissions include calcium ion influx into cells, autonomic upregulation, disruption of endocrine balance and melatonin production, heat shock protein stimulation, blood–brain barrier interference, radical pair spin disruption due to the Zeeman effect discovered in 1896 (causing breaks to appear in DNA due to failure of recombination), transduction effects around magnetite particles in the brain and interference with body intracellular signaling systems. As a noxious stimulus with biological effects, it would be surprising if the presence/absence of EM fields did not have effects on human health synergistically with all the other factors noted above—and for a sensitive being such as a human, the first things to be noticed may be symptoms rather than gross tissue pathology…

Agarwal[12] in Cleveland published an observational study correlating mobile phone use with decrease in sperm quality, the review by Vignera et al.[13] confirms this across species including man, whilst Gye and Park[14] from Korea reviewed the adverse effects of EM field exposure on sperm, germ cells, endocrine hormonal cycles, embryonic development and pregnancy success.

In view of the biological provenance, and the proven biological effects of weak extraterrestrial electromagnetic fields on human health and symptoms, and the adverse effects on biology of many species including humans—it would be indeed surprising if some human beings did *not* have symptoms from electromagnetic fields, especially those way

in excess of the background adaptive level. Readers of the other chapters in this book may not be surprised by this—if therapeutic physical effects can be achieved by weak EM fields—then it is not stretching credibility to think that mere symptoms could also be caused by EM fields!

> Electromagnetic (EMF) pollution may be the most significant form of pollution human activity has produced in this century, all the more dangerous because it is invisible and insensible.
>
> **Dr. Andrew Weil, MD**

Genuis and Lipp (2011) have published a comprehensive paper titled "Electromagnetic Hypersensitivity: Fact or Fiction?" which scopes and analyzes the whole field from an orthodox scientific view, complementing the present article which seeks also to give philosophical context and biological rationale.[15]

SYMPTOMS

Many studies list symptoms from mobile phones and masts, radio and TV masts, and power lines.[16–51]

Symptoms may be none, or include tiredness, poor quality sleep, irritability, heart palpitations, headaches and a feeling of pressure in the head, speech and thinking disturbance, brain fog, dizziness, tinnitus, vertigo, tinglings and odd sensations in the limbs, joint pains, rashes, and others.

Prevalence of EHS: many studies give 3%–5% of the general population.[52,53] The WHO (2005) stated: "A survey of occupational medical centers estimated the prevalence of EHS to be a few individuals per million…a survey of self-help groups yielded much higher estimates. Approximately 10% of reported cases of EHS were considered severe… The reported incidence of EHS has been higher in Sweden, Germany, and Denmark, than in the UK, Austria, and France." Others suggest 3% show severe symptoms, 35% moderate and up to 50% mild.

Prevalence of Doctors accepting ES: In 2009 29%–58% of German GPs "associated EMF with health complaints,"[54] and in 2006 Swiss GPs "judged the association…plausible" in 54% of cases.[55] The Austrian Medical Association issued EHS guidelines in 2012.

Case Study 2

Case 2 is Mrs S, a 54 year old female. I found her a credible and truthful witness. She gives a history of symptoms of severe head pain, nausea, dizziness (which can make her faint), chest pain, tingling skin/nerves, blanks in her visual field of up to 50%, insomnia resulting in constant tiredness and an inability to concentrate or remember things as a result of all of these. She has identified that these symptoms are brought on when she is in the vicinity of WiFi, mobile phones and "smart" technology, although she suffered for several years before making this link. Having made the link, she is able to avoid them as much as possible, and when free from them becomes symptom-free.

She describes times when her thoughts feel jammed, unable to remember pupils' names, and a train of thought disappearing. Initially concerned that she might have a brain tumor, she sought help from her GP and a Neurologist. Fortunately investigations have ruled out such a cause.

However, she became so ill that she was unable to continue working in her post as a Secondary School Teacher and had to hand in her notice. At this point she had not yet identified the environmental triggers of wireless technology that cause her disability and illness. Since then, she has had exposure levels measured at work, and found that they are extremely high, at between 3 and 6 V/m—many sensitive people are symptomatic at as little as 0.02 V/m, and the ambient level in a wireless free house is <0.02 V/m.

She has, of course, eliminated all wireless technology from her home, however the school environment has high levels of wireless signal, widespread use of mobile phones, and uses smart technology such as interactive whiteboards. It is therefore not possible for her to work there. Other schools have similar levels of use of wireless technology.

She has been supported by her GP and by her NHS Neurologist, both of whom have noted the connection with wireless technology. Her GP and neurologist suggested using amitriptyline and dosulepin to downregulate her sensitivity (not as antidepressants) but these agents were not effective.

Currently, when exposed to domestic wireless technology, such as on a recent visit to a relative's house, she rapidly becomes symptomatic within minutes to the extent of disability and an inability to concentrate sufficiently to drive. She is unable to stay in houses, hotels or other accommodation with wireless technology without becoming symptomatic, sometimes severely. She describes passing certain mobile phone masts on roads and feeling severe symptoms as though someone was trying to stick an axe through her head, a feeling that abates when she has passed the mast.

An area with good signal coverage is in effect a polluted area which gives rise to increasing symptoms for Mrs S.

This is a clear history of neurological and other system symptoms in response to environmental exposure to transmitting technology, and which abate when exposure ceases.

The diagnosis is electrosensitivity (severe degree), a diagnosis understood in Sweden for many years, but only recently becoming known by the medical community in the UK. Indeed, many physicians may not yet have heard of it, and certainly did not learn about it at medical school. Fortunately, the Austrian Medical Association (2012) adopted a guideline for differential diagnosis and potential treatment of unspecific stress-related health problems associated with electrosmog including wireless signal pollution. Its core element is

a patient questionnaire consisting of a general assessment of stress symptoms and advice on specific assessment of electro-smog exposure. The guideline is intended as an aid in diagnosing and treating EMF-related health problems. It is thought that perhaps 20% of the population are mildly affected (and may not realize), around 3%–5% moderately, and less than 1% severely affected. In Sweden, the illness/disability is recognized as such, and taken account of by medical and other approaches.

The condition is managed by attention to health, and above all by avoidance of unnecessary exposure. Should Mrs S be exposed to levels of wireless signal for more than short periods of time, her ability to recover from each episode of exposure is likely to diminish, her level of functioning during that time will be impaired and her health will further suffer.

The implementation of transmitting technology has been rapid (in evolutionary terms) and current UK safety levels for exposure are based largely on thermal heating effects of electromagnetic radiation. We are becoming aware that the signal (not power) effects of transmitting radiation affect biological systems by a number of mechanisms including upregulation of the adrenocortical axis, affecting the blood–brain barrier, calcium influx into cells, and disruption of inter- and intracellular signaling (a bit like jamming the enemy's radar…). As yet, UK safety exposure limits take little account of these factors.

The following Table 47.1 is of symptoms noted over a series of years of research.

Notes on Symptoms

- *Accumulation*. Cumulative exposures can produce symptoms, making symptoms from chronic exposure more difficult to recognize than from acute exposure.[56]
- *Delay.* Symptoms can be delayed after acute exposure for a few hours[32,57] or even days. This is said to become more common the longer the patient has been sensitized.
- *Diurnal state.* Symptoms vary according to the diurnal state of the person's body. A person's own

TABLE 47.1
Symptoms

Auditory
Earaches
Imbalance
Lowered auditory threshold
Tinnitus

Cardiovascular
Altered heart rate
Chest pains
Cold extremities especially hands and feet
Heart arrhythmias
Internal bleeding
Lowered/raised blood pressure
Nosebleeds
Shortness of breath
Thrombosis effects

Cognitive
Confusion
Difficulty in learning new things
Incoherent talk (temporary or permanent)
Lack of concentration
Short/long-term memory impairment
Spatial disorientation
Spoonerisms

Dermatological
Brown "sun spots"
Crawling sensations
Dry skin
Facial flushing
Growths and lumps
Insect bites and stings
Severe acne
Skin irritation
Skin rashes
Skin tingling
Swelling of face/neck

Emotional
Anger
Anxiety attacks
Crying
Depression
Feeling out of control
Irritability
Logorrhoea/verbosity
Mood swings

Gastrointestinal
Altered appetite
Digestive problems
Flatulence
Food intolerances

Genito-urinary
Smelly sweat/urine
Urinary/bowel urgency

Musculoskeletal
Aches/numbness/pain/prickling sensations in bones, joints and muscles in ankles/arms/elbows/feet/hips/legs/lower back/neck/pelvis/shoulders/wrist
Cramp/tension in arms/legs/toes
Muscle spasms
Muscular paralysis
Muscular weakness
Pain in lips/jaws/teeth with amalgam fillings
Restless legs
Tremor and shaking

Neurological
Faintness, dizziness
"Flu-like" symptoms
Headaches
Hyperactivity
Nausea
Numbness
Sleep problems
Tiredness

Ophthalmologic
Eyelid tremors/"tics"
Impaired vision
Irritating sensation
Pain/"gritty" feeling
Pressure behind eyes
Shiny eyes
Smarting, dry eyes

Other physiological
Abnormal menstruation
Brittle nails
Hair loss
Itchy scalp
Metal redistribution
Thirst/dryness of lips/tongue/eyes

Respiratory
Asthma
Bronchitis
Cough/throat irritation
Pneumonia
Sinusitis

Sensitization
Allergies
Chemical sensitivity
Light sensitivity
Noise sensitivity
Smell sensitivity

Source: Adapted from Bevington MJ. *Electromagnetic Sensitivity and Electromagnetic HyperSensitivity: A Summary*. Capability Books: Bucks; 2013. With permission.

endogenous electromagnetic field often declines during the day.
- *Duration.* Individual symptoms can last for a short or long time. As a group symptoms can become worse. They can fade after two to 12 months without electromagnetic radiation (EMR) exposure.
- *Frequencies.* The sufferer may react first to a single frequency or source but later to more (e.g., first to WiFi but later to mobile phones and power cables).
- *Intensity.* As the condition progresses the level of sensitivity can increase: a person may first have pains from a phone next to the head but later from one at three meters.
- *Ionizing similarities.* Studies indicate symptoms from exposure to electromagnetic (non-ionizing) radiation are similar to those from radioactive (ionizing) radiation.
- *Severe reactions.* Severe reactions can include paralysis, convulsions, seizures, loss of consciousness and stroke, or they can exacerbate an existing medical condition.
- *Variety.* Individual variation in tissue/bone density, acidity, salt content, skin conductivity, size, and so on, affect absorption.[58] This may relate to the variety of symptoms.

SOURCES OF ELECTROMAGNETIC RADIATION

Human beings, as other organisms on the planet, developed over millions of years in an environment of day and night, seasons, blue (sky) and green (plants), and a background EM field from the earth of around 50 μT—with NO man-made artificial sources.

One hundred and fifty years ago there was no such thing as mains electricity—and the only high voltage phenomena were the natural ones of lightning discharges.

A hundred years ago mains electricity using alternating current was in its infancy—it is now ubiquitous. Milham has chronicled the interesting epidemiological phenomenon of child leukemia remaining rare in rural USA until electrification in his seminal book *Dirty Electricity.*[58]

Fifty years ago wireless technology meant television, radio, and radar. The only home transmissions were for radio hams (home radio transmitting enthusiasts)—who knew all about the dangers of being too close to the transmitter. Cordless phones, mobile phones and masts, and microwave movement detectors such as in home alarm systems were all dreams for the future, let alone wireless routers, wireless central heating controls, interactive whiteboards, smart meters, Blackberries, iPhones and laptop and palm computers that can only work by wireless.

Electromagnetic problems for biological organisms, including humans, are caused by

1. *Field effects* from cables and appliances (such as lights, hairdryers, washing machines, cookers, bedside radios, etc.).
2. *Signal and power effects* from microwave transmitting technology, such as microwave ovens, mobile phone masts, cordless phone base stations and handsets, mobile phones, wireless routers, Wii devices, laptop computers, printers, home and office alarm sensors, iPads, Blackberries and other smart phones, baby alarms, smart meters for utilities, wireless central heating controls, and Bluetooth devices in the car.
3. *Dirty electricity*—This is the phenomenon of (jangly) transient high frequency harmonics in mains electricity supplies superimposed on the (smooth) 50 Hz sine wave—sources are rapid switching devices such as in computers, and so on, fluorescent lighting, dimmer switches, and ingress from external sources such as mobile phone masts.

Table 47.2 gives an overview of sources.

There are individual risk studies.[59–62] For total RF exposure, the most frequent risks are: phone masts, mobile phones and DECT phones.[63,64] MF exposure is highest at home.[65]

Case Study 3

Electrosensitivity—A Personal Story—Dr. Andrew Tresidder MBBS MRCGP

I've always considered myself healthy, but had mumps as a junior doctor. This hit me so hard that I had to take three months off work, for it took this long to recover my energy—a post-viral fatigue (with the virus being mumps). As a result, I have always been more aware of my vitality levels (how much charge there is in the batteries) and more sensitive to things than many people—for instance, for years after the mumps, coffee and tea would give me a headache, whilst other negatives would make me feel depleted with aches in my parotid glands, the original site of the mumps. Coincidentally, finding in the Practice Library a copy of Dr. Richard Mackarness "Not All in the Mind" gave me valuable insights to explain food intolerances and their impact on health.

One summer I returned from holiday to find the computer screens had been changed. My small black and white monitor had been changed for a larger color cathode ray tube (CRT). Within hours of sitting in front of this, I felt sick and unwell. The same happened the next day, and the next, with recovery after avoiding exposure—so we changed the cathode ray tube for a flat screen monitor (at a time when they cost £700), and I felt well again. (A flat screen works on just a few volts, whereas a CRT bombards your body with charged particles if you sit too close—children are always told not to sit too close to the television…)

The next electromagnetic insult was the first time I used a mobile phone—I developed a marked headache and slurred speech within seconds. Ever since, I have used mobiles and cordless phones (which have a similar,

though less intense, effect) as minimally as possible. Instead, I use a corded phone on a landline whenever possible, and ring people back using one of these. Each time I use a mobile phone to my head, I still get the headache. So I use an earpiece and have the phone several feet away from me. (Remember from physics that the intensity of the field diminishes with the inverse square of the distance—so a phone say 1 cm away from your head has a field 10,000 times stronger than when it is a meter away.)

At work, I changed the fluorescent tubes for spot lighting, as this is softer and feels more comfortable. I am also able to look out the window at some plants, which is very calming.

With our last photocopier, I was unable to sit near it, especially if the computer a few feet away was on—the combined effect was most uncomfortable. The current photocopier has a less intense effect, but I still avoid being near it.

More recently I develop mild headaches on the motorway or road when approaching a mobile phone mast—the symptoms abate as I drive away again

Bluetooth in a car gives me an intense headache immediately, as the phone and device are in constant wireless contact.

Most recently we changed internet service provider to a large British one, who sent a wireless Home Hub. Thirty seconds after switching this on, I developed an intense headache, the Hub being a few feet from where I sat at the computer. So I have returned to a wired router and a Local Area Network that uses the mains wiring system of the house.

I have a device that detects mobile phone, cordless phone and WiFi and mast frequencies—needless to say it goes off very loudly with all of these.

At work, when the building was extended, we changed the alarm sensors from passive to active/passive. By the end of the first day I had a headache and felt irritable—but it took a few days for me to realize that the new sensor was the cause. Removing it made me feel better in my room, but I became more and more fragile in the rest of the building, to the point that I had to leave meetings after half an hour. So we had the whole building changed back to passive sensors. A week later, several of our receptionists said to me how much better the atmosphere felt, and one senior colleague stated "I'm not sure I did believe in this, but I have to say I feel much better, and think there is something in it now—it was right to have them removed."

And in another workplace, one day I felt a headache developing within minutes of sitting at my desk. And then I opened the email that said how the WiFi system in the building had just been upgraded. The building is also only a few hundred meters from a major mobile phone base station, so I minimize my exposure due to the headaches I develop there, and the muddled thinking that occurs after an hour.

A recent trip meant that I spent the best part of three days in a WiFi enabled hotel in a city, and was unable to get out from it much. Interesting…first the strange dull headache, then the slight irritability, then mild fatigue. Also, presumably due to the duration, or the intensity, of the exposure, a tingling in my lips and metallic taste, and a sensation in the front of my mouth, as well as a runny nose (not the same as a cold), which lasted a few days. Of course, removing self from exposure helped. It was very interesting to then use an electrosmog detector—scary… and how about everyone else…

Changing my car recently gave me problems—my head felt unsteady and my legs ached—I was suspicious that there was an in-car alarm system and high magnetic fields round the legs from the alternator and wiring loom. Actually the problem was partly too much static electric charge in the car, so an earthing strip has partially eased my symptoms in the car; however, there are high magnetic fields in the front of the car which continue to cause a problem—some other cars with lower fields feel much less tiring to drive.

Some people use a silver bobbinet canopy to sleep under, to protect themselves in a type of Faraday cage, or wear protective clothing.

An engineering friend once told me that a microwave oven tester said that if his mobile phone was an oven, it would have been condemned as too dangerous because of the RF emissions, and also that as a radio ham in the 1970s he would have lost his UK license had he constructed a transmitter of the same power as a domestic WiFi hub.

Putting all this together, I would diagnose myself as electrosensitive.

I have been fortunate in all these cases to recognize the cause—and eliminate it, thereby stopping myself feeling ill. Unfortunately, there is a phenomenon called tolerance.

Tolerance is when your body has an alarm symptom to a nasty stimulus—but if the stimulus is continued, it downgrades the symptoms so you don't notice—but damage is still happening under the surface. Many people feel quite ill with their first cigarette—but as they continue to smoke, they get used to it. This explains why when I was explaining this to a doctor friend recently, she said, "Yes—I got a headache when my husband put in WiFi—but it wore off after four days." Classic alarm symptoms followed by tolerance (but with long-term ill effects likely). The General Adaptation Syndrome of Prof Hans Selye neatly explains the mechanism of tolerance, but unfortunately is not taught at most medical schools.

There are lots of people who have developed a level of tolerance, or resistance—but this actually is resistance to an ongoing harm, which will (like being exposed to other noxious stimuli long-term) cause immune system dysfunction and other adverse effects on the body, leading eventually towards illness.

One important concept in the field of health and of understanding contributory causative factors of ill health and illness is that of a maintaining cause.

If you have a stone inside your shoe—no matter how many times you change your socks, develop super strength support socks, use special pressure relieving calipers, or take cleverly designed pain killers—every time you walk on that foot, the stone will jab in and give you pain. The only (and very simple) answer is to remove the stone…

Tolerance, Adaptation, and Long-Term Harm; TILT and Kindling

Selye's General Adaptation Syndrome is of particular relevance here. An individual, exposed to a noxious substance or stressor, may first experience an Alarm reaction, next develop an outer appearance of Tolerance (Resistance), and then reach a final stage of Exhaustion. Repeated stimuli exhaust

TABLE 47.2
Sources of Electromagnetic Fields and Signals Causing Human Sensitivities

Higher Risk	Lower Risk	Risk for Sensitized
Depending on proximity and length of exposure	*Depending on proximity and length of exposure*	*Depending on the sensitized frequencies and other factors*
Personal Laptops Mobile phones Tablets	*Personal* Bluetooth headset	*Personal* Electric wrist watches, Mercury amalgam fillings, Metal-framed spectacles, Metal prostheses, Other people retaining EMR, Water exposed to EMR on skin
Household Bedside mains radio alarm clocks, DECT cordless phones, Electric blanket switched on, Fuse panels, Old CRT TV monitors, Transformer chargers, WiFi, Wireless smart meters	*Household* Baby digital alarms, Computer screen, Electric garage door motors, Electricity from some solar panels, Hairdryers, Some energy-saving bulbs, *Blocks of flats:* Incoming main electric cable	*Household* Compact fluorescent lights, Computer keyboard, Computer mouse, Delivery signature devices, Dishwashers, Electric cookers, Fluorescent tubes, Fridge electric motors, Inkjet printers, Large fan electric heaters, Metal-sprung mattresses, Microwave detection sensors, Microwave ovens, Plasma TV monitors, Satellite dishes, Stereo speakers, Under-floor heating, Washing machines
Neighborhood Mobile phone masts <400 m, Overhead power cables, Tetra masts, WiFi, office, WiFi, school	*Neighborhood* Mobile phone masts >400 m, Neighbors' DECT phones, Neighbors' mobile phones, Neighbors' WiFi, Neighbors' wireless smart meters, Substations, Underground power cables WiFi, hotel, shops	*Neighborhood* Ambient mobile use, especially during rain or far from mast, Electronic security detectors, Loop hearing systems, Radio frequencies on wiring or power cables, Radio microphones, Road radar and celldar, Some electric cars, Street lights
Area Airfield radar	*Area* Area WiFi, WiMAX, Radio transmitters <2 km, TV transmitters <2 km, Satellite broadcasts, Satellite communications	*Area* Aircraft ground radar
Occupational Aircraft crew, Computer engineers, Electric train/truck drivers, Electric welders, Electricity power workers, Military (offensive weapons, jamming equipment, radar) Performers with radio mikes, Personnel under microwave surveillance, Plasma etchers, RF induction heat sealers, Radio/TV/phone mast workers, Sewing machine workers, WiFi installers	*Travel* Aircraft, Electric cars, Electric trains	

Source: Bevington MJ. *Electromagnetic Sensitivity and Electromagnetic HyperSensitivity: A Summary*. Capability Books: Bucks; 2013.With permission.

the organism, and repeated stimuli may bring about a variety of alarm symptoms from the autonomic nervous system and other mechanisms. Long-term degenerative harms and chronic disease are inevitable in this well-accepted model.

Toxicant-induced loss of tolerance (TILT) has been proposed as a methodological approach to identifying the trigger process. Toxicant-induced loss of tolerance can be seen as leading to *Sensitivity-Related Illnesses (SRI).*[66] Electromagnetic-sensitivity shares features of other SRI, or environmental intolerances. SRI are triggered by low-level xenobiotic environmental toxic exposures. Alterations of catalase, glutathione-transferase, and peroxidase detoxifying activities correlate with Multiple Chemical Sensitivity, with 80% overlap with EHS.[67]

Kindling is the repeated stimulation of an organism at initially subthreshold levels which results in hypersensitivity. Once the organism is charged or kindled, it can sustain a high level of arousal with little external stimulus. It may also result in oxidative stress.[68]

ES DIAGNOSIS

The mainstay of diagnosis is a good *history*, of health problems and EMF exposure, and particularly of resolution of symptoms when removed from the stressors/noxious stimuli. Observation from a third party can be useful to corroborate the story. Exclusion of other diagnoses is important (e.g., in Case Study 1, the physician had in mind many possible diagnoses of physical causes, however never proceeded beyond blood tests to expensive scans, and so on, because of the rapid and complete resolution of symptoms by removal of the patient from exposure). Measurement of EM fields with simple inexpensive meters such as electrosmog detectors, and EM field detectors is valuable (and in Case Study 1 led to self-diagnosis and treatment).

The Austrian Medical Association Guidelines of 2012 are most helpful and are available on the web at this site amongst others: http://electromagnetichealth.org/electromagnetic-health-blog/oak-emf-guidelines/. They look at the problem comprehensively and give useful protocols, questionnaires and further information, including on testing for signal and EM fields.

Examination findings may be normal, or may show signs of sympathetic upregulation.

Pathological markers are not widely known in the USA or UK. The following are used around the world by leaders in the field, who must be considered as pioneers:

1. *Cerebral brain perfusion scans:* (Prof Belpomme)—Seem fairly convincing proof on a case by case study of ES sufferers.
2. *Environmental bioregulation of the autonomic nervous system:* Tests for the adaptability of the biosystem to pulsed high frequency EMFs and thus diagnosis of electrosensitivity, its extent and pre-existing damage. In three phases, resting, exposure and recovery, in a single blind test; exposure from a DECT phone at 1000 $\mu W/m^2 = 0.6$ V/m.
   a. *Heart rate variability and bandwidth* (distance between ECG R-peaks, with spectral analysis (fast Fourier transform, FFT) to the base signal and its harmonics). EHS results: a lower heart rate variability (HRV) in the harmonic frequencies. A limited resting HRV can show pre-existing and irreversible damage of the vagus nerve stimulation (VNS).
   b. *Microcirculation* (Laser Doppler imaging at the earlobe). Results: microcirculation is controlled by the VNS, thus showing bioregulation.
   c. *Active electrical skin potentials* (a sensor on the left lower arm) for stress and blockages. (Dr. Lebrecht von Klitzing, Wiesenthal, Germany. www.umweltphysik.com.)
3. *Pulsed echo-doppler brain scan:* A decrease in the pulsatility of several brain areas; *blood stress proteins* increased; *urinary melatonin* decreased (in 50% of patients).

   To identify two phases of the "EMF Intolerance Syndrome": (a) headaches and neurological problems, heart rhythm disturbances, and concentration difficulties; (b) three chronic symptoms, insomnia, fatigue and depression, sometimes with memory and behavioral problems, irritability, aggression, and suicidal tendencies. (Professor Belpomme, France, and ARTAC.)
4. *Multiple parameters.* Tests with three types of EMF (50 Hz, modulated RF and unmodulated RF), latent reaction periods, assessment of previous home and work EMF exposure, EEG, ECG, blood analysis, psychological and physiological tests, assessments of the thyroid and adrenal glands, and the brain alpha-rhythm. (Centre for Electromagnetic Safety, Moscow, 2009.)
5. *Lymphocyte chemical sensitivity.* A blood test for lymphocyte sensitivity, against seven common allergens (benzoate, burnt petrol exhaust, formaldehyde, metabisulfite, natural gas, nickel, salicylate) before and after EMF exposure. Exposure to chemicals to which someone is sensitive can increase calcium levels inside white blood cells which are further increased by EMF exposure. Calcium displaces magnesium in the cell, interfering with ADP/ATP metabolism, producing fatigue. (Dr. John McClaren Howard, Acumen Laboratories, 2008.)
6. Neurochemical marker antibody evaluation may signify screen dermatitis.[69]
7. *Skin conductance* may indicate a greater likelihood of electrosensitivity.[70]
8. *Photodermatology:* Tests for skin sensitivity, rashes, tingling, and prickling related to photosensitivity to electromagnetic fields from lighting, daylight or computer screens. (Dr. Robert Sarkany, Photodermatology Department, St Thomas's Hospital, London.)
9. *Live blood analysis* may show the formation of rouleaux in red blood films much earlier than in normal

subjects, and without abnormal blood proteins—possibly because the red cells have been slightly damaged, lost their membrane's negative charges and so, instead of remaining separate, clump as rouleaux.
10. *Measurement of micro DC voltages in the body* is a possible future development. Early anecdotal reports indicate a difference between the normal and the ES subject.

Subjective testing, often not recognized by orthodox medical practitioners

1. *Applied kinesiology with EMFs as an allergen.* Kinesiology uses muscle reaction to allergens[71] and EMFs for EHS diagnosis and therapy.
2. *Subjective provocation to specific frequencies of EMFs.* The Miller Technique, based on provocation–neutralization therapies, uses subjective clinical tests with EMFs at the frequency and coherence to which a patient appears sensitive.[72]

ES SOLUTIONS

There are no easy solutions as ES often appears when health has already been compromised, or is no longer at peak levels.

Rigorous attention to health, using both environmental and nutritional approaches is absolutely crucial.

Minimization and avoidance of EM stimuli is vital to help the organism cope with the stressor load, and use of detectors to identify sources is important.

Sadly, with the relentless rollout, particularly of transmitting radiofrequency (RF) technology (which used to be called microwave, but has been "rebranded" as RF), the environmental load is steadily and rapidly increasing, which will sensitize ever more individuals, and make life ever more unbearable for severely affected people.

Until the professions and health departments take the issue seriously, frankly the future is bleak. The issue facing us with ever more people sensitized by the proliferation of transmissions, let alone the potential burden from chronic disease contribution, is nothing less than disastrous, and is possibly the biggest Public Health challenge ahead.

It is a greater problem than smoking, lead in petrol, asbestos, and hydrogenated vegetable oils put together, and currently ignored except by the "canaries in the coalmine" and a few pioneers.

However, human ingenuity is wonderful, so once there is a drive and impetus to find solutions, they will be found—however they may involve a great deal of education, some considerable courage in public health arenas, and an increased responsibility by all members of the population to attend to health as a concept and as a personal responsibility.

Possible solutions to be found are

- Design of *all* technology with health in mind—rather than with the arrogant presumption of "no harm, because we are within ICNIRP limits"—see below.
- An initial simple, energy saving solution would be for all WiFi routers, all cordless phones, and all building alarm detectors, to be "off" as a default when not actually in use. Many Gigawatts of power must be used globally to power devices not actually in use. And those living in the house can justifiably ask "Why should I be irradiated with a Class 2b possible carcinogen without my knowledge and against my will?"
- All systems should be wired as a default, not wireless.
- Multiple use of Stetzer filters or similar to reduce dirty electricity.
- Rewiring of networks to prevent excessive use of the ground as the only return.
- An analysis of and attention to all factors that contribute to an individual's health, such as nutritional, sleep quality, environmental, and other.
- Provision of white zones where sensitive individuals can live, thrive and regain health (the area in Virginia, USA, which is radio silent for the purposes of astronomical observation is a haven for many, as are remote areas in some countries).
- "White zones" need to be free of man-made radiation for all schools, hospitals, old people's homes, and about 20%–30% of all housing if 20%–30% of the population are indeed slightly ES.
- Bedrooms and sitting rooms and where people are likely to be stationary for long periods of time need appropriate design of wiring in housing to reduce EM fields, and no HAN or WAN (wireless "smart" meter systems) should be near homes.
- No dwelling should be between another dwelling and the nearest mast, since then the radiation passes straight through the intervening dwelling.

ICNIRP limits, set by a private group sympathetic to wireless industry wishes affiliated group are six minute heating limits, are only thermal and are for the healthy adult male, and not one of the subsections of population more vulnerable, for example, children, the elderly, and those with compromised health and immune systems. It was advised by ICNIRP in 2002 to all governments that these people would need lower limits than those for adult males. It can be seen from the paper above that to take thermal limits as a safety guide for RF transmissions is an outmoded and outdated approach—though possibly with attractions to vested interests. Very different nonthermal biological long-term, low-level limits prevail around the world (USSR 1958 on, India (partial) 2013 on; BioInitiative 2007 and 2012, Seletun 2011, EU and EC, WHO's IARC in 2001 and 2011).

Below is a summary of approaches currently taken to help sufferers, but since the pathology of EHS is not fully understood, there is no single treatment. Thus, as with most environmental pollution the primary treatment is *avoidance of or protection from EMR*.[73]

A. *Principles: parasympathetic restoration after sympathetic arousal*[74–78]

1. *Triple intervention protocols:* (a) Shielding, to prevent EMR-induced cell membrane protective responses; (b) restoring intercellular communication, using neurological rebalancing, ion-channel opening, mitochondrial function enhancement, interstitial cleaning and intracellular detoxification; (c) rebuilding cell membranes with, for example, nutritionals, antioxidants, and supplements.[79] Patient management depends on EMFs (The Safe Wireless Initiative, USA).[80]
2. *Autonomic Response Testing* (ART) based on biofeedback through muscle tone changes using resonance phenomenon along with markers (Dr. Dietrich Klinghardt).[81–83]
3. *Symptomatic therapy:* Polyparametrical diagnosis, electrical unloading and individual medication (Draft standard, the Federal Medical Biophysical Centre, Health Dept., Russia).

B. *Established techniques*

1. *Preliminary procedure: detection and assessment of radiation exposure*.
   The home and work environments are assessed for harmful electromagnetic radiation using appropriate meters.
2. *Avoidance of radiation exposure*.
   Avoidance of EMR is the most effective procedure to prevent EHS worsening.
   a. *Newly sensitized patients* should aim to avoid all EMR for six weeks after sensitization.
   b. *Mains electricity* should be switched off at night (Dr. D. Klinghardt).
   c. *Changes in lifestyle,* for example, ceasing to use a mobile phone, DECT cordless phone, and WiFi. Under disability laws, workers should continue their jobs, helped by shielding a computer from EMR.[84]
   d. *Moving house* to avoid external radiation, such as nearby phone masts and WiFi, DECT cordless phones, and mobile phones from neighbors. EMF-free communities have been established in Europe and the USA, pending effective EMF environmental pollution control.
3. *Protection with shielding (RF and MW frequencies).*
   Effective protection against RF and MW radiation is difficult without significant expense and inconvenience. It can be almost impossible to shield against extremely low frequency (ELF) frequencies from power lines.
   a. *Shielding the body* with clothing made with silvered netting can be effective. This creates a Faraday cage to protect from RF and some EM fields.
   b. *Shielding the home* from external radiation, often with iron-based paint, aluminum foil, window foil or silvered netting, can help reduce regular exposure. Current advice stresses the need for reducing electric and magnetic fields as much as possible in sleeping areas.
4. *Protection or healing with EMR, subsonic longitudinal waves or subtle energy.*
   Some devices claim to work as follows, although there is limited evidence on their efficacy:
   a. Boosting and amplifying the body's existing endogenous EMR biorhythms.
   b. Providing "noise" or anti-matter frequencies to mask or block the harmful radiation.
   c. Producing EMR or subsonic sound waves at frequencies beneficial to the human body.
   Some devices apparently use scalar waves or subtle energy but these can be measured only in their effects.[85–88] EMR-induced changes in water may be significant.[89,90]
5. *Supplements to strengthen the immune system and chelation*.
   Supplements are used where EHS is seen as impaired immunity or deficiency in calcium, melatonin, magnesium or vitamin B. Antioxidants may be ineffective,[91] but garlic may help.[92] Chelation of heavy metals is suggested.[93] Dr. T. Rau, Medical Director of the Paracelsus Clinic in Switzerland, suggested (2009) treating EHS patients with probiotic supplements and removing metal dental fillings with neurotoxic mercury which can act as a radio antenna.[94]
6. *Applied kinesiology, homeopathy, complementary therapies and plants*.
   Some EHS sufferers claim benefit from complementary therapies, such as applied kinesiology; some say homeopathy is beneficial and helps related allergic reactions. Acupuncture may help.[95] Radiation from plants can also provoke a parasympathetic response.[96]
7. *Health oriented group therapy and cognitive behavioral therapy.*
   Health oriented short-term multidisciplinary group intervention gave mixed results.[97] Cognitive behavioral therapy has been suggested,[98] presumably for EMF phobia rather than actual EHS; it may have a placebo effect if the patient feels their condition is being taken seriously.[99] If all symptoms can be alleviated through cognitive therapy, the supposed EHS is unlikely to be biophysical EHS but EMF phobia. Mobile phone use can match perception of risk.[100]

8. *Anecdotal evidence.*
Some case reports have indicated redressing mineral balance, especially with magnesium supplements, amongst others, may be of help. Others suggest that "earthing" is important to them, either barefoot or using earthed mats in bed or in the house. The earth's surface is at 0 V potential, the top of a tall plant or tree 0 V, and the top of the human head 0 V as well (if one is barefoot on the earth). The ionosphere is at many thousands of volts. However, if one wears insulating rubber shoes, other footwear, sits in a car with rubber tires, and so on, rather than walking barefoot, the potential when upright is approx 190 V from head to foot. This unresolved tension means that every cell in vertical line through the body is subject to electrical potentials outside the design specification—and may contribute to electrosensitivity as well as inflammation, and may yet be found to be another cause of chronic degenerative illness.[101–107] However, whilst earthing in a rural environment with minimal man-made ground current may help the body with a DC flow, in an urban area the unwanted effect of large AC potentials may ensue, as the ambient AC is several V/m, so the effect may be less beneficial (Table 47.3).

TABLE 47.3
Exposure Levels and International Limits

1. Electric fields—milliVolts/meter: 0.3–300 GHz, microwave (WiFi, mobile phone masts and phones, cordless phones) (peak to peak)

Nature	Biological Response Threshold	Nonthermal, Biological Limit (Burger-Form Proposed)	Nonthermal, Biological Limit (Salzburg Indoors)	Conscious Symptom Threshold (Some EHS)	Conscious Symptom Threshold (30% Gen. Population)	Nonthermal, Biological Limit (Bio-Initiative Indoors)	Nonthermal, Biological Limit (Bio-Initiative Outdoors)	Heating Limit, 6 min Average, ([a]PHE, ICNIRP)
<0.02	0.1	2	20	<20	<60	194	600	61,000
				Volts/meter				
<0.00002	0.0001	0.002	0.02	<0.02	<0.06	0.19	0.6	[a]61

2. Electric fields—milliVolts/meter (V/m): 0.3–300 GHz, microwave (peak to peak)

Near Transmitter (mV/m)		Nature (mV/m)	Some Conscious Reactions (ES) (mV/m)	Nonthermal Biological Limit BioInit., Coun. Eur. (mV/m)	Heating Limit [a]PHE, ICNIRP mV/m
					61,000 (61.0 V/m)
Mobile phone/Wi-Fi router	6000 (6.0 V/m)				
Wi-Fi laptop	1000 (1.0 V/m)				
Phone mast	900 (0.9 V/m)				
dLAN, at 1.5 m[114]	40–220 (0.04–0.22 V/m)				
				[b]600 (0.6 V/m)	
				[c]194 (0.19 V/m)	
			<20 (0.02 V/m)		
		0.02 (0.00002 V/m)			

3. Electric fields—milliVolts/meter: 300 kHz–300 MHz, radio frequency (AM, FM, UHF, VHF radio, TV) (peak to peak)

Biological Response: Peripheral Nerve Stimulation	<5 miles RF/TV Transmitter: Brain Tumors	Non-Thermal, Biological Limit (BioInitiative Indoors)	2 km from AM: Increased Childhood Leukemia	Non-Thermal, Biological Limit (BioInitiative Outdoors)	3 km from FM, TV, UHF Masts: × 5 Child'd Cancers	AM Exposure Adult Leukemia	Heating Limit, 6 min. av., ICNIRP
0.6	~194	194	870–5500	614	2000	2200–4600	28,000
				Volts/meter			
0.0006	~0.194	0.194	0.87–5.5	0.614	2	2.2–4.6	28

(*continued*)

TABLE 47.3 (continued)
Exposure Levels and International Limits

4. Electric fields—milliVolts/meter (V/m) and dBm (decibels related to mW), by power of transmitter (milliWatts): some wireless smart meters, Wi-Fi routers, laptops (measured levels vary considerably)

	Transmitter Power (milliWatts)				
	ZigBee HAN (10 mW; UK, EU) (Inside Home Smart Meter)		Laptop	Mobile Phone WAN; ZigBee HAN (100 mW; USA) (Area Wireless Smart Meter) (Inside Home, USA)	
Distance (meters)	10 mW Transmitter		25 mW	Wi-Fi Router [e]100 mW Transmitter	
	dBm	mV/m (V/m)	mV/m (V/m)	minimum, mV/m (V/m)	maximum, mV/m (V/m)
0	–30	2000 (2)	3000 (3)	2000 (2)	7000 (7)
0.5	–48	40 (0.04)	140 (0.14)	1100 (1.1)	4900 (4.9)
1	–51	20 (0.02)	70 (0.07)	700 (0.7)	2800 (2.8)
2	–72	10 (0.01)	30 (0.03)	400 (0.4)	1500 (1.5)
5	–76	4 (0.004)	10 (0.01)	100 (0.1)	700 (0.7)
10	–80	2 (0.002)	7 (0.007)	50 (0.05)	400 (0.4)
20	–90	1 (0.001)	3 (0.003)	30 (0.03)	200 (0.2)
50			2 (0.002)	10 (0.01)	100 (0.1)
100				6 (0.006)	50 (0.05)

5. SAR heating (specific energy absorption rate)—Watts/kilogram: 2.0 W/kg heating averaged for 10 g of tissue for 6 min. for male adult: ICNIRP 1998 & EU. (1.6 W/Kg heating averaged for 1 g of tissue for 6 min. for male adult: USA 1997 & Australia)

Biological Damage Threshold	Biological Limit: Whole Body [f]Long-Term (Seletun)	Neuron Death ([f]max. BBB Leakage)	SAR Heating Limit: (Whole Body)	Wi-Fi Laptop at 1 m	Mobile Phone, (Good Reception)	Mobile, Full Power <3 cm to Head	SAR Heating Limit: Head	Wi-Fi Laptop on Lap, Access Point	SAR Heating Limit: Limbs
0.00002	0.00033 [f]0.000033	0.012 [f]0.001	0.08	0.05–0.11	0.1	0.12–1.6	2.0	2.0	4.0
				MicroWatts/kilogram					
20	330 [f]33	12,000 [f]1000	80,000	50,000–110,000	100,000	120,000–1,600,000	2,000,000	2,000,000	4,000,000

Averages reduce SAR substantially, for example, DECT cordless phone handsets emit 100 bursts of 0.4 ms every second (i.e., 100 Hz) at 250 mW, but averaged: power = 10 mW, transmission rate 2.5%, and SAR 0.008–0.06 W/kg.
A biological limit 50 times below the lowest known damage is 0.0000004 W/kg (0.4 μW/kg).

6. Magnetic fields (including time-varying)—nanoTesla: power lines etc. (100 nT = 0.01 microTesla = 1 milliGauss = 100,000 pT)

Human Sensitivity: Aurora Disturbance (Solar Flare)	Human Brain Entrainment: Schumann Resonance	Typical House	Conscious Symptom Threshold (Some EHS)	Nonthermal, Biological Limit (California Education Dept. Proposed)	Nonthermal, Biological Limit (Seletun, Bio-Initiative)	Childhood Leukemia $\times 3$[115] * $\times 3.8$[116] Ch. Acute Lymphoblastic Leuk. $\times 5$	Non-Thermal, Biological Limit (Italy (Parts))	ICNIRP (50 Hz, 2010)*[h] UK (HPA, DECC, 50 Hz, 2012[117])**
Rise/fall of 0.0004 nT at 0.0013 nT	0.05 nT	2–12	Rise/fall of 5 nT at 7 nT	10	100	≥100 >300*	200	200,000* 360,000**

TABLE 47.3 (continued)
Exposure Levels and International Limits

7. Power flux density—microWatts/m squared: (100 microW/m² (uW/m²) = 0.1 milliW/m² = 0.0001 W/m² = 0.01 microW/cm² = 0.00001 milliW/cm² = 10 nanoW/cm²)

Nature (uW/m²)	[g]Sleep Disorder **ES Symp. ***EEG Alt. (uW/m²)	Non-Thermal Biological Limit (uW/m²)		Near Transmitter (uW/m²)		Heating Limit (uW/m²)	
						UK	58,000,000
						ICNIRP, 1800 MHz	9,200,000
				Some mobile phones	2000–1,800,000	ICNIRP, 900 MHz	4,500,000
		Bulgaria, Italy[g], Paris, Poland, Russia	100,000	iPad WiFi	700,000		
				Wi-Fi access 0.5 m	87,000		
		China outdoors	60,000	iPad airplane	30,000		
		Switzerland[h]	40,000	Laptop, 0.5 m	22,000		
		Luxembourg	20,000	Mobile phone mast, 100 m	100–10,000–100,000		
		Counc. of Eur., 2011	1000				
		Seletun (or 1700)	170				
		CEur. (med.) AMA, Kumar[h]	100				
		Salzburg outdoors 2002	10				
		BioIn., 2012, gen. pop.	6				
		BioIn., 2012, sens., children	3				
	*20	Salzburg indoors 2002; BUND outdoors 2008	1				
	**<1	Burgerform sleeping	0.01				
	***0.00001			Mobile phones can work at	0.00003		
0.000001[h]							

8. Voltage transients ("dirty electricity")—GS units: High frequency (Graham-Stetzer units, measured with a Stetzerizer meter)

Typical House (Dimmer Switch, TV, Microwave Oven)	Nonthermal, Biological Limit (Fisher[118])	Conscious Symptom Threshold (Some EHS)	Nonthermal, Biological Limit (Kazakhstan)	Energy Saving Lights, Compact Fluorescent Lights	MS	Cancer Risk Increased by 13% after One Year	Cancer Risk Increased by 26% after One Year	Severe Ill Health: Diabetes, Asthma, MS, Cancers
25–50	30	27–40	50	15–2000	580	1000	>2000	>2000

Source: From Bevington MJ. *Electromagnetic Sensitivity and Electromagnetic HyperSensitivity: A Summary*. Capability Books: Bucks; 2013. With permission.

Note: For most toxins safety limits are usually 50 times lower than the human threshold.

[a] 1,952,000 mV/m (1952 V/m) peaks allowed.

[b] BioInitiative (2007, indoors).

[c] Council of Europe (2011, medium term).

[d] Some 100 mW values come from the Swiss government report *Electrosmog in the Environment* (2005, p. 54).

[e] The Seletun (2010) biological safety limit for long-term exposure is 0.000033 W/kg (33 μW/kg) based on a benchmark for adverse health of 0.0166 W/kg. A biological limit 50 times below the lowest known damage is 0.0000004 W/kg (0.4 μW/kg).

[f] Sensitive areas (schools, hospitals, housing, offices, playgrounds).

[g] 0.000000001 uW/m²: altered genetic structure in *E. Coli* (Belyaev, 1996).

[h] ICNIRP (<1 Hz, 2009): 2,000,000,000 uncontrolled; ICNIRP (MRI workers, 2014) 2,000,000,000 change within 3 s.

CONCLUSION

We conclude that electrosensitivity exists as a very real problem. There is ample biological evidence to enable an understanding of this widespread phenomenon. Recent studies suggest possible genetic links,[108] confirm positive subjective evidence,[109,110] and confirm that voltage-gated calcium channels are an established mechanism for EM effects at nonthermal levels.[111] Problems stemming from the conceptual context explain why even well-intentioned investigators may be tempted to deny, defer, obscure, or otherwise divert truth. It is also noted that there are vested interests at stake. As a result a great deal of EM and RF technology has been developed on the mistaken "presumption of no harm." Unfortunately, ES not only exists but affects many, many people, the great majority of them undiagnosed (because of lack of medical knowledge) and either expensively investigated or mistreated, or worse still ignored, dismissed or ridiculed. Three case studies are noted, including one of the authors, which may of course incur criticism of bias, but perhaps may achieve an acknowledgement of the use of the human as an instrument of experimentation as well as an honest scientifically trained witness to symptoms. The Austrian Medical Association Guidelines provide a useful tool for the Practitioner.

Until there is a political will to grasp the issue and work upon safety and solutions, the future is bleak for those who already suffer and for those who will soon develop the problem. It is intriguing that the proliferation of widespread EM and RF technology is coincidently accompanied by an increasing burden of chronic illness. The perfect storm of a public health disaster is slowly unfolding before our eyes, whilst, as a society, we continue to keep our eyes tightly closed and pretend "there isn't a problem." World renowned architect Thomas Saunders describes the problems of sick buildings and alludes to the adverse effects of ever increasing quantity of EM and RF fields upon society in "The Boiled Frog Syndrome"[113]—if you put a frog into boiling water, it will jump out—but if you place it in cold water and slowly raise the temperature to boiling point, it stays quietly and allows itself to be boiled alive.

On the bright side, human ingenuity is amazing, and if given the desire and resources can solve any problem, once recognized, scoped, and evaluated.

So perhaps dealing with ES is "not a problem, just a project," and, as they say in the airline industry, "safety may be expensive—but the cost of a mid-air collision…" Better that approach than a fairy story becoming horribly true…

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Section X

Looking Back, the Current FDA Fiasco, and a Peek into the Future

48 Creating the Bakken
A Library and Museum of Electricity in Life—A Mystical Memoir

*Dennis Stillings**

CONTENTS

In 1968, with the enthusiastic financial support of Earl E. Bakken—then president of Medtronic, Inc.—I began collecting the materials that would become The Medtronic Museum of Electricity in Life. Today it is simply called The Bakken, a private educational foundation located on Lake Calhoun in Minneapolis, Minnesota. The holdings of The Bakken represent the most concentrated and comprehensive collection of books and original devices documenting the history of medical electricity and magnetism in the world. It contains over 10,000 publications and approximately a thousand instruments. There are also several complementary subcollections including cardiology, neurology, natural history, and anatomy.

The following paper gives an account of my personal adventures in the development of this institution (Figure 48.1). These adventures are illustrated by my discoveries and speculations during this journey.

At present, I am living in somewhat less than quiet retirement 300 miles from The Bakken museum in distance, and over 30 years in time. I spent roughly 12 years—from 1968 to 1980—building its collections and developing the institution. Information on The Bakken, its history and current activities, can be accessed at http://www.thebakken.org/.

Too many of the details involved in creating that institution have fled my mind. What remains are mostly memories of the pleasures of discovery, not only of rare volumes and historical objects in themselves, but also of the historical ideas they expressed. Many modern electromedical devices and therapies were anticipated and even utilized over 200 years before they became part of modern medical practice; for example, electrical stimulation for pain, resuscitation (defibrillation), drop-foot, tinnitus, cardiac pacing, local electroanesthesia, respiratory difficulties, and bone-healing.

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In the late 1960s and early 1970s the early history of medical electricity and magnetotherapies was being pursued by very few scholars, and there were even fewer collectors of books on the subject. Original early texts and electromedical devices were easily acquired. That soon changed. This more or less forgotten material was "discovered."

In 1968, I was working as a research librarian at Medtronic, Inc., a major manufacturer of medical devices, in particular the implantable cardiac pacemaker. Shortly after beginning my job, my department manager presented me with a list of special requests made to the library by Earl Bakken (Figure 48.2), then president of Medtronic. The library staff had been unable to fill those requests for at least a couple of years. (There was no internet at that time, and information was nowhere near as readily available as it is today.) Although I was an untrained librarian, I filled all the requests in less than a week.

My success caught Earl Bakken's attention. He approached me in person and told me that, for sentimental reasons, there were a number of old instruments he wished to acquire. As I recall, two of the devices were a sliding coil stimulator of a certain type, and a one inch oscilloscope. I failed at this first assignment, partly because Bakken's professional contemporaries also had sentimental attachment to these very instruments and were unwilling to part with them.

In the meantime, I noticed that several photocopies of eighteenth- and nineteenth-century books on medical electricity and electrophysiology were filed on the company library shelves—works by Giovanni Aldini (1762–1834), the nephew of Luigi Galvani (1737–1798), and by Duchenne de Boulogne (1806–1875), a French neurologist who revived Galvani's research and greatly advanced the science of electrophysiology. I also learned that these photocopies had been obtained at Bakken's request.

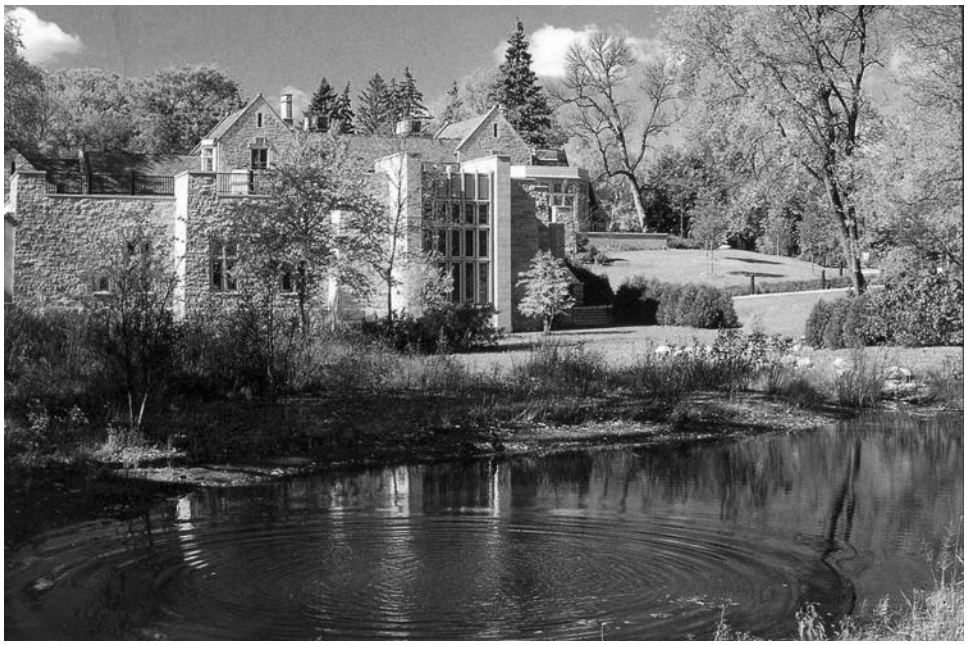

FIGURE 48.1 The Bakken. (Courtesy The Bakken.)

At my next meeting with Bakken I informed him that I had run into a dead end on obtaining the devices, but that I had noticed the photocopied texts. I asked if he would like to own the originals?—Yes, he replied, he would.

A friend of mine at the Smithsonian told me about Bern Dibner and the Burndy Library in Norwalk, Connecticut. The library was located on the premises of the Burndy Corp., a manufacturer of electrical connectors. Dibner, president of the company, collected key works in the history of science with emphasis on those having to do with electricity. I made an appointment to meet with him.

My visit turned into a seminar on identifying and collecting rare books and devices relating to the history of electricity. Dibner gave me leads on similar collections and recommended a couple of dealers in rare scientific books and instruments that I should contact. This was a major turning point.

FIGURE 48.2 Bust of Earl Bakken.

PREFIGURATIONS OF ELECTRICAL SCIENCE

I must admit that, before I took on this project, I had far more interest in getting out of the company library than I had in the history of electricity. At this time, I was teaching Humanities at the University of Minnesota and was immersed in German studies in graduate school, where my chief interest lay in applying the methods of C. G. Jung's analytical psychology to the interpretation of literature. It was through Jung's work, especially his *Psychology and Alchemy*, that I first came to develop an interest in the history of electrical theory and practice since, through Jung, I was able to see that much of the imagery and language of alchemy had been transferred into the language and speculations of the nascent electrical science. This made it possible to trace the myths, metaphors, and archetypal images that permeated eighteenth- and early nineteenth-century electrical theorizing back to alchemical, and even to early Gnostic writings. I was able to understand some of the peculiar ideas about electricity and magnetism—some resulting in serious developments, others in dead-ends and superstitions that persist to this day. The association of electricity with mystical and occult forces that persists in modern times has been noted by Michael Persinger:

> The persistence of an interest in the effects of magnetic fields can also be traced to psychological factors. Every researcher's personal environment is a product of language and the processes by which it is generated. Despite maturational (developmental) shifts in the cognitive schemes by

> which we assimilate information, there are concepts from previous stages [archetypal images–Ed.] that remain. One of them is the fascination with invisible forces (animism). This idea serves as a conceptual core around which cluster ideas of infantile mysticism, paranormal experiences and sometimes a modified form of omnipotence. It is so closely tied to the concept of self that if care is not taken, magnetotherapies become a personal quest. It acquires the dynamics of a belief.[1]

Some years ago there was energetic and widespread popular interest in the positive and negative effects of microwaves, ELF, magnetic fields—and, in short, all the invisible forces that have been conjured up by technology. These popular beliefs generated cultish notions that seemed very much a replay, in modern guise, of old beliefs in fairies, demons, angels, devils, and Divine Providence; indeed, it was said by some that a frequency of 6.66 Hz (The Frequency of the Beast) was particularly harmful. Electromagnetic speculations became a screen upon which amateur EMF enthusiasts projected cosmic imagery from the collective unconscious (as Jung would put it), as well as projecting elements of their own personal psychology. The properties of ELF waves made them particularly suitable for the projection of divine attributes of either a positive or negative nature: they travel with the speed of light, penetrate everywhere (omniscient, omnipresent), cannot be shielded against (omnipotent), can heal or harm at a distance and are, of course, invisible.

These and many other projections of fantasy onto the real properties of EMFs gave rise to dire predictions regarding the fate of the planetary ecology and scenarios involving epidemic cancer and mind-control. Projection arising from personal neuroses can result in paranoid delusions ranging from the merely eccentric to the near-psychotic. These delusions are often composed of wild fantasies about persecution by CIA and KGB agents and about psychotronic or electromagnetic "death frequencies" being directed at successful investigators by jealous colleagues. I have witnessed these, and related delusions, manifested in full bloom. This condition of mind is prevalent enough among the population of amateur EMF researchers as to be considered an occupational hazard.

Let me hasten to add at this point that just because these projections affect some researchers in these areas, it does not follow that there is no reality to the claims regarding these effects but, as far as I know, most remain to be proven. I also doubt that any researcher into these areas would be totally exempt from fantasies. But the projection of collective and/or personal psychological issues into the realm of serious research—of whatever kind—leads to distorted observations, falsification of data, and exaggerated and bizarre claims. For the nonscientific person, who is unconsciously fearful of invisible forces, the notion that there are harmful EM frequencies allows him, without seeming the fool, to entertain once again those fancies of old—to reenter the lost world of spells, hexes, curses, voodoo, the evil eye, and the need for protective charms (Figure 48.3)—which have taken the form of Teslar watches, tin foil hats, and other techno-talismans.

FIGURE 48.3 From Abbé Sans [Pierre Bertholon de Saint Lazare], *De la Guérison de la Paralysie par l'Électricité* (Perpignan, 1771).

ELECTRICAL THEOLOGY

In 1974, I presented a paper at the 24th International Conference on the History of Medicine in which I emphasized some of the early images and ideas that led to the association of the cardiovascular system with electrical activity.[2] In the course of the conference, a couple of people approached me and asked if I knew of the recently published work by the theologian Ernst Benz—*Theologie der Elektrizität* (Mainz, 1970). Upon my return, I obtained a copy through a local foreign book search service. A brief glance at the contents was exciting: it looked as though Benz was the only other person besides myself (which was not the case) who had perceived the hermetic background of early electrical theorizing. I commissioned Wolfgang Taraba, then Chairman of the University of Minnesota German Department, to translate the work.[3] This was another turning point.

From the beginnings of recorded history, electricity and magnetism have been associated with religious and spiritual images and ideas, such as all-pervading invisible forces, divine judgment, and the soul and its relationship to the divine. The thunderbolts of Zeus were cast down upon offenders; the lodestone, as well as amber and other electrics, were perceived as possessing a kind of soul or spirit

capable of acting invisibly at a distance. For William Gilbert (1544–1603), who was the first to clearly demonstrate by scientific experiment the differences between electricity and magnetism, the earth's magnetic field was its "soul." Gilbert, as well as other early natural philosophers of the time, believed that magnetism was an analogy of God's love, the *amor Dei* that linked God with the human soul.

If magnetism seemed, for a time, a far more impressive phenomenon than static electrical effects, the situation changed dramatically with the development, in the late seventeenth and early eighteenth century, of more efficient electrostatic generators. Inspired by the observation of strange lights and sparks in and around the evacuated glass chambers of air pumps, electrical machines eventually made possible the generation of massive discharges of static electricity. Francis Hauksbee (c. 1666–1713), Stephen Gray (c. 1670–1736), John Desaguliers (1683–1744), and others immediately began to use these machines in a wide range of animal and human experiments. The dramatic effects of static electricity could easily be demonstrated with the new machines and appeared to establish the power of the divine in nature. As Joseph Priestley (1733–1804) commented in 1761, the electrical machine exhibits "the operations of nature, and the God of nature Himself."

It was commonly assumed in alchemy that matter contained within it an invisible light or fire as an active principle. Electricity was the "ethereal fire," the "desideratum," the "quintessential fire," the *medicina catholica*, the "cheap thing to be found everywhere," and the long-sought *panacea*. These very terms were all used to characterize the nature and effects of the alchemical philosophers' stone. In one of his unpublished alchemical manuscripts, Isaac Newton (1642–1727), inspired by the work of Hauksbee, spoke of light as an active spirit that was present in all bodies and was responsible for many of the properties of matter, because it was such "a prodigious active principle." Similar ideas appeared in print in his "Hypothesis Explaining the Properties of Light," read to the Royal Society in 1675, and in the "Queries" that he added at the end of his *Opticks* (1704, 1706, 1717). These ideas inspired, among others, Hermann Boerhaave (1668–1738), professor of chemistry at Leyden University, who postulated that fire was an active substance that pervaded the whole universe, penetrating even the innermost recesses of solid bodies and endowing them with many of their properties. It was an easy matter to identify Newton's light and Boerhaave's fire with electricity. When electrical machines spectacularly demonstrated how sparks of fire or light could be elicited from various kinds of matter, including even water, it seemed natural to suppose that truths foreshadowed in alchemy had been confirmed. Alchemical influence can be seen in Otto von Guericke's (1602–1686) preNewtonian experiments on electricity when he tried to generate electricity in a spherical *terrella* made of sulfur turned on a winch (1663). When rubbed, this miniature "model of the world" produced sparks of electricity. It was also a favorite pastime of the alchemists to construct *terrellas*, and it is perhaps more than coincidence that one of the earliest electrical generators was constructed from an alchemical alembic.

The eighteenth century was the most significant period in history for the impact of electrical theory on religion. Clerics demonstrated a special interest in electricity. John Wesley's (1703–1791) *The Desideratum: or, Electricity Made Plain and Useful, by a Lover of Mankind and of Common Sense* (1760) went through several editions. The usefulness of electricity for Wesley lay in its potential for combating atheism. This is clear from the comments he made after he had attended one of the popular public demonstrations of electrical effects: "How must these [experiments] confound those poor half-thinkers who will believe nothing but what they can comprehend. But who can comprehend how fire lives in water, and passes through it more freely than through air? How there issues out of my finger, real flame, such as sets fire to spirits of wine? How these and many more as strange phenomena arise from the turning round a glass globe? It is all mystery, if haply by any means God may hide pride from man" (Figure 48.4). Similar ideas flourished after Benjamin Franklin (1706–1790) showed how the natural power of lightning could be used to charge a Leyden jar using a lightning conductor. As Priestley commented in his *History and Present State of Electricity* (1767): "What would the ancient philosophers, what would Newton himself have said, to see the present race of electricians imitating in miniature all the known effects of that tremendous power, nay disarming the thunder of its power of doing mischief, and, without any apprehension of danger to themselves, drawing lightning from the clouds into a private room and amusing themselves at their leisure by performing with it all the experiments that are exhibited by electrical machines?"

Priestley's history is important because of his attempt to interest the public in the performance of experiments. Public lecturers in experimental natural philosophy would display electrical phenomena in a manner that conferred authority on themselves as manipulators of the forces God had built into creation. Priestley also practiced "electroexorcism," casting out spirits by the application of static electrical sparks. Electroexorcism has been practiced for centuries,

FIGURE 48.4 John Wesley's electrostatic generator.

beginning with the ancient practice of throwing "possessed" persons into pools filled with electric fish. Electroexorcism reemerged in modern times. The physician Carl Wickland (1861–1945) used a static electrical generator (Wimshurst machine) to drive spirits out of his patients and into his mediumistic wife. Wickland would then converse with the spirit through his wife and convince it to quit its habitation in the patient and move on to its spiritual destiny.

In his *Theology of Electricity*, Benz pursues the relationship between electricity and eighteenth-century theology, attempting to establish the claim that the "discovery of electricity and the simultaneous discovery of magnetic and galvanic phenomena were accompanied by a most significant change in the image of God." He argues that these discoveries led to a "completely new understanding of the relation of body and soul, of spirit and matter." Benz considers, in particular, the ideas of Friedrich Christoph Oetinger (1702–1782), Johann Ludwig Fricker (1729–1766), and Prokop Divisch (1696–1765). These "electrical theologians" saw electricity as the very light of creation, the "first light" of Genesis 1:3-4, which informs matter and is the impetus toward its evolution into higher forms. The Last Judgment and damnation for the "enemies of God" is an "Anti-Creation," involving "the deprivation of the original life force, of electricity."

The researches of Galvani in the 1780s (published in 1791), in which he examined electrically-induced convulsions in dead frogs, gave rise to a belief that the "subtle electric fluid" that was assumed to be responsible for electrical effects was also present in living bodies and responsible for various life processes. Although contested, notably by Alessandro Volta (1745–1827), who insisted that the electrical effects noticed by Galvani were merely the result of connecting two different metals by a passive moist body, the notion of "animal electricity" became widely accepted. By the late eighteenth century, many prominent European physiologists were convinced that electricity was intrinsic to all life processes. During the French Revolution, experiments on the plentiful freshly decapitated corpses made it plausible that electricity was the vital fluid and that its proper application could potentially raise the dead. In 1818, the Scottish chemist Andrew Ure (1778–1857) tried to revive an executed criminal by administering electric shocks. Mary Shelley's (1797–1851) *Frankenstein; or, The Modern Prometheus* (1818) was not, at the time, considered to be entirely fictional. In fact, in the 1830s, the amateur scientist Andrew Crosse (1784–1855) earned a reputation as an "atheist, a blasphemer, a reviler of religion" for claiming to use an electrochemical process to create a living insect, *Acarus electricus* (Figure 48.5). It is small wonder, then, that electricity continued to be under theological scrutiny. As recently as the 1930s, Dr. Albert S. Hyman of New York City was accused of "tampering with providence" for his pioneering work on the artificial cardiac pacemaker, now routinely used for the electrical control of cardiac arrhythmias.

Electricity was the last of the classical sciences to arise at a time when the rule of the materialistic, mechanistic view of nature and man was gathering momentum. The Gnostic/

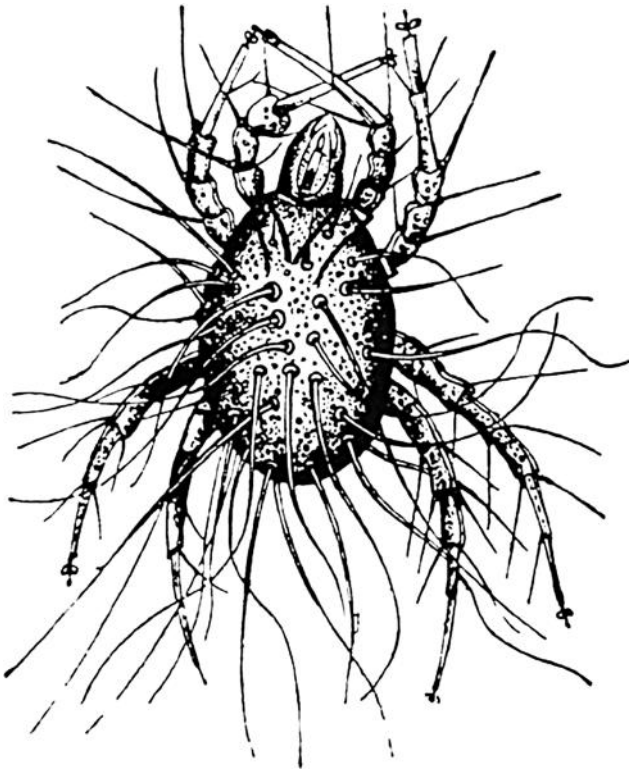

FIGURE 48.5 *Acarus electricus.* (From H. M. Noad, *Lectures on Electricity*, London, 1849.)

alchemical imagery imbedded in electrical theorizing, however, operated *sub rosa* as a sort of subversive quasi-spiritual factor within mechanistic scientific thought. On an unconscious level, electricity still evokes images of that paradoxical figure of alchemy, Mercurius, and of the elusive "vital fluid." These unconscious associations of imagery have persisted and re-emerged in our time within quantum-mechanical speculations on the role of consciousness in the material world.

THE BODY ELECTRIC

That a force field of some sort could surround what we call today an "inanimate object" was observed very early in the mysterious invisible attractive force surrounding amber and lodestone.

The lodestone (magnetite) is of particular interest. Sometime in the mid-1970s, when I was out for a walk in downtown Sherman Oaks, I spotted an antique shop that looked promising. The owner dealt in a wide variety of odd and exotic items including, for instance, an elaborately decorated Turkish gunpowder flask made from a bull's scrotum. After a fascinating tour of the place, I was shown a couple of trays of Mesopotamian cylinder seals (Figure 48.6). Cylinder seals were made of a variety of materials and were inscribed with cuneiform figures and writing. A hole was bored lengthwise through the center of the cylinder so that it could be worn on a thong around the neck. It was used for signing documents and at the same time as an amulet.

FIGURE 48.6 Sumerian cylinder seal.

Out of the whole collection, four of the seals were particularly interesting. They were carved from magnetite, were of Sumerian origin, and were approximately 4000 years old. One had a figure of Marduk, the patron deity of the city of Babylon, one of whose traditional attributes was He-Who-Acts-At-A-Distance. The fact that the cylinder seal was made from magnetite gave support to the truth of the legend that magnetite mines existed in ancient times in or near Mesopotamia; in particular, Turkey. The existence of lodestone mines in this region has been regarded as legendary in several ancient natural histories as well as in modern books discussing the history of electricity and magnetism. There were even legends of magnetite mountains on an island off the coast of Turkey so powerful that they could pull the nails out of passing ships and sink them.

When I got back to the office, I began playing around with the cylinder seals. It was clear to me that simple observations about magnetism could well have been made in antiquity. For instance, the attraction and repulsion between two cylinder seals could be observed. It also occurred to me that the magnetic field itself might have been noted by the Ancients. While drilling out the core of the cylinder seals, the resulting magnetite dust might have been seen to form a pattern around the ends of the magnetite cylinders. It may even have been observed that slivers of magnetite aligned themselves in a north–south direction.

The idea of an invisible energic entity inhabiting living things could be said to have originated with the idea of a soul or "subtle body" that inhabits the physical body. Early ideas of this "energy" range from primitive beliefs in *mana* or *mulungu* to the elaborate system developed from the millennia-old Chinese concept of *qi,* a nonphysical "energy" which flows, by way of "meridians," throughout the body and determines the overall health of the organism. In health, *qi* flows freely through the body; blockage of *qi* results in disease. Acupuncture is the therapy used to re-establish the proper flow of *qi*. This internal energy system is used both for diagnosis and treatment.

In the West, a related idea of a nonmaterial physiology was developed by Paracelsus (1493–1541) and Johann Baptista van Helmont (1580–1644). They conceived of the *archeus*, an entity that orders the form the body will take. It is through the *archeus* that disease-states are manifested and cures can be effected.

Hans Driesch (1867–1941) believed that the facts of regulation, regeneration, and reproduction indicated there was something about living organisms which remained a whole even though parts of the physical whole were removed; it acted on the physical system but was not itself part of it. He called this nonphysical causal factor *entelechy*. He postulated that entelechy organized and controlled physicochemical processes during morphogenesis. The genes were responsible for providing the material means of morphogenesis, but the ordering itself was brought about by entelechy.

In his 1981 book, *A New Science of Life*,[4] Rupert Sheldrake reworked this idea in his concept of morphogenetic fields.

> Morphogenesis does not take place in a vacuum. It can only begin from an already organized system which serves as a morphogenetic germ…. The morphogenetic field can be thought of as a structure surrounding or embedding the morphogenetic germ, and containing the virtual final form; this field then orders events within its range of influence in such a way that the virtual form is actualized. In the absence of the morphic units which constitute the parts of the final system, this field is undetectable; it reveals itself only through its ordering effects on these parts when they come within its influence.[5]

Even though Sheldrake proposed several ways to test his ideas, the book raised considerable controversy. As far as I know, in spite of proposing and conducting several experiments to substantiate his claims, Sheldrake's theories remain in scientific limbo.

It appears that a biological field-concept has persisted for centuries, it has been taken up again from time to time, and has raised new speculations and generated experimental efforts to establish and exploit its existence.

To bring these matters down to a more familiar level, we will turn to the work of Harold Saxton Burr (1889–1973), Professor of Anatomy at Yale.

Burr hypothesized that disturbances in energy fields could indicate the presence of disease. Burr found he could detect electrical fields around mammals, salamanders, worms and earlier life forms. He showed that the electrical characteristics of these fields changed during growth, regeneration, and during the formation of tumors. When he connected his voltmeters to trees he found that, over time, their energy fields varied not only in response to changes in light and

moisture, but also in response to electrical storms and sunspots. Although he had spent years designing sophisticated vacuum tube devices, the sensitivity of Burr's detectors and instruments was insufficient to gain accurate measurements of the minute changes in the weak electrical forces he believed might have important implications for health and life. Despite this, he made a number of important observations, many of which have recently been confirmed.

Burr's most important contribution was the proposal that all living things—from men to mice and trees to seeds—were molded and controlled by "electro-dynamic fields" that could be mapped and measured. These "fields of life" or "L-fields" were the basic blueprints of all life. Although invisible and intangible, they were analogous to magnetic fields that cause iron filings scattered on a card held over a magnet to arrange themselves in the magnet's force field pattern at both poles. If the filings are discarded and new ones are scattered on the card, they will immediately assume this same symmetrical pattern.

Burr thought that something similar might be happening in the body. Although cells and molecules are constantly being destroyed and rebuilt, they inevitably arranged themselves in the same pattern as the old ones. The L-fields act as a matrix or mold to preserve the shape or arrangement of any material poured into it, no matter how often this is changed. Burr wrote, "When a cook looks at a jelly mould, she knows the shape of the jelly she will turn out of it. In much the same way, inspection with instruments of an L-field in its initial stage can reveal the future 'shape' or arrangement of the materials it will mould. When the L-field in a frog's egg, for instance, is examined electrically, it is possible to show the future location of the frog's nervous system because the frog's L-field is the matrix that determines the form which will develop from the egg." Could L-fields be used to evaluate health in humans?

As Burr explained in his 1972 work *Blueprint For Immortality*, just as a cook who uses a battered mold expects to find some dents or bulges in the jelly, an L-field with distorted voltage patterns might indicate the presence of abnormalities well in advance of any signs or symptoms. He reasoned that if healthy cells had an L-field matrix that programmed normal tissue growth, cancer cells with atypical rapid growth patterns would have quite different field characteristics. In 1936, he began studies on a strain of mice that spontaneously developed mammary tumors and found large voltage changes in electrodes placed on the chest 10 days to two weeks before the tumors could be otherwise detected. In another strain prone to develop cancer following the implantation of malignant tissue he found that voltage gradients started to increase within 24–48 h after the procedure and rose steadily to a maximum of five millivolts around the eleventh day, after which they began to decline. This increase corresponded with the period of most rapid growth of the cancer.

Burr showed that changes in electrical fields could detect precisely when ovulation took place in animals and that in humans, some women ovulated throughout the menstrual cycle, some ovulated without menses, and some had menses without ovulation. One of his patients who had tried unsuccessfully to conceive for years was studied daily for weeks until ovulation could be detected, following which she promptly became pregnant. Louis Langman confirmed the value of this technique and also extended Burr's cancer studies in over 1000 patients admitted to the Gynecology Service at New York's Bellevue Hospital. By measuring changes in potential between one cervical electrode and another placed on the abdomen, he found that almost 99% of 75 patients with documented cancer showed electronegativity of the cervix. In the remaining 353 patients, presumably admitted for a nonmalignant disorder, the cervix was significantly positive with respect to the abdomen in 82%. Electronegativity in the remainder was due to some other benign cause, such as ovulation. Another larger study of 840 consecutive admissions confirmed these results in patients with various malignancies of the cervix, body of the uterus, ovary, or vagina.

Recent research supports Burr's theories. Skin surface potentials can now be used to differentiate between malignant and benign breast lesions, and the FDA recently approved a cancer detection device based on differences in electrical impedance in malignant tissues. AIS (American Institute of Stress) Congresses have demonstrated how Sodi Pallares' electromagnetic field therapy and Nordenström's weak direct current application to metastatic lung lesions have resulted in amazing regressions if not cures in patients with terminal malignancies. The availability of more sensitive devices like SQUID and magnetoencephalography have also confirmed Burr's belief that energy fields can reflect emotional as well as physical health.

EPILOGUE

The sheer acquisition of the materials that make up the collections of The Bakken captivated me. It would not be an exaggeration to say that I was enthralled by the process. I had been warned by seasoned collectors of rare science and medicine that many key items were almost impossible to find anymore. This was not true. I had the mystical impression that these items were looking for The Bakken, not that I was looking for them. The collection grew quickly and now contains virtually all the historical literature and classic instruments relevant to the history of electricity and magnetism in relation to medicine and physiology.

As I examined the items and wrote about them, I discovered many old techniques of electrostimulation that anticipated modern electromedical practice. I expect that there are many others to be discovered. Once, to my amusement, a young doctor came into the museum excited over his discovery that the appropriate application of electricity to the wrist area could induce sufficient anesthesia in the hand to permit surgery. I handed him an 1890 article discussing a patented device that did just that. The illustration of the device showing how it worked was little different from his own invention. I suppose that doing this was mean of me…

However, what excited me beyond all else was discovering that certain centuries-old ideas about electricity, magnetism, and other "energies"—real or imagined—persist to the

present day. These ideas and images have risen and fallen, then reappeared again, some discredited, but others modified and supported by new discoveries, new observations, and more adequate technologies.

DEDICATION

I wish to dedicate this essay to Earl E. Bakken, founder of Medtronic, in this his 90th year. In the context of the history of electromedicine and also in that of the 200-year-old and still relevant legend of Frankenstein, I have, with more than mere whimsy, thought of Earl Bakken as the anti-Frankenstein. Whereas Dr. Frankenstein, whose Faustian meddling with the divine power of electricity led to the creation of an amoral, destructive monster, Bakken's life's work in medical electronics has gone far toward improving the quality of life for millions of people worldwide.

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49 Problems with the FDA Approval Process for Medical Devices

*Tracey B. Kirsch and Daniel L. Kirsch**

CONTENTS

On February 10, 2012, the U.S. Food and Drug Administration (FDA) personnel warned their Neurological Device Panel (NDP) 25 times during the daylong meeting that cranial electrotherapy stimulation (CES) devices have the potential to cause seizures. While we were there, we were gagged having only been given 45 minute to speak in the morning and then not allowed to comment on the subject matter being presented all day. Finally, towards the end of the day, NDP member Michelle Carras from Johns Hopkins University Bloomberg School of Public Health asked the FDA to explain the details about the alleged seizures. FDA epidemiologist Lauren Min, PhD responded by making this statement, quoted here from the official transcript.[1]

> The seizures occurred in a paper by Philip, and I can tell you that this was a study of psychiatric inpatients with major depressive disorder, and in this study two patients had new onset epileptic seizures during a five-day washout period that occurred prior to CES treatment. So, this is a case where it's like the seizures are likely not attributed to the CES device, but we reported it here simply because we were reporting all of the adverse events that occurred in the studies.

How does an adverse event that occurs prior to administration of a treatment become a "potential risk?"

In other words, despite the fact that the audience and the media were repeatedly led to believe that convulsions were common and of considerable concern with CES, these convulsions all occurred prior to CES therapy. There are other examples, but before describing these, it would be helpful to put this in perspective by briefly reviewing the history of the FDA and its current system of classification of medical devices.

THE ORIGIN AND EVOLUTION OF THE FOOD AND DRUG ADMINISTRATION

Although the FDA can trace its origins back to the creation of the Agricultural Division of the Patent Office in 1848, it became a protection agency with the passage of the 1906 Pure Food and Drugs Act. There had been numerous bills proposed over the previous two decades because of concerns about the safety of foods due to contamination and the use of dangerous adulterants. This new law was primarily a response to public outrage over the shockingly filthy and unsanitary conditions at the Chicago stockyards that had just been described in lurid detail by Upton Sinclair in *The Jungle*. The urgent need for comprehensive Federal health protection had been vigorously promoted by the chief chemist of the Department of Agriculture, and this position eventually evolved into the commissioner of food and drugs.

By 1937 it already became apparent that the Food and Drug Act was ineffective and needed to be revised. The 75th U.S. Congress under a Democratic majority in both the House and the Senate passed the Food, Drug and Cosmetic Act (FD&C) which was signed into law by President Franklin D. Roosevelt on June 25, 1938. This new law changed FDA's

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mission from a police agency to a regulatory agency whose primary responsibility was to evaluate new drugs.

The FD&C also included authority for the FDA to regulate medical devices defined as instruments and accessories intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals, and to affect the structure or any function of the body of man or animals.

DEVICE REGULATION

Over time, the drug approval process became more complicated, causing delays that often deprived health care practitioners and their patients of beneficial treatment options that were available in other countries.[2] However, at first, medical devices were not regulated as drugs, so hundreds of small medical device businesses were established by scientists, physicians, engineers, and others to investigate and manufacture devices that could help diagnose and treat patients. These products included life-supporting heart valves and pacemakers, orthopedic implants, intraocular lenses, kidney dialysis and heart–lung machines, and a wide variety of diagnostic products. These remarkable innovations occurred, with very few exceptions, without any input or oversight from the FDA or other federal regulatory agencies. Despite the lack of the intense regulatory oversight we see today, or perhaps because of it, the device industry had a remarkable and successful history of introducing safe products that delivered countless benefits for patient health.[3] Unfortunately, the previous statement is in the past tense for a reason.

The FD&C was updated again in 1976 with Medical Device Amendments that conferred gatekeeping powers to the FDA. It distinguished devices from drugs in that devices do not achieve any of their principal intended purposes through chemical action and do not depend upon being metabolized. At the time all devices were placed in Class I, II, or III, except about 25 categories of devices that were dumped into Class III because the FDA did not believe that sufficient information existed to insure the devices were reasonably safe and effective. The law required the FDA to complete the classification rulemaking for these temporarily placed Class III devices within 36 months of the initial classification process in 1976. In 2009, the Government Accountability Office (GAO) officially reported on the FDA's failure to classify these devices 33 years later.[4] Under pressure from other governmental agencies, the FDA is finally reclassifying these preamendment Class III devices now, although they are doing so in an arbitrary and capricious manner overly burdening some (such as cranial electrotherapy stimulators) with impossible requirements while reclassifying other technologies (such as transcranial magnetic stimulators) with much less valid scientific evidence.

The 1976 Medical Device Amendments established a flexible review process intended to tailor the FDA oversight of new and improved devices to a level of regulatory control sufficient to provide a reasonable assurance of safety and effectiveness. Most new devices incorporate fairly modest changes or improvements to previously marketed devices. The previously marketed devices were referred to as "predicate devices" to denote their existence on the U.S. market prior to the enactment of the 1976 Medical Device Amendments. An estimated 90% or more of the devices now on the market have been authorized for commercial sales through what is known as the 510(k) process. Section 510(k) of the FD&C Act is a grandfathering clause which accommodates devices already in commercial distribution prior to the enactment of the Medical Device Amendments. Products that use the 510(k) path to market do not go through a full premarket approval (PMA), but they are nevertheless subject to numerous and burdensome legal requirements to ensure their safety and effectiveness.[3]

Members of Congress worried that an FDA substantial equivalence determination was not the same as a determination that a device was safe and effective, so they passed legislation to strengthen the 510(k) requirements. Congress enacted the Safe Medical Devices Amendments (SMDA) of 1990 to address this and other concerns. Today, device manufacturers are subject to new requirements for device tracking, reporting of any correction or removal of a device from the market, postmarket surveillance, mandatory device recalls, preproduction device validation, and fines for violations of the Act.[5] In many cases, the stringency of these and other requirements exceed those that are applicable to new drugs. However, a major change in the 510(k) process was arguably the most important feature of the 1990 Amendments. Congress gave the FDA new authority over the 510(k) process, transforming it into what has come to be known as a "mini-PMA."[6] Passage of the SMDA gave the FDA discretionary authority to require clinical data when reviewing 510(k) applications. The process then morphed into a rigorous premarket review instead of a notification process originally intended to verify the correct classification of a medical device. As a result, the industry experienced substantial and detrimental increases in review times by the FDA.

The 510(k) process was originally designed to ensure that new products were assigned to the correct classification. It was not intended to establish an independent safety or efficacy review process akin to PMA because the regulatory controls associated with the classification system itself are sufficient to provide a reasonable assurance of safety and effectiveness.[3]

The device classification system does not relate to the inherent risk of a device type. Instead it was developed to classify devices based on their complexity and intended uses. The FDA is required to regulate devices in the least burdensome method to provide reasonable assurance of safety and effectiveness. The objective of the classification system was to establish regulatory standards, or controls with each higher class being subject to greater controls and an increasing level of scrutiny to provide a reasonable assurance of safety and effectiveness.

CLASSIFICATION OF DEVICES

Class I devices are usually simple nonprescription products such as tongue depressors, surgical gloves, elastic bandages,

and handheld surgical instruments. For these devices, compliance with what the statute calls General Controls—dozens of very specific legal requirements, such as registration of the "establishment" responsible for the manufacture or distribution of a device, periodic reporting to the FDA, and adherence to Quality System Regulations (QSR)—are sufficient to provide a reasonable assurance of safety and effectiveness. The QSR sets forth general requirements for design controls, production, storage, labeling, distribution, complaints, and so on. It sets up a general framework for each manufacturer to consider when adopting procedures for its devices. Some Class I devices are exempt from the QSR. The company's marketing Class I devices are required to list their devices annually, have truthful and accurate labeling, and maintain records. Each manufacturer must maintain complaint files, and promptly report to the FDA if a medical device might have caused or contributed to a death or a serious injury, or malfunctioned in a way that could lead to death or a serious injury. Corrective actions (e.g., refund, repair, replacement, or recall) may be necessary for problem devices. They also have prohibitions against adulteration and misbranding as these terms are defined by the FDA.

Class II devices are those that General Controls alone are thought to be insufficient to assure safety and effectiveness. These are somewhat more important, such as artificial joints, powered wheelchairs, infusion pumps, and transcutaneous electrical nerve stimulators (TENS). These are subject to various "Special Controls" and performance standards as the FDA might require of them. No Class II devices may be marketed until the manufacturer submits a 510(k) notification providing a substantial amount of data from laboratory testing, bench trials, and comparative data demonstrating substantial equivalence to a predicate device. Although clinical testing is not explicitly required by the statute, "substantial equivalence sometimes can be evaluated only in the clinic," according to David Feigal, former director of the FDA's Center for Devices and Radiological Health (CDRH).[7] Therefore, in many cases, Class II device manufacturers must also present clinical testing data that support a substantial equivalence determination, as well as safety and effectiveness claims. Class II device manufacturers are inspected by the FDA every two years. They must conduct postmarketing surveillance, maintain patient registries, meet user-trainer requirements and, most daunting of all, must have their "labeling" (i.e., everything written, broadcast or spoken) blessed by the FDA and must not deviate from what the FDA allows them to say. Truthful and nonmisleading statements are not a defense against the powers of the FDA.

A relatively small percentage of devices are in Class III, mainly new devices for which no predicate device exists. If a new device is believed to not qualify for Class III status, it is theoretically possible to petition the FDA for reclassification, but, in our case, they have never reviewed several mandatory, extensive, expensive, and time-consuming reclassification applications submitted by us since 1997. All Class III devices must go through a rigorous FDA PMA process that typically involves extensive human clinical trials as well as prior inspection of facilities for compliance with good manufacturing practice requirements to demonstrate that the device is safe and effective, or they may go through a reclassification process. The PMA process is a very expensive and rigorous undertaking, similar to putting a new drug on the market. A CES PMA was estimated by the FDA to cost manufacturers $1,000,000 and require 670 man hours to develop. The FDA asserted that it would then cost taxpayers $8,400,000 annually for it to regulate the CES industry.

Class III devices are those explicitly intended for a use in "supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or a device that presents a potential unreasonable risk of illness or injury."[8] A good example is the artificial heart valve. People tend to mistakenly equate the device classes with a measure of risk. However, the classification system is not based on the inherent risk posed by the devices, but rather on their complexity and function. Class III includes such devices as extended-wear contact lenses and many diagnostic tests, which are not risky *per se*. The unfortunate tendency to confuse device classification with a measure of risk has profound consequences. Even for a Class III device, the FDA confirms by approving the PMA application that the product is reasonably safe and effective for its intended use and does not pose a "high risk."[3]

In 1976 the FDA dumped their 25 unclassified product categories into Class III because they believed there was insufficient information for the device to be placed in Class I or II. This wrought terrible confusion about safe and effective devices among medical practitioners and institutions, the insurance industry, and the general public who believed these devices were life-sustaining, life-threatening, or potentially high risk when they were often nothing of the sort. This chapter will focus on how CES devices, an extremely safe and effective technology, were misrepresented.

FOOD AND DRUG ADMINISTRATION PRACTICES

During the past 30 years, the FDA has become more aggressive in using their authority, and has required more and more devices to go through the full PMA process. This has drawn out both 510(k) and PMA review times and has created an atmosphere of unpredictability and uncertainty about what will be necessary to get products to market. Yet, critics in Congress and the media have increasingly called for even more legislative and regulatory burdens. It is that knee jerk overreaction of politicians to prevent future problems when someone is injured, or even when an injury is deemed possible, that causes more and stricter regulations to be written and the FDA to deal with the products it regulates in a harsh manner. In some cases, such as the one cited below, side effects attributed to the device occurred prior to its use.

The FDA's current burdensome 510(k) regulatory process has hindered innovation and slowed the growth of the domestic device industry. As a result, more new devices are now

being developed and marketed in other countries where regulatory requirements are more balanced. A study by the consulting firm Emergo Group examined 510(k) process review times for the years 2006 and 2010. The average time for review in 2006 was 96 days, but it had grown to 132 days by 2010.[9] This is after the device application is complete where both the manufacturer and device meet all the FDA requirements to market the device. While a long review delay may seem somewhat normal in an industry such as pharmaceuticals where review cycles over one year are common, it can be devastating in the medical device industry. The typical product life-cycle for a new medical device is just 18–24 months, meaning that most devices are replaced by new or improved products within two years.

Roughly 80% of device manufacturers are small businesses with fewer than 50 employees. Yet the cost of bringing a new medical device to market through the 510(k) clearance process amounts to an average of some $73 million.[10] In contrast, the European Medicines Evaluation Agency takes only half the time on average as the FDA does to review new medical devices.[11] Many small and medium sized manufacturers have responded by moving research facilities overseas and by marketing new devices in Europe or Asia first. America's leading device scientists go where R&D is to innovate for foreigners leaving Americans to contend and literally be forced to live with small incremental changes in our available devices.

Since 1976, more than 150,000 different types of useful devices have become available to health care professionals and consumers through the 510(k) substantial equivalence process, which is based on the understanding that compliance with the Class I and Class II regulatory controls is sufficient to provide a reasonable assurance of safety and effectiveness.[12] The 38 year success record of the 510(k) process supports those who claim that less FDA interference, rather than more, is the best alternative.[3]

In 2002 the Medical Device User Fee and Modernization Act (MDUFA) was enacted, imposing user fees upon industry for product reviews. PMA, Product Development Protocols (PDP), Premarket Notifications (510 k), and Biologics Licensing Application (BLA) would only be reviewed by the FDA after the necessary fees were submitted by industry. A PMA review is assessed a $154,000 fee and a 510(k) review would be assessed a $5,170 fee. Small businesses can qualify for fee reductions. Congress is required to reauthorize MDUFA every two years. Representative Bob Aderholt (R, AL) Chairman of the House Appropriations Subcommittee observed that FDA funding has increased "to a degree very few [federal] agencies have experienced." He noted that the FDA's appropriated funds for fiscal 2014 were up by nearly half over the levels appropriated five years earlier. Additionally, the FDA total user fee collection was up by 93% over the same five year period. Unfortunately, industry has not seen an increase in FDA performance with the infusion of additional resources. He also noted that the FDA's regulatory decisions "can mean life or death to businesses across the world."[13]

FOOD AND DRUG ADMINISTRATION REGULATION OF CRANIAL ELECTROTHERAPY STIMULATION DEVICES

A major problem appears to be that FDA reviewers have had no personal experience with CES and tend to cite those references that support their current position.

Electromedical Products International, Inc. (EPI) is the manufacturer of the Alpha-Stim CES device indicated for the treatment of anxiety, insomnia, and depression. EPI has been in continuous business since 1981 and is the world's leading CES manufacturer and source for safety and effectiveness data for CES devices.

The FDA was mandated with completing the classification process for all device categories available prior to 1976. The FDA has previously proposed a rule (or even adopted a final rule) requiring PMA for CES devices on five different occasions: September 4, 1979,[14] January 6, 1989,[15] August 31, 1993,[16] August 24, 1995,[17] and June 4, 1997.[18] In each instance, the FDA has either elected not to proceed to a final rule on the requirement, or, in the case of the August 24, 1995 ruling, the FDA issued a final rule requiring a PMA for CES devices. EPI filed for injunctive relief through the judicial system on November 26, 1996 to stop the PMA process because the FDA failed to follow its own statutory procedures. Prior to receiving a ruling by the courts, the FDA reversed its PMA decision on CES and the June 4, 1997 FR notice was published ambiguously outlining this decision. CES was once again condemned to Class III purgatory by the FDA.

In 2009, the General Accounting Office (GAO) noted that the FDA had still not fulfilled its statutory requirement (some 33 years after given the mandate) by failing to address the classification of 25 different categories of medical devices which included CES. On April 9, 2009, the FDA required all of the manufacturers of devices in those 25 categories to submit information, consisting of all known research and safety data for their devices.[4] The request for information by the FDA required that the manufacturers of devices in the 25 different categories submit information within 120 days that either supported a request for reclassification to either Class I or Class II or supported a request for PMA of the device. EPI, along with two other CES manufacturers, elected to request reclassification of CES as a Class II device. EPI filed a 275 page Petition for Reclassification.

Nothing further was heard from the FDA until 2011 when the FDA published another Proposed Rule in the Federal Register.[19] In accordance with very explicit procedural requirements published in 21 C.F.R. Part 860, EPI described in its updated 2011 Petition for Reclassification all the reasons why a PMA submission was not warranted and that the very broad and comprehensive regulatory controls for Class II devices were sufficient to provide reasonable assurances of safety and effectiveness. Perhaps more importantly, the principal criteria for application of Class III controls relate to devices which are life-supporting, life-sustaining or pose a potential risk to health. CES devices do not provide

or claim life-supporting or sustaining benefits. EPI's Alpha-Stim CES technology has been in commercial distribution for over 30 years so it is well documented that it also does not pose a potential risk to health.

In support of its Petition for Reclassification, EPI demonstrated that, throughout its 30-plus year history, continuous compliance with all Class II regulatory controls demonstrated that these controls were sufficient to provide reasonable assurance of the device's safety and effectiveness. There have been no reports of serious injury, recalls, or supportable consumer or licensed practitioner complaints related to safety or effectiveness in the USA or throughout the rest of the world. Any potential side effects are minor and self-limiting (e.g., headaches and skin irritation). Alpha-Stim has been approved by regulatory authorities in China, Europe, Japan, Korea, Australia and Canada, to mention a few, and the device is available over-the-counter worldwide except in the USA where a doctor's prescription is required.

The content of the 2011 Petition clearly provided the necessary support for reclassification in accordance with EPI's history of compliance with the often burdensome requirements for Class II devices. In addition, EPI's data were in compliance with the FDA's definition of Valid Scientific Evidence.[20] Additionally, it suggested and endorsed the inclusion of Special Controls and that the FDA could and should require submission of clinical data for each CES device separately as they are all very different technologies.

The response by the FDA was to hold a NDP meeting.

THE 2012 NEUROLOGICAL DEVICE PANEL MEETING

In preparation for the February 10, 2012 NDP meeting, in the Proposed Order to require a PMA for CES devices, the FDA listed the following "Risks to Health:"[21]

- *Worsening of the condition being treated*—If the device is not effective and the patient is not treated in a conventional manner, the patient's psychological condition may worsen.
- *Skin irritation*—The electrodes or the conductive cream used with the electrodes may cause skin irritation.
- *Headaches*—Reported cases of adverse effects of CES devices include headaches following treatment with electrical stimulation.
- *Potential adverse effects from electrical stimulation of the brain*—The physiological effects associated with electrical stimulation of the brain by these devices have not been studied systematically; therefore, adverse effects which may be caused by these electrical stimuli remain unknown.

It should be noted that the potential side effect of worsening of the condition being treated is true with every intervention the FDA has ever approved or cleared. For example, antidepressant drugs are by no means effective for even half the people who try them and their listed side effects pose a much greater risk to health than the real side effects of CES devices. There is no drug or device that is 100% effective so the potential of worsening of the condition exists in every drug or device, and should be addressed in the consideration of the effectiveness of the drug or device, and not as a risk to health.

The FDA's hypothetical "worsening of the condition being treated if the device is not effective" was adequately responded to at the 2012 NDP hearing by psychiatrist Jason Worchel, MD, Medical Director of East Hawaii Mental Health Centers. Dr. Worchel said,

> In some ways this is almost an insult to those of us who are physicians because what we do every day; we see a patient, we provide for them a recommendation for treatment and then if we are doing our job we're monitoring our patients in an ongoing fashion to determine whether or not the treatments we prescribed are effective and what side effects may also be emerging as well…The question before this Panel is if this is going to be a device which is prescribed by a licensed practitioner, it is not the issue that the device may be ineffective, our medications are ineffective…Of course we monitor our patients and if it's ineffective we would change [the prescription].[22]

As to potential adverse effects from electrical stimulation of the brain, none have surfaced in over 40 years that CES has been on the market in the USA and the FDA does not consider this a problem for other stimulators such as the implantable vagus nerve stimulation (VNS) or repetitive transcranial magnetic stimulation (rTMS) which the FDA categorized as Class II although rTMS has far less research with smaller effect sizes than CES studies, lacks three decades of safety data, and has more serious adverse effects reported in a far greater incidence. How can this disparity be justified?

The FDA admitted in its 2013 Proposed Order, which was nothing more than a repeat of the 2011 Proposed Order, which the FDA abandoned yet again, that its prior inclusion of "seizures and blurred vision" as Risks to Health had been eliminated by the NDP in its February 10, 2012 meeting to consider the classification petitions of CES manufacturers. As noted previously, the listing of seizures as a "Risk to Health" was eliminated when the FDA admitted that the only seizures found with regards to CES use were in a study conducted in France on a CES device that was never sold in the USA where the subjects had the seizures during a drug wash-out period prior to even using the CES device. How can this conclusion be justified?

EPI has provided the FDA in its submissions and multiple requests for reclassification with an abundance of data collected over its 30 plus years in business, and the data all support the conclusion that CES is very safe, and no "potential adverse effects from electrical stimulation of the brain" have been found. As EPI reported to the FDA and the NDP, from 2007 through 2011, 58,030 of EPI's Alpha-Stim CES devices were sold, resulting in an estimated 8,248,920 treatments. This is derived from an individual home Alpha-Stim

CES user survey conducted in August 2011 where patients used Alpha-Stim an average of three months, three times per week (36 treatments), and a practitioners in-office treatment survey, conducted in December 2011, where practitioners reported an average of 10.1 treatments per week for 48 weeks per year. During that time period 15 adverse events were reported to EPI for an incident rate of 0.0018%. Of those 15 adverse events, 11 were reports of skin irritation at the electrode site, two were reports of tinnitus, and one report of a panic attack and one of a black tongue—which was later determined to have been caused by an over-the-counter medication (Pepto Bismol®).

The NDP concluded at the end of their February 10, 2012 meeting that CES devices are safe. As NDP member Dr. Suresh Kotagal stated, "I just have a very simple comment, that the device is safe. There is really no convincing evidence of any potential adverse effects. With regard to the stimulus parameter, we all know biologically there is variability, and we see that in some of the other devices, like the vagus stimulator, the amplitude, the frequency, the pulse. They all seem to vary in terms of what stimulus is going to produce the most optimum response."[23]

The NDP even questioned the FDA as to why "potential side effects" were being discussed on a device that had been so widely used and on the market for over 30 years. NDP member Dr. Kenneth Steier asked the FDA, "The devices have been used for approximately 30 years. There were, for instance, over 8.5 million treatments administered between 2007 and 2011. They're also used worldwide, even without a prescription. Over that immense period of time, if there was truly a safety issue, isn't it likely that that would be very obvious and we wouldn't have to concern ourselves with potential issues or problems?"[24]

The FDA's response to this question is interesting, especially when you consider the scant valid scientific evidence the FDA used in the very same Proposed Order as justification for its down-classification of sorbent hemoperfusion devices.[25] Dr. Malvina Eydelman of the FDA stated at the NDP meeting, "When we evaluate information, we base it on the valid scientific evidence. So, having said that, we'll look at published literature as well as we will look at the official MDR reports. Unfortunately, if there's a wide use and not a well-documented body of information, that does not help us."[26]

Use of the MAUDE (Manufacturer and User Facility Device Experience) database and the manufacturer's reports on safety were sufficient justification to determine that sorbent hemoperfusion devices are safe enough to be in Class II for the treatment of poisoning and drug overdose. CES devices, which the FDA attributes "potential" side effects to that have never been reported in over 30 years of longstanding use, also have no MAUDE adverse event reports and all minor, self-limiting actual side effects have been reported by EPI to the FDA. But, as Dr. Eydelman pointed out, those data are not sufficient, in the case of CES, to avoid the consideration of "potential" risks to health. This is another example of an unfair conclusion that led to refusal of a request for reclassification based on safety concerns.

FOOD AND DRUG ADMINISTRATION ABUSE OF AN EXPERT DEVICE PANEL

The purpose of the "expert" Device Panels are to allow the FDA to approach experts in a field and seek guidance in an area where the FDA might not have the necessary experience or expertise. The FDA noted that "it believes that there must be a specialist with noninvasive brain stimulation and neurophysiology perspective in order to understand the stimulation risks and have a thorough deliberation of CES devices. At this time, there are no other neurophysiology specialists with expertise in noninvasive brain stimulation on the Panel; therefore, the Center believes that one such specialist must be present for the panel discussions." As a result of this finding, Dr. Alvaro Pascual-Leone, Professor of Neurology at Harvard and Director of the Berenson-Allen Center for Noninvasive Brain Stimulation, was issued a waiver of a potential conflict with work he had done for a rTMS manufacturer and was invited to serve on the expert Panel as a nonvoting member. Dr. Pascual-Leone ranks number one among authors worldwide in the specific field of "Transcranial Magnetic Stimulation" and "Noninvasive Brain Stimulation" (http://www.authoratory.com/) and is the author of over 450 papers and several books. He had accepted the assignment and we were anxious to hear his assessment but he was not present as promised. Why? The FDA reported that he had a scheduling conflict. After the meeting, when Fisher Wallace, another CES petitioner, asked him about his absence from the Panel meeting, Dr. Pascual-Leone explained that he had looked forward to participating, but was subsequently told by the FDA that he was no longer needed. In addition, the refusal to allow many well-credentialed expert witnesses to testify and censorship of opposing opinions from industry representatives gave the impression that the purpose of the meeting was to support a conclusion that had already been made rather than obtain an objective and fair evaluation from qualified sources.

No member of the Panel, whether voting or nonvoting, had any experience with CES devices, thus none of them would be a "qualified expert" as required by law.[27] Yet, the FDA appointed nine additional nonvoting individuals as consultants to the Panel, none of whom had any expertise with CES devices. Consequently, there were no "qualified experts" among the 14 people who were asked to evaluate CES and make recommendations to the FDA.

At the NDP meeting, no member of the audience was allowed to question, comment, or clarify statements made by Dr. Eydelman of the FDA who spoke freely whenever she liked, or any panel members. Before the FDA's presentation by FDA Team Leader Tim Marjenin and during its presentation, the industry representative on the Panel expressed the need for clarification or evidence criteria on several occasions asking about "valid scientific evidence" in particular. This was due to the fact that representations were made by the FDA as to safety and effectiveness in the context of adequate or acceptable scientific evidence which is only appropriate for PMA submissions. The NDP was not tasked with evaluating PMA submissions that day.

EPI and the other two manufacturer-petitioners found substantive misuse of the NDP by the FDA, to such an extent that all three manufacturers submitted complaints to the FDA Commissioner Hamburg in March 2012 requesting that the FDA's process of using this NDP be thoroughly reviewed. At the February 10, 2012 hearing, the NDP was asked to rule on the safety and effectiveness of CES devices. The NDP ruled that there were no safety concerns with CES devices, even though the FDA wanted the NDP to indicate a risk of seizures, death, and "worsening of the condition." The "death" the FDA continually mentioned turned out to be one individual who died three months after a CES treatment. No further details or causality was offered by the FDA, so the NDP ignored that "potential risk." The absolute failure to utilize at least one "qualified expert" with the requisite knowledge of and experience with CES devices nullifies any recognition of effort by FDA personnel and the members of the panel. EPI requested the Commissioner reject the effort applied by the FDA and recuse all FDA personnel involved in any way with that Petition from any future involvement until a thorough independent inspection of FDA performance is initiated, completed and available to the public. Commissioner Hamburg did not respond to these complaints as of this writing, more than two years later.

A review of the standards imposed for each device also shows a clearly arbitrary and inconsistent process of review which the FDA is implementing in its determination of a device's classification.[21] It is difficult for a manufacturer of a medical device in the United States to determine what the FDA's standards for safety and effectiveness are when certain devices are deemed safe and others are deemed unsafe when the data for both are so similar, and when certain data are considered for one device and largely ignored for the other. Consistent standards must be applied in reviewing devices so that manufacturers can adequately anticipate what data the FDA needs in order to determine if a device is safe and effective. Arbitrary standards of safety and effectiveness do no one any good, especially the general public who is placing their faith in the FDA's evaluation process. Unfortunately, the experts at the FDA craft regulations based on analysis that would not meet the same rigorous standards the FDA requires from corporations seeking drug approvals. Maybe it's time that the safety and effectiveness standard applied to industry should also be applied to the regulations.[28]

FOOD AND DRUG ADMINISTRATION IGNORES ITS OWN DEFINITIONS

The FDA actually has reasonable definitions for safety and effectiveness but it applies these definitions arbitrarily in evaluating the scientific literature of therapeutic devices. The Code of Federal regulations state:

"Valid scientific evidence is defined as evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use."[20]

The FDA is charged with determining "whether the evidence, when taken as a whole, is adequate to support a determination that there is a reasonable assurance that the device is safe and effective."[29] "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."[30]

There were 392 CES studies identified by the FDA according to the FDA's presentation to the NDP. The FDA discarded all but 32 of those studies without even reviewing the results, and did so based on arbitrary criteria the FDA established solely for its review of CES, such criteria being outside of the statutory definition of valid scientific evidence. For example, they discarded all studies done on patient populations other than Diagnostic and Statistical Manual definitions of General Anxiety Disorder, Primary Insomnia, and Major Depressive Disorder. Yet, the Code of Federal Regulations definition does not say any of that, but, rather, a cranial electrotherapy stimulator is defined by the FDA as a device that applies electrical current to a patient's head to treat insomnia, depression, or anxiety.[31] It is well established in the medical literature and in practice that all three of these indications for use are ubiquitous across all human populations.

Of the few remaining studies the FDA saw fit to leave in initially, 59% were published during the 1970s. The FDA then discarded these few old remaining studies as well based on more arbitrary criteria, leaving their NDP with no useful data upon which to make their recommendation as to effectiveness of CES in the treatment of anxiety, insomnia, and depression.

Despite the fact that many supportive studies of CES efficacy were ignored, the Patient Representative, the Industry Representative, and two of the voting members of the Panel voted that all three indications should be Class II and another panel member voted that anxiety should be Class II and depression and insomnia Class III.[32]

The entire 31 year marketing history of EPI, the leading CES manufacturer, was completely ignored by the FDA at the 2012 meeting and in various actions the FDA conducted against EPI since that time. The two other CES manufacturers marketing history were also ignored as were the hundreds of letters to the docket supporting CES from the military, physicians, psychologists, scientists, and patients.

EPI provided the FDA with substantive data showing the effectiveness and use of CES for the treatment of anxiety,

insomnia, and depression but, instead of reviewing the data submitted, the FDA's procedure of evaluation was to apply 2012 research standards to studies dating back to 1970. The FDA dismissed all mechanistic (e.g., functional magnetic resonance imaging [fMRI] and electroencephalogram [EEG]) and all animal studies, studies with specific patient populations, such as the statistically significant and robust findings of improved sleep in three double-blind studies conducted at American universities on fibromyalgia populations. The FDA also discarded unpublished studies and those without a null hypothesis in the publication, although no major medical journal or the FDA's own regulations require a null hypothesis for accepting studies.

The Code of Federal Regulations is clear that the evidence should be "taken as a whole," but the FDA did not follow this mandate in an attempt to justify their position. For example, the FDA admitted to using an "arbitrary" criteria of no less than 50 subjects per study and threw out most of the psychometric tests used in the studies although all were in common use and validated, and even discarded all the objective physiological tests used in the research. This process of selective elimination removed every study on currently available CES devices. Thus, from what was left of the available scientific evidence the FDA misled the NDP to believe the science did not demonstrate that CES provided a reasonable assurance of effectiveness for the indication of anxiety, insomnia, and depression. It seems unlikely that unbiased reviewers, especially those with expertise in this area, would have reached this conclusion if all the relevant material had been available.

The Alpha-Stim CES devices have been on the market continuously since 1981 and have been subjected to the FDA review seven times in three decades. Such reviews have always required scientific evidence of effectiveness as part of their determination of "substantial equivalence" to preamendment devices. EPI undergoes biannual FDA inspections as well and has never had any reports of significant adverse effects. It is hard to believe that the FDA is now claiming EPI should undergo a Is PREmarket correct in original or should this be premarket? approval process as a Class III device defined as life-supporting, life-sustaining, or a potential risk to health. CES meets none of the criteria for a Class III device. Outside the United States, Alpha-Stim CES has been rigorously evaluated and then approved for over-the-counter sales by regulatory agencies in most of the world's major markets.

The following quotes are excerpted from the February 10, 2012 NDP meeting regarding panel member Dr. Richard Fessler's question about the uniquely rigorous criteria the FDA placed on CES devices.[33]

DR. HURST, Chairman: "We have one last question from Dr. Fessler, and then we're going to move to the discussion phase, during which time we can address further questions to the FDA if issues come up."

DR. FESSLER: "So, first let me apologize for the inflammatory nature of this question. And I'll address it to any of you. Can you name me, honestly, any currently available device or product in the United States that would stand up to the rigors that you just listed for the device we're talking about today? I can't think of any."

DR. EYDELMAN, Director, Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices, Office of Device Evaluation: "Yes."

DR. FESSLER: "Name it."

DR. EYDELMAN: "This is not the appropriate place or forum to do so, as we can't compare."

FDA epidemiologist, Dr. Lauren Min, explained the criteria the FDA imposed on CES research before it would take a study into consideration: "For each study listed here, we examined whether or not there was a control group; the presence of successful masking to minimize placebo effects; an *a priori* statement of the study hypothesis; if sample size was adequate using an arbitrary cutoff of 50; use of DSM diagnostic criteria to evaluate a specific indication; use of validated and appropriately applied outcome measures; determination of a prespecified endpoint for success, and statistical adjustment for key confounders."[34]

Although there are an adequate number of CES studies having a comparator group to see that the placebo effect is negligible, every study that lacked double-blinding should not be thrown out, nor should any of the other reasons stated by Dr. Min have been used to discard valid scientific evidence supporting CES. At least not according to the FDA's published definition of valid scientific evidence.

The FDA has not initiated any rulemaking process to change the indications for use of CES devices to DSM diagnostic criteria. Nor is there any criterion within the Food, Drug and Cosmetic Act that suggests any indications for any device should automatically change to meet criteria published by any outside, private institution. Yet the FDA threw out all the research that met the above stated indications for CES from the Code of Federal Regulations if they did not meet DSM-IV diagnoses. Much of the research was not conducted to evaluate on DSM-IV criteria because either the DSM-IV criteria did not exist at the time of the study, or the researchers were not aware that CES was to be held to a DSM-IV standard. The indicated uses for CES as stated in the Code of Federal Regulations are for the treatment of "insomnia, depression, or anxiety" and the FDA has no authority to impose DSM-IV criteria on valid scientific evidence used to support those three indications.

Another excerpt from the transcript of the February 10, 2012 NDP Meeting:[35]

NDP member DR. FESSLER: "My comments—obviously I've already made one of them. I think the rigor that we're asking of these studies and of this device is extreme, to say the least. I think we should be considering safety separately from efficacy. I think they've demonstrated safety beyond any reasonable doubt. Efficacy, I'm not so sure of. And, finally, to do a twofold thing of ignoring 30 years of history is just silly, and then to eliminate all of the available data because it is not typical in research papers to state your hypothesis—and generally, that's implied by the research—and it is not typical to state a predetermined endpoint; you're just looking for statistical significance, and you will state what that is. So, to eliminate papers based on that, I think, is just completely unfair."

DR. HURST: "Other comments from the Panel regarding those issues? Yes, Ms. Carras."

MS. CARRAS, Patient Representative: "I was thinking that, as a new student of epidemiology and biostatistics, it's my impression that these types of study designs haven't been around that long, and this level of discrimination of study design is fairly new, so I think that should probably be taken into account, that maybe the FDA is expecting a higher standard; whether that's a valid way to assess things, I don't know."

We were then given all of three minutes to comment on the day's proceedings. Chairman Dr. Hurst stated: "Thank you. Are there any summations, comments, or clarifications from the petitioner? Each of the petitioners has three minutes. Please approach the podium one at a time based on the order of your presentations."[36]

Scott Elder, EPI VP and Corporate Counsel summarized by saying, "I'd like to thank you all for taking the time to be here today and to hear their presentations. I would like to point out that there's an inherent unfairness to this procedure in that we received, just yesterday, the FDA's list of studies that were excluded from our presentation. And I believe if those studies were more accurately considered by this Panel, that you would conclude that there is valid scientific evidence establishing that the device is both safe and effective. But, obviously, we did not have the time to respond to the deletions of studies for reasons which I would believe all of you would find invalid if we had time to discuss that. But when you have 45 minute to present your device and all the science, some things are going to be left out, unfortunately. And when you have a day to prepare a response to their deletions of a lot of good research, you are going to, unfortunately, not have time to address it."

FOOD AND DRUG ADMINISTRATION NEVER COMPLETES THE PROCESS

The FDA has yet to review all of the valid scientific evidence supporting CES as an effective and safe treatment for anxiety, insomnia and depression from the data provided it from the Proposed Rule issued August 8, 2011, the NDP Meeting on CES Device Classification held February 10, 2012, and the April 4, 2013 Proposed Order. Before one of the Proposed Orders becomes final we asked that the FDA review all of the valid scientific evidence and present it to the NDP in a fair and unbiased manner so that the Petitions for Reclassification submitted on behalf of CES devices can be adequately considered. There was never any response to our dozens of letters to the FDA on this matter.

SPECIAL CONTROLS ONLY GOOD ENOUGH FOR SELECTED DEVICES

It is also appropriate to highlight the standards the FDA has imposed on CES manufacturers in the FDA's review of their petitions to reclassify CES as a Class II device and compare that with the standards imposed by the FDA in its review of sorbent hemoperfusion devices which the FDA somehow grouped together in their 2013 Proposed Order. A review of the standards imposed for each device shows a clearly arbitrary and inconsistent process of review which the FDA is implementing in its determination of a device's classification. Special controls are being implemented for some devices while the FDA claims it is not able to implement special controls for other devices.

In the 2013 Proposed Order, part of the reason the FDA proposed to reclassify sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose as Class II devices is because "the Agency has identified special controls that would provide reasonable assurance of their safety and effectiveness."[25] The FDA then goes on to explain that sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose are prescription devices, but acknowledges that prescription restrictions are general controls. The special controls the FDA outlines for sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose include:

1. Performance testing to ensure that the device is effective, is adequately designed and includes adequate safeguards
2. Labeling to inform users of inappropriate use controls
3. "General controls"[37]

The FDA emphasizes that the prescription requirement is helpful and also points out in the Proposed Order that the decision to reclassify sorbent hemoperfusion systems intended for the treatment of poisoning and drug overdose was on the FDA's "own initiative."[25]

In EPI's prior submissions to the FDA we outlined the special controls under which EPI has manufactured and marketed its Alpha-Stim CES devices since the early 1980s. However, the FDA has elected to determine that "Without greater knowledge of the critical stimulation parameters and ranges that may be effective, FDA believes special controls cannot be written for CES."[38]

The FDA's argument that "special controls cannot be developed" for EPI's Alpha-Stim CES device falls flat when one considers that the device

1. Has been on the market for over 30 years and is now in significant use by the United States government (Department of Defense (DOD) and Veteran's Affairs Medical Centers (VA))
2. Has an abundance of data, all provided to the FDA, showing the device is safe
3. Has an abundance of data, all provided to the FDA, showing the device is effective
4. Has no adverse reports listed in the FDA's MAUDE database
5. Is manufactured by a company that has a good compliance record with the FDA
6. Is manufactured and marketed subject to strict special controls already
7. Is approved by many regulatory agencies throughout the world as a Class II, over-the-counter device

In reaching their conclusion, the FDA has completely ignored the substantial and compliant three decade long regulatory and inspection history of EPI in the manufacturing and distribution of its CES devices. EPI has self-imposed substantial "special controls" consisting of the following, as presented at the February 10, 2012 NDP meeting. We list them here in Table 49.1, side by side with the specific controls that the FDA has approved for rTMS devices, which the FDA proposed to classify as Class II devices one week before issuing its initial Proposed Rule in 2011 seeking to require PMA for CES devices.[39] As can be seen in Table 49.1, Alpha-Stim CES is manufactured and marketed pursuant to almost identical special controls as the FDA required of rTMS in placing that device in Class II.

Ironically the biggest investor in CES is the United States government. The NIH, DOD, and VA are spending millions of dollars researching and utilizing CES. Two psychiatrists, a retired General and a Major in the U.S. Army Reserves, as well as the former Chief Psychologist for the U.S. Army Reserves testified before the NDP in 2012 that CES is in use by the military and within the VA System and that it works better than other available treatments in the Iraq and Afghanistan theatres of war. However, NDP member Murray Stein, MD, MPH, of the University of California San Diego attempted to disparage the Service Members' testimony by saying he called some friends of his in the DOD (one of who Dr. Stein stated was at the National Intrepid Center of Excellence—"NICoE") during a break in the proceedings and no one he called knew of CES. Although Dr. Stein's hearsay testimony was allowed, NDP Chairperson Robert W. Hurst, MD refused to allow LTC Ross Pastel, a NICoE researcher who was present at the hearing to testify and refute Dr. Stein's hearsay testimony and to explain that Alpha-Stim CES is in widespread use within the DOD and used with every patient at some military facilities, including NICoE.

TABLE 49.1
A Comparison between the Voluntary, Self-Imposed Special Controls Initiated by EPI for CES Devices which the FDA Has Not Responded to, and the FDA Accepted Special Controls for rTMS

Self-Imposed Special Controls Implemented for Alpha-Stim® CES by EPI In Practice by EPI Since 1990s	Class II Special Controls for Repetitive Transcranial Magnetic Stimulation (rTMS) Finalized by FDA July 26, 2011
1. Risks to health	1. Risks to health
2. Device description	2. Device description
3. Non-clinical analysis and testing	3. Non-clinical analysis and testing
4. Biocompatibility	4. Biocompatibility
5. Electrical equipment safety	5. Electrical equipment safety
6. Electromagnetic compatibility	6. Electromagnetic compatibility
7. Risk management	7. Software life cycle and risk management
8. Clinical testing	8. Clinical testing
9. Labeling	9. Labeling
Directions for use	Directions for use
Indications for use	Indication for use
Contraindications	Contraindications
Warnings	Warnings
Precautions	Precautions
Adverse effects	Procedure precaution
Electrical safety	Adverse events
Electromagnetic compatibility	Electrical safety
Caution statement for prescription use in USA	Electromagnetic compatibility
Technical specifications	User training
10. Operational and process controls	Patient labeling

CONCLUSION

Medical device regulations have been poorly managed by the FDA. As a result, the FDA is driving away one of America's most successful and important industries.

Congress has not conducted a serious review of problems within the FDA since 1993, when the House Energy and Commerce Committee conducted a series of hearings on the performance of the FDA's CDRH. A staff report published following that extensive investigation found that the FDA weaknesses included "inadequate attention to warnings of likely problems, excessive delays, and disorganization in the review and approval process, poor communication inside the FDA and between the industry and the FDA, and an inability to correct internal problems."[40] The report concluded that the FDA had adequate legal authority to ensure the safety and effectiveness of devices reviewed under both the 510(k) and PMA processes. The report found, however, that FDA personnel often lacked proper training, failed to assess submitted data critically, and did not use expert advisory committees efficiently or effectively. Obviously all of that and more are still clearly present in the FDA handling of CES devices.

Since the 1993 Congressional hearings, FDA staff has been increased, and the Medical Device User Fee and Modernization Act of 2002 has boosted their financial resources considerably, even as the annual number of 510(k) submissions has fallen from an average of over 6000 in the early 1990s to around 4000 during the past decade.[41] In addition, the Food and Drug Administration Modernization Act of 1997 requires the FDA to use the "least burdensome" means of demonstrating substantial equivalence and to develop guidance documents clarifying when a 510(k) clearance is appropriate.[42] Despite all this, the FDA's performance in managing the 510(k) and PMA review process has continued to deteriorate. Delays in the review of 510(k) notifications are endemic, and the entire process is riddled with confusion, unpredictability, and a lack of transparency. At their root, many of the criticisms of the FDA practices seem to be based on nothing more than a belief that a full evaluation through the PMA process is the only way to prevent unsafe products from reaching the market.[3]

Americans have reaped substantial benefits from America's innovative medical device industry. Congress enacted the 1976 Medical Device Amendments in the expectation that FDA regulatory activities would not disrupt the dynamic and

successful progress of the medical device industry, an expectation shared by the medical community. This optimism has turned to pessimism among those who monitor the consistent behavior of the FDA. It is time for Congress to conduct a massive oversight investigation of the FDA's performance and impose new legislation that would require the FDA to be honest and not hamstring developments in this important and innovative industry. As attorney Jonathon Emord said, "Unlike many other regulatory agencies, decisions made by the FDA can determine whether people live or die. The consequences of FDA corruption and abuse of power are not only dire for the economy, they are grave for our health."[43]

As Carl Sagan said in *Thoughts on Life and Death at the Brink of the Millennium,* "A central lesson of science is that to understand complex issues (or even simple ones), we must try to free our minds of dogma and to guarantee the freedom to publish, to contradict, and to experiment. Arguments from authority are unacceptable."[44]

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50 Afterword
A Peek into the Future

*Paul J. Rosch**

CONTENTS

NONINVASIVE DIRECT CURRENT DEEP BRAIN STIMULATION

As indicated in the Preface, we were unable to include numerous recent advances, such as the use of noninvasive Deep Transcranial Magnetic Stimulation (dTMS) to improve learning skills, memory and cognitive function. In a recent survey, 87% of respondents said they would utilize this if it could enhance their performance at school or work. Noninvasive dTMS is cleared by the U.S. Food and Drug Administration (FDA) for the treatment of drug resistant depression but it can be prescribed off label for other indications, which poses a problem, since it is used in Europe for numerous disorders and some do-it-yourselfers have built their own devices for home use. In a March 2014 *Wall Street Journal* article, two prominent researchers predicted that brain implants to improve cognitive skills will some day be as common as plastic surgery is today. They believe that, if computing power continues to increase at the same rate as it has for the past few decades, a single computer will likely have the computing capacity of a human brain by 2023, and, by 2045, a single computer could have the processing capability of all human brains put together.

Google is a potential cognitive implant that provides information on almost any topic within seconds and would not require you to do a search since you would know the answer. Such enhancements raise troublesome philosophical, ethical and moral questions. If you're the parent of a student applying to an Ivy League or other leading university, why not buy a brain implant to gain an advantage over competitors who can't afford one, especially when it's SAT time? Oxford University researchers have already demonstrated that noninvasive dTMS can improve the math skills of adults and children as young as eight. Electrodes are placed in a tightly fitted cap worn around the head that can be targeted to specific areas of the brain or applied generally, and are powered by an ordinary 9 V battery. In addition to depression, dTMS may also be effective for other mood disorders and withdrawal symptoms. The Air Force has been using it to reduce the time needed to teach drone pilots how to identify targets in radar images and the Department of Defense utilizes it to train snipers.

The Focus v1 is a transcranial direct current stimulator that uses a headband with electrodes that are placed over the right and left temples. It also claims to improve concentration and focus and can be purchased by gamers anxious to approve their skills for less than $250. Since it makes no claims for the diagnosis or treatment of any disease, it does not come under the jurisdiction of the FDA and has Federal Communications Commission (FCC) approval for commercial sales. The amount of current delivered to the frontal cortex is only 2 mA, much less than a 9 V battery delivers, but little is known about possible adverse long-term effects.

OPTOGENETICS, LIGHT EMITTING DIODE VERSUS COLD LASER THERAPY AND NEAR-INFRARED

Optogenetics refers to the insertion of light responsive proteins called opsins into targeted cells, which, when exposed to light, become tiny openings that allow electric charges to pass through. The brain and nervous system are particularly suited for this type of intervention, and researchers are exploring its use in autism, schizophrenia, drug abuse, anxiety, depression, nerve regeneration, Parkinson's disease and other neurological and psychiatric disorders. Johns Hopkins scientists also believe it may be able to treat life-threatening cardiac arrhythmias because it can be directed at very specific areas, involves very little energy and is less harmful than electricity. As one explained, "*When we use a defibrillator, it's like blasting open a door because we don't have the key. It applies too much force and too little finesse. We want to control this treatment*

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in a more intelligent way. We think it's possible to use light to reshape the behavior of the heart without blasting it."

Optoacoustic technology is a new tool to improve the diagnosis of breast cancer and prevent unnecessary biopsies. It fuses optogenetics with ultrasound to produce "light-in and sound-out" images that provide a unique picture of blood flow in and around suspicious breast masses. Since malignant tumors grow more rapidly, they require larger amounts of blood and oxygen, and a network of blood vessels grows around them that can readily be detected with this technique. Each year, 1.7 million women in the United States undergo needle or surgical breast biopsies after a suspicious mass is found, and four out of five are benign. While not available here, the Imagio device was just approved in Europe. In one study of Imagio images from 73 patients with 74 breast masses, all of those with cancer were correctly identified and benign ones were correctly graded for malignant potential.

Light emitting diode (LED) technology was developed towards the end of the last century, when NASA began investigating the effects of microgravity on the health of astronauts. It had been established that gravity was necessary for normal human cell growth and that wounds did not heal as well in space as they did on earth. LEDs stimulate cytochromes in the mitochondria, which furnish the energy for all cellular activities. Cytochromes respond to light and color, and when activated, increased energy promotes tissue growth and regeneration. In one NASA study, DNA synthesis in fibroblasts and muscle cells quadrupled when exposed to LED light. The Celluma LED light therapy device uses three distinct wavelengths of light energy to treat various disorders depending on their location and depth, and is now approved by the FDA for

1. Acne
2. Muscle and joint pain
3. Muscle spasms
4. Arthritis
5. Muscle and joint stiffness
6. Compromised local blood circulation

Cold or low level laser therapy systems differ from hot lasers that generate heat and are used as a scalpel to burn or cut tissues. Their output is measured in watts whereas cold lasers are measured in milliwatts, and, like LEDs, are also available in several different wavelengths ranging from green (532 nm) to red (650 nm) to near-infrared (NIR, 750–950 nm). Each of these has different effects. Green laser light is absorbed very rapidly by skin and blood and is used only to help heal surface wounds like decubitus and diabetic ulcers. Red lasers have greater penetration but are still generally used for surface conditions such as burns, acne, and hair restoration. IR (infrared) and NIR lasers penetrate much deeper and can help heal muscle, ligament or even bone. Cold laser acupuncture (usually red) is another example of combining traditional Chinese medicine with modern technology. Its advantages are that you only have to stimulate the acupoint for 5–50 s rather than 20 min for an acupuncture needle, and since the skin is not punctured, there is no risk of infection. As indicated in Dr. Niemtzow's acupuncture chapter, benefits may be due to mitochondrial stimulation similar to that which results from physical contact with acupuncture needles.

While cold lasers are often confused with LED since they have comparable effects on cell regeneration, reduction of pain and inflammation, they are monochromatic (single color wavelength) and coherent (wavelengths are in phase), whereas LEDs are not coherent and generate multiple wavelengths. LEDs are very inexpensive and are most commonly used in electronic devices such as cell phones and VCRs to indicate whether they are on or off. While LED pointers are often referred to as "laser" pointers to increase sales, they have a maximum output of 1–5 mW for safety reasons. In contrast, since infrared and near-infrared laser light pass readily through the skull, they can have a significant effect on brain neurons, which are exceptionally rich in mitochondria. Some studies suggest these lasers can speed recovery from stroke and traumatic brain injury, and improvement has been noted in an animal model of Alzheimer's disease.

These and similar claims that have been hyped in the media have also led to abuses by chiropractors and others who use laser therapy to treat musculoskeletal complaints. This is particularly true for electromagnetic radiation in the 750 nm near-infrared region that increases the production of ATP in mitochondria. Near-infrared radiation allegedly increases blood flow to the brain, so it is not surprising that it is being marketed as a noninvasive, safe treatment to help stroke and brain injury patients recover cognitive and motor function and to prevent or reduce the ravages of Alzheimer's and other neurodegenerative diseases. The problem is that there are no clinical trials to support anecdotal claims of remarkable recoveries in patients who might have improved without treatment. One such trial showed 36% improvement compared to 31% in controls, which was not clinically significant, so the sponsor raised $50 million from investors to do a much larger more rigorous study in stroke patients. It was halted prematurely when it became apparent there was no improvement and the company declared bankruptcy last year. Proponents maintain that stroke may not have been the best end point to select since subsequent studies have demonstrated improvement in traumatic brain injury, so the jury is still out.

PREVENTING OR TREATING EPILEPSY AND HEADACHE WITH ELECTRICAL STIMULATION

The Terminal Man by Michael Crichton was published in 1972, and was so popular that a movie version starring George Segal was released two years later. The plot centers on a man who was implanted with a microcomputer in his brain to predict and control his epileptic seizures. The computer was attached to numerous electrodes at different brain sites to determine which ones would stop his seizures, but the results were disastrous, since the purpose of the movie was to show the dangers of attempting to control the mind. Now, more than 40 years later, the FDA has approved a modern version of this to treat epilepsy in over 4,000,000 Americans whose seizures cannot be controlled by antiepileptic drugs or brain surgery.

The Neuropace RNS (responsive neurostimulation) system was approved in November 2013 for adjunctive treatment of epilepsy in patients 18 or older resistant to medications and who had at least three disabling seizures a month. It consists of an ovoid shaped battery-powered neurostimulator smaller and thinner than an implantable heart defibrillator, which is placed just under the skull. It is connected to one or two insulated wires that end with electrodes inserted into the areas of the brain where seizures originate. The device is programmed to detect any increase in activity and immediately deliver a small jolt of electricity to prevent it from causing a seizure, and is currently limited to patients with no more than two epileptogenic foci.

In one study, patients with stimulators turned on reported a 38% reduction in seizures over three months, compared to only 17% in those whose stimulators were off. After two years, patients with active stimulators reported a 50% or greater reduction in seizures. For some individuals, it can completely transform their lives. A 26-year-old man who suffered up to 20 seizures a day was essentially housebound when the device was implanted in 2008. He now can drive, has a full time job, is married, and recently had a son.

Cyberonics VNS (vagus nerve stimulation) therapy was approved in 1997 as adjunctive treatment for partial onset seizures in certain patients, and in 2005 for treatment of resistant depression. It consists of a titanium-encased generator the size of a small pocket watch weighing less than an ounce inserted under the left clavicle, which is connected by a thin wire lead electrode tethered to the vagus nerve in the neck. The vagus is the longest of the 12 cranial nerves and its name is derived from *vagus*, the Latin word for "wandering" or "uncertain." Early anatomists noted that the vagus wanders from the brain stem to innervate vital structures in the neck, thorax and abdomen, which explains why it is involved in the regulation of almost every organ, especially the brain. Stimulation of the vagus induces a state of relaxation that is opposite to the numerous increased sympathetic nervous system activities seen during "fight or flight" responses to severe stress.

The Cyberonics lithium battery-powered generator sends mild pulsed signals to the vagus that activate various areas of the brain. Treatment is automatically delivered at regular intervals 24/7 and can be programmed externally to adjust the duration, frequency and intensity of stimulation. Patients can also use a handheld magnet to deliver additional stimulation to stop a seizure by briefly placing it over the generator. The Aspire High Capacity (HC) fifth generation VNS device was approved by the FDA in 2011 for patients who consistently require larger jolts of electricity. VNS has been used for more than 20 years in over 100,000 patients without any significant adverse effects. However, since any surgical procedure is inherently risky and batteries have to be replaced every two or three years, noninvasive stimulation would be preferable if it could provide similar benefits.

This has been intensively investigated over the past four years by ElectroCore, a New Jersey based company with branches in the UK, Germany, Italy, Australia and New Zealand. Their gammaCore is a portable handheld device the size of a smart phone that sends electrical impulses through the skin to the vagus nerve on either side of the neck. It is preloaded with 50, 150, or 300 doses, each of which is equivalent to approximately 90 s of stimulation and is administered by the patient after appropriate training in its application. Treatment protocols vary depending on the condition, and it is approved for sale in Australia and Canada for cluster headache, migraine, and drug-induced headache. In one study, 13 of 14 patients suffering from intractable cluster headache were significantly improved with two doses in the morning and two in the evening. Benefits included fully aborting or significantly reducing their frequency and severity. If headaches recur, an additional dose usually provides relief for 5–8 h. In patients with acute episodic migraine, 72% had mild or no pain within 15 min after one dose, and this increased to 85% by 30 min. Unlike traditional VNS, patients can have a six-month trial to determine whether treatment works for them. The gammaCore device has received the CE-Mark in European Union countries not only for headache, but also depression, anxiety, epilepsy, irritable bowel syndrome and other stress-related gastrointestinal disorders. A randomized controlled, parallel-group, crossover trial for preventing epileptic seizures is currently under way at two sites in Australia and FDA sanctioned clinical trials are being conducted in the United States to gain approval here for the treatment of headache.

Cerbomed, a privately held German company, has developed the NEMOS, another noninvasive VNS device that works differently. It consists of a neurostimulation device the size of a mobile phone that transmits electrical signals to an ear electrode that is worn like a headset. These signals are then transferred through the skin to the auditory branch of the vagus where they reach higher centers in the brain. Patients can regulate the intensity of stimulation according to their personal sensitivity, which can vary from day to day. To obtain optimal effects, intensity should be adjusted to a level that produces a slight prickling or tingling sensation that does not cause any discomfort or interference with normal activities. Based on clinical trials, stimulation is done for approximately one hour four times a day at conveniently spaced intervals but the duration and frequency of treatment can be adjusted since responses vary. There are no side effects save for occasional transient local skin irritation but it may take several weeks for benefits to be noticeable. Patients who do not respond within four to six months can get a partial refund of the 4000 Euros ($5500) cost. The NEMOS device received European Union approval for the treatment of epilepsy and depression in 2010 and for pain in 2012, and is available in Germany, Austria and Italy, but not the United States.

The FDA has recently approved two transcutaneous nerve stimulators for migraine patients. The Cerena Transcranial Magnetic Stimulator was approved by the FDA in December 2013 as the first device to relieve migraine headache pain. The patient applies the stimulator to the back of the head using both hands and presses a button to generate a focused,

single pulse of magnetic energy that induces a mild electric current in the occipital cortex. This reduces the hyperactivity in areas of the brain that are associated with migraine headache attacks. The magnetic field is approximately half the strength of an MRI device, patients do not feel the mild electrical stimulation and treatment takes less than a minute. The device is approved for patients over 18 and appears to be more effective in those with auras that warn of an impending headache.

In one study of over 200 patients with moderate to strong migraine headaches, that had preceding auras at least 30% of the time, 38% were pain-free two hours after using the device compared to 17% of controls. After 24 h, nearly 34% of the Cerena users had no pain, compared to 10% in the control group. The device, which is manufactured by eNeura Therapeutics of Sunnyvale, California has been in use for several years in Great Britain, where it is sold as the Spring TMS Total Migraine System.

The price tag for the device is approximately $1200, but since some migraine medications cost $250 a month, it could pay for itself in six months, and will likely be offered for rental so patients can try it out first.

In March 2014, the FDA also approved Cefaly as the first device to prevent migraine headaches in adults. It uses a battery-powered headband-like appliance that sits across the forehead and over the ears and is positioned in the center of the forehead just above the bridge of the nose and eyes with a self-adhesive electrode. It delivers 16 mA electrical pulses at 60 Hz intervals that are targeted to the supratrochlear and supraorbital branches of the trigeminal nerve for just 20 min a day. The device, which is manufactured in Belgium, is available without a prescription in Europe and Canada, and, as with prophylactic migraine medications, may take weeks before significant improvement is noted.

In one study of over 2300 migraineurs from Belgium, France and Switzerland, who rented the device over the Internet for a 40-day trial costing 49 Euros, over half elected to purchase it. Only subjects using specific antimigraine drugs, and thus most likely suffering from migraine, were included in the survey. Adverse events and willingness to continue were monitored via phone interviews after the trial period. No significant adverse effects were reported. Built-in software allowed monitoring the total duration of use and hence compliance in subjects who returned the device to the manufacturer after the trial period. Analysis of these data in unsatisfied renters revealed they had used it for only 48% of the recommended 20 minutes a day.

In another study of 67 adults with at least two migraine attacks per month, either a sham or active device was used 20 minutes daily for three months. After one month, there was a 20% reduction in attacks in both groups, but by three months, the stimulation group had fallen an average of 30%, compared to no further improvement in the controls. While the difference between the two cohorts didn't reach statistical significance, the simulation group had three times more responders with at least a 50% drop in migraine days. Their headaches were also less severe and they required less pain medication. The U.S. price has not been established as yet, but it sells for about $300 in Canada.

MORE ELECTROCEUTICALS AND PIEZOELECTRIC BATTERIES THAT ARE PERMANENT?

"Electroceutical" refers to any type of electrical or electromagnetic energy that has a therapeutic effect similar to that achieved with drugs or surgery. Such interventions date back over 2000 years when Scribonius Largos used the electric shock from torpedo fish to relieve painful attacks due to headache and gout. After Leyden jars or crude batteries became readily available, Giovanni Aldini, Benjamin Franklin and others championed the application of stored electricity to treat severe depression and other psychiatric and neurological disorders. In 1933, Albert Hyman used a hollow needle carrying an insulated wire to deliver an electric shock to the heart to correct life-threatening disturbances in rhythm that did not respond to drugs. In 1958, Earl Bakken developed the first wearable external cardiac pacemaker in Minneapolis and the first fully implantable pacemaker designed by Rune Elmqvist was inserted at the Karolinska Institute in Sweden. Since then, there have been numerous improvements in cardiac pacemakers and defibrillators as well as combination devices.

Deep brain stimulation is routinely used for patients with drug resistant depression, Parkinson's disease and epilepsy, vagus nerve stimulation can provide similar benefits, and, as illustrated in this volume, many other conditions may respond to different electroceutical interventions, some of which are noninvasive. The problem is that, although there are various theories, nobody really knows how any of these work. Electroconvulsive shock therapy is still the most effective treatment for severe depression, and although it has been used for 75 years, we still don't know why it is effective. Alim-Louis Benabid's discovery that electrical stimulation improved Parkinson's disease in the early 1980s was also a serendipitous accident. The French neurosurgeon had been treating the disorder by producing lesions in the thalamus and noting their effects and decided to see what results applying various electrical frequencies would have. He was surprised when a frequency of 100 Hz completely suppressed the patient's tremors and the rest is history.

Nevertheless, electrostimulation is still based on a trial and error approach. To treat depression and other disorders, electrodes are placed at sites that sophisticated brain imaging studies show have different activity than surrounding tissues. The fact that no one knows what the optimal dose is or why stimulation is effective has not deterred researchers from investigating further indications or funding for such studies. In April 2013, GlaxoSmithKline (GSK) announced it would provide $50 million to "fund up to 20 external research projects that aim to advance the field of 'bioelectronic medicine' even further to develop a new class of therapies, dubbed 'electroceuticals'." In addition to the numerous applications already cited, researchers at a recent conference reported that electrostimulation of the occipital nerves at the back of the neck in fibromyalgia patients reduced symptoms an average

of 64% after six months. Another study, which showed that pain relief was controlled by the limbic system, found that pain scores were reduced 50% by electrostimulation. In 144 patients with refractory angina who had a spinal cord stimulation device implanted, 90% reported significantly fewer symptoms after almost eight years of follow-up.

The vagus nerve is often referred to as the neural superhighway, since it carries a multitude of efferent motor and afferent sensory fibers and has so many branches in the brain, neck, thorax, and abdomen that it influences almost every organ and system in the body. Electrical stimulation can affect both types of fibers depending on location and dosage. Stimulation of efferent fibers slows heart rate, promotes gastrointestinal motility, dilation of arterioles, constriction of the pupils and other activities that are the opposite of those seen in "fight or flight" responses to severe stress. It now appears that inhibition of inflammation should be added to this list based on the groundbreaking research of neurosurgeon Kevin Tracey and his colleagues.

Over a decade ago, Tracey was evaluating the ability of an experimental drug to limit brain damage after a stroke. His group was injecting the new drug into the brains of rats during a stroke and noted that, although inflammation and swelling were reduced locally, this immune system response seemed to occur throughout the body. The dose injected was so small that it could not have resulted from any humoral signal transmitted via the blood stream and the only other explanation was the nervous system. Subsequent investigations revealed that it was due to stimulation of efferent fibers of the vagus nerve that reduced the production of cytokines, protein molecules that signal cells to move to sites of injury. This suggested that anti-inflammatory drugs, which often have undesirable side effects, might be replaced by specific types of vagal stimulation that were more precise and much safer. Inflammation is the immune system's protective response to infections and sterile injury, but it must be regulated within strict limits, since not enough and especially too much can cause significant damage. Increased inflammation has been incriminated as a cause of heart attacks, stroke, accelerated atherosclerosis, hypertension, type 2 diabetes, Alzheimer's disease, and certain cancers, as well as rheumatoid arthritis, multiple sclerosis, lupus, thyroiditis and other autoimmune disorders.

Tracey mapped out the details of what he called "The Inflammatory Reflex" in 2000, and, two years later, described how vagal stimulation reduced inflammation via cholinergic anti-inflammatory pathways. He subsequently established SetPoint Medical, a biomedical technology company that utilizes vagal stimulation to treat patients with rheumatoid arthritis, Crohn's disease and other autoimmune diseases. Inflammatory cytokines like TNF (tumor necrosis factor) are greatly increased in rheumatoid arthritis and accumulate in joints where they cause pain due to inflammation, swelling, and tissue breakdown. Treatment currently consists of injectable drugs that block TNF like Enbrel, Remicade and Humira, but these only provide significant benefits 50% of the time and can have serious side effects such as decreased resistance to infections. Many carry a black box warning that immunosuppressive side effects can be extremely dangerous, or even fatal, and costs can run as high as $30,000/year with no insurance and $15,000 to $20,000 for patients with coverage.

SetPoint therapy is based on the premise that by mapping out the neural pathways of a disease, you can then stimulate or inhibit those circuits that are not working properly to restore health without flooding the body with dangerous drugs. It uses a miniature neuromodulator (95% smaller than current devices) with a wireless charger that is implanted directly on the vagus nerve. It also differs from other VNS devices since it delivers fewer pulses over a shorter duration of time with a different pattern and can be controlled by an iPad. The company began clinical trials in rheumatoid arthritis because it responds fairly rapidly to drug therapy and if there is no improvement after two or three weeks it is very unlikely to work. There are also objective markers and established standards that allow evaluation of efficacy.

In the initial pilot trial of eight patients in 2012, the first was a truck driver crippled by rheumatoid arthritis because of inflamed painful joints that prevented him from driving, doing other work, or even playing with his children. After years of disability and pain and failure to respond to drugs, he volunteered to have the SetPoint device implanted on the vagus nerve in his neck. Improvement began within four or five days and, eight weeks later, his arthritis was in remission and he was able to drive and return to work and resume his normal life as a father. The other patients also experienced significant improvement and there were no adverse effects. The company will receive the first of the GSK grants, has liberal funding from other sources, and further trials are planned in patients with Crohn's disease and other inflammatory disorders for which adequate treatment is not available.

One of the problems with pacemakers, defibrillators and implanted deep brain stimulation devices for Parkinson's disease and depression is that the batteries must be replaced every three or four years, which requires surgery. Those like the one just described that use wireless charges last much longer but will also eventually require a change. In addition, patients with some pacemakers or other implanted devices are warned to avoid having an MRI since it could disrupt their proper operation. These problems may vanish in the future with the advent of fabric batteries that continually deliver piezoelectricity generated within the body.

Piezoelectricty refers to the ability of certain materials to build up an electrical charge when subjected to pressure. One example is bone, which is stimulated to grow by a piezoelectric signal generated whenever physical stress is applied. This explains why wrestlers and marathoners have stronger than normal bones and astronauts lose an average of more than 1% bone mass for every month spent in weightless space. It also led to the use of electricity to unite fractures that had persisted for years. Attempts to harvest power from activities in the body are not new, and have ranged from capturing the energy released during the breakdown of glucose to minute changes in temperature. A much more practical and powerful

method would be to exploit the energy provided by motion in the body, and animal studies indicate that this is now quite feasible.

As reported in the January 21, 2014 issue of *Proceedings of the National Academy of Sciences*, University of Illinois scientists used a "nanoribbon" lead zirconate titanate (PZT) material that is film-thin and completely flexible as their source of piezoelectricity. Strips of PZT were placed on very thin, bendable plastic to create wrap-like sheets with a thickness one third of a piece of paper. These were sutured to the surfaces of the hearts, lungs, and diaphragms of cows, sheep and pigs, whose organs are approximately the same size as those in humans. The energy harvesting PZT sheets were then connected to AC/DC conversion devices and microbatteries. The researchers reported that the sheets did not appear to interfere with the normal function of the heart or lungs and they were able to capture and store enough electrical power to meet or exceed the requirements of standard implantable devices.

It is much too early to see if this can be used in humans, since these observations were made in anesthetized animals and no studies have yet been done for extended periods of time in animals with their chest closed and engaged in normal activities. Although there was no evidence of bioincompatability, the body's reaction to foreign substances varies. Long-term studies are needed to evaluate this as well as how long this source of electricity will last. As the lead investigator noted, "So far we have shown it lasts for half a day or so, but we will have to show that this method will generate sufficient electricity for at least a decade, because if not, there's no point." Animal research does not always produce the same results in humans, but an authority not involved in this study stated that "The technology is certainly viable," and along with others, believes that body-generated energy will eventually be a reality with broad practical applications.

ENVOI

There are numerous other devices that could be mentioned, such as the Calmare "Scrambler System." Long available in Europe, it was recently cleared by the FDA for relief of chronic pain in patients with cancer, herpes, reflex sympathetic dystrophy (RSD) and degenerative disk disease. It sends a blocking signal to electrodes applied to the skin over the affected site that immediately prevents the pain message from getting to the brain. Relief lasts for varied amounts of time that increase with repeated treatments. A series of 10 treatments costs $1500, it is not yet covered by insurance and is contraindicated in pregnancy and patients with pacemakers or other implantable devices. With respect to the advances in bioelectromagnetic and subtle energy discussed in this volume, it is difficult to predict which will have the most influence on the practice of medicine over the next few decades. It seems likely that there will be major changes in how we treat cancer and that doctors may be prescribing frequencies that are more effective and much safer than drugs and chemotherapy. New discoveries could also confirm the validity of acupuncture, meditation, and other traditional and time-tested practices. The Cleveland Clinic has already established a Chinese herbal-therapy ward for patients suffering from chronic pain, fatigue, poor digestion, infertility and sleep disorders that have failed to respond to conventional therapies. As the clinic's medical director noted "Western medicine may not have all the answers."

One of the most promising developments has been the discovery of biological or EZ water that acts like a battery to supply energy to cells. It is well established that living things respond to electromagnetic fields with intensities far below levels that would produce heat, and that, contrary to previous dogma, these nonthermal fields can have powerful biological effects such as inhibiting the growth of cancer cells. All living things have associated electromagnetic fields and there is an emerging electromagnetic paradigm that posits illness results when these are disrupted. Energy homeostasis can be restored by certain pulsed electromagnetic fields and especially resonance signaling from combinations of fields such as ion cyclotron resonance (ICR). An illustration of ICR can be found in the chapter on Holistic Electromagnetic Therapy, which is effective for a wide range of medical disorders. How these benefits are achieved is not clear, but one intriguing possibility is that it is via the effects of nonthermal fields on biological water.

While tap water that is magnetically conditioned by exposure to electromagnetic fields is different than biological water, it has long been used to remove limescale from plumbing and boilers, probably by effects on calcium-sensitive enzyme systems. It can also increase or decrease the growth of crops and yeast cultures, depending on the dosage. With respect to the latter, less than 30 s of conditioning stimulated growth but higher doses inhibited it. Since Adey's group had shown in 1975 that weak electromagnetic fields (EMF) could affect calcium ion transport in brain cells, it seems likely that conditioned water and weak EMFs work via similar mechanisms. Analogous dual effects have been demonstrated for ionizing and nonionizing radiation, which can both help or harm depending on dosage and other factors. As Paracelus noted 600 years ago, "*Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.*"

This is a problem for EMF research, since it is not clear whether new discoveries will open a treasure chest or Pandora's box. And even when serious potential hazards are discovered with novel technologic advances, they may be suppressed to preserve profits or ignored because they have become so essential. There are now over 7.3 billion cell phones, more than the number of people on the planet, and at least 100 countries where the number of cell phones exceeds the population. Ninety seven percent of American adults have cell phones, the majority of which are "smart phones" that contain a radiofrequency identification (RFID) chip that can track our every movement via GPS or cell tower triangulation. Unlike a barcode, the chip does not need to be within line of sight of the reader and may be embedded in the tracked object. In addition, microphone cameras that come standard on every phone can be remotely activated by law enforcement surveillance systems.

Despite this intrusiveness, they are accepted as the norm by billions of people worldwide, and many pay top dollar to have the best tracking device available. Some predict that this technology will eventually become so prevalent that it will be impossible to open a bank account, get a credit card, driver's license or buy a car without having your hand or your face scanned. It is rumored that Obamacare will require an RFID chip, and that, as this catches on, such chips will be voluntarily implanted under the skin for everything from access to high security sites and grocery store purchases. Like cell phones, public acceptance will be driven by peer pressure, its time saving convenience and ease of use. The same will likely happen with Google Glass as the price comes down, and most of our grandchildren will be surfing the web with the ability to record everything they see and instantly upload it to the Internet. Electromagnetic pollution will undoubtedly increase and the likelihood that this will have adverse effects, including cancer, especially in children, is not a deterrent. Many people can no longer live a normal life without their cell phones, and with respect to cancer, the general attitude seems to be "*I wouldn't believe it even if it were true*." The challenge will be to find ways to make these technologies safer or to block their harmful effects. There are numerous devices and even jewelry that make these claims on the web but no scientific studies to back them up, and to the best of my knowledge, they are all are worthless.

Despite these caveats, I am optimistic about the future and the ability to improve on the safe and effective innovative devices described in this volume. One of the most fruitful areas to explore is the potential for resonance signaling. Since ICR is obtained by combining any of thirty alternating magnetic field frequencies with the earth's geomagnetic frequency, a variety of different signals can be generated. As noted in the chapter "Electromagnetic Therapy: A Primer," in addition to the benefits achieved by the Seqex device, ICR magnetic fields have been found to increase the ability of stem cells to repair damaged heart tissue and, in animal studies, to dissolve the β-amyloid plaque seen in Alzheimer's disease, and significantly reduce cancer growth. Another area of interest is whether they can help to explain the "memory of water" enigma, or provide insights into the nature of consciousness, described in a recent book as "The fourth stage of matter."

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I am appreciative of the expertise of Naomi Wilkinson, the Commissioning Editor, Nick Barber, Project Manager, and the cooperation of all the authors in complying with the strict schedule. Special thanks are due to Professor Abraham Liboff, not only for his cutting-edge chapters, but also for reviewing and providing valuable advice about others.

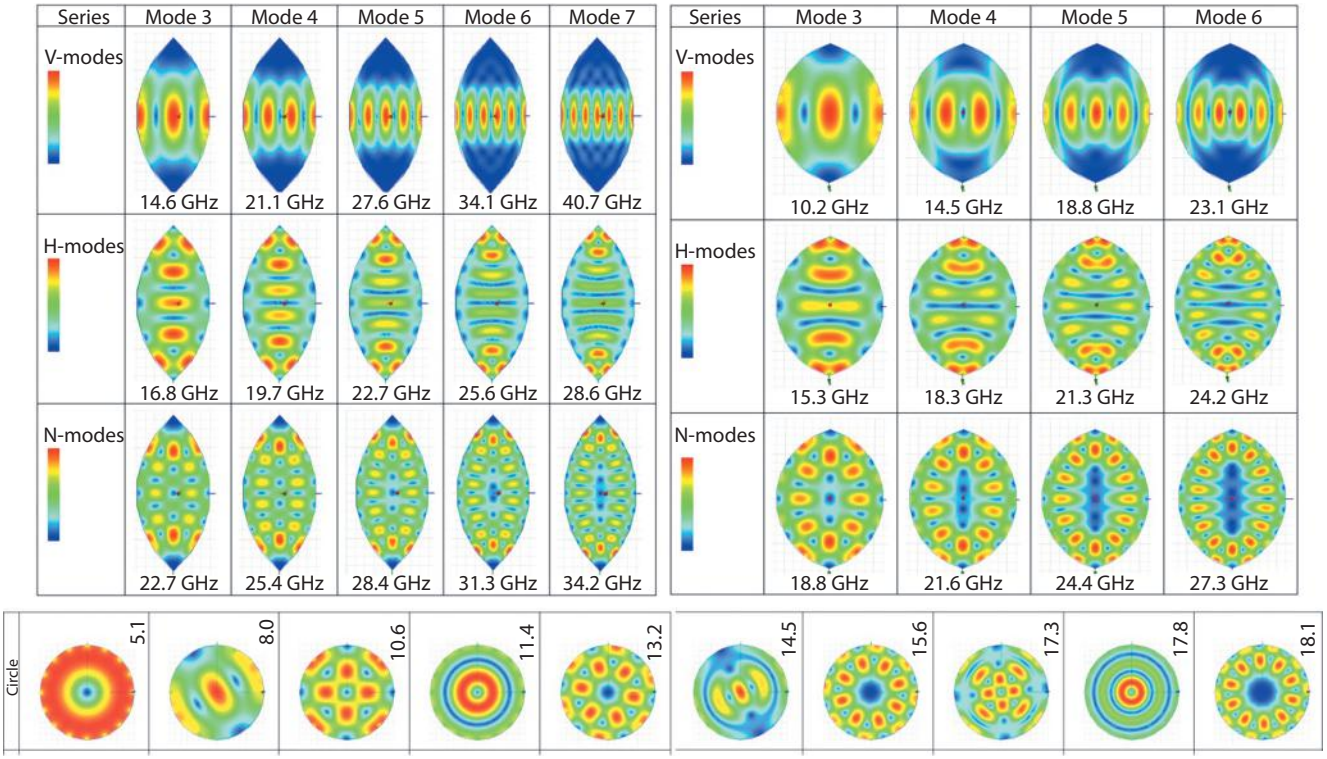

FIGURE 10.4 Resonant modes in elliptical and spherical resonators generated by finite element analysis and the resonant frequencies in GHz; V, vertical, H, horizontal, N, nodal. (Rearranged from Pietak AM. *J Phys Conf Ser* 2011;329:012012. doi:10.1088/1742–6596/329/1/012012.)

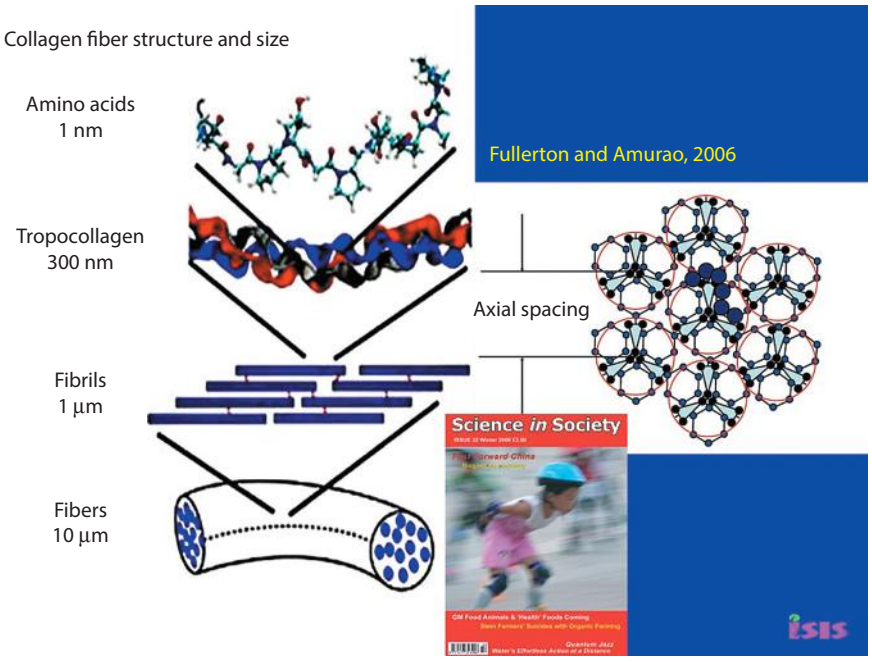

FIGURE 10.8 Collagen water structure revealed.

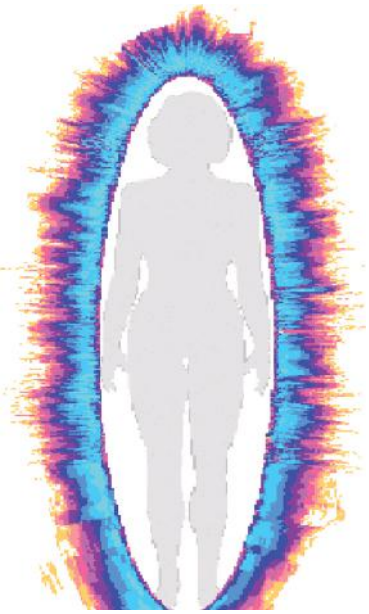

FIGURE 12.1 Human energy field of a healthy person.

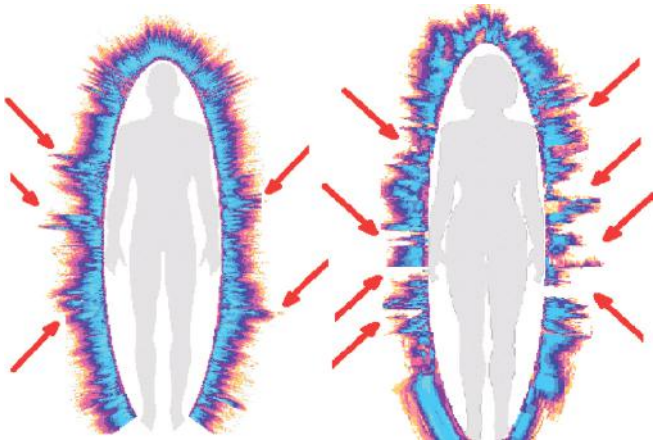

FIGURE 12.2 Human energy field of an apparently healthy person with problems. Areas indicate the areas of attention.

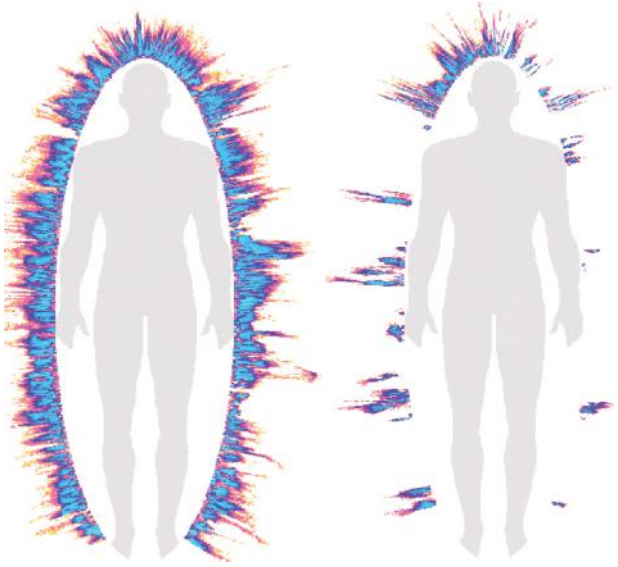

FIGURE 12.3 Energy field of an orchestra conductor before and after symphony performance.

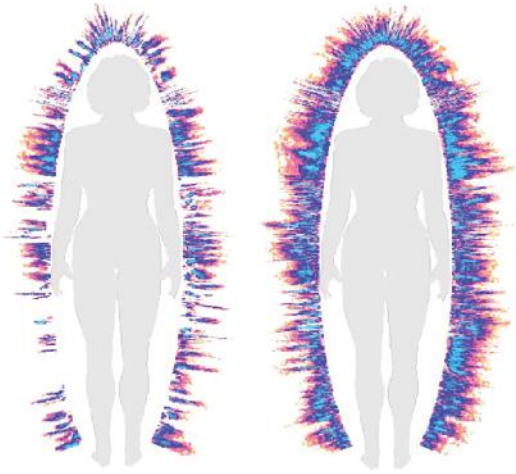

FIGURE 12.4 Energy field of a person before and after the course of acupuncture.

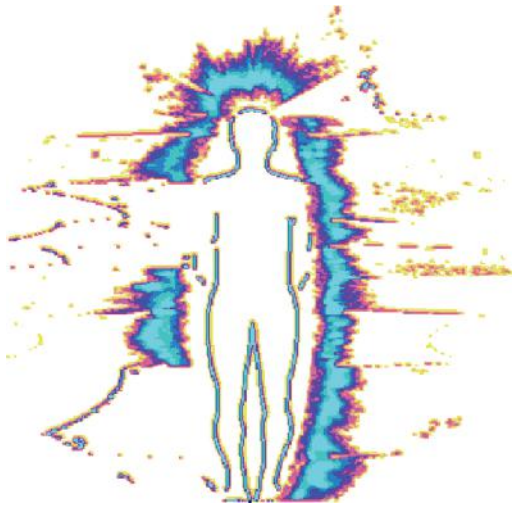

FIGURE 12.5 Energy field of a person in an altered state of consciousness in the process of Ajurvasco ceremony.

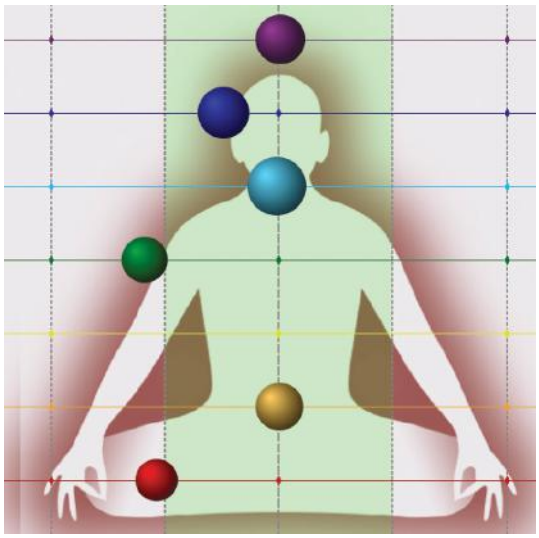

FIGURE 12.6 Ideal chakras distribution.

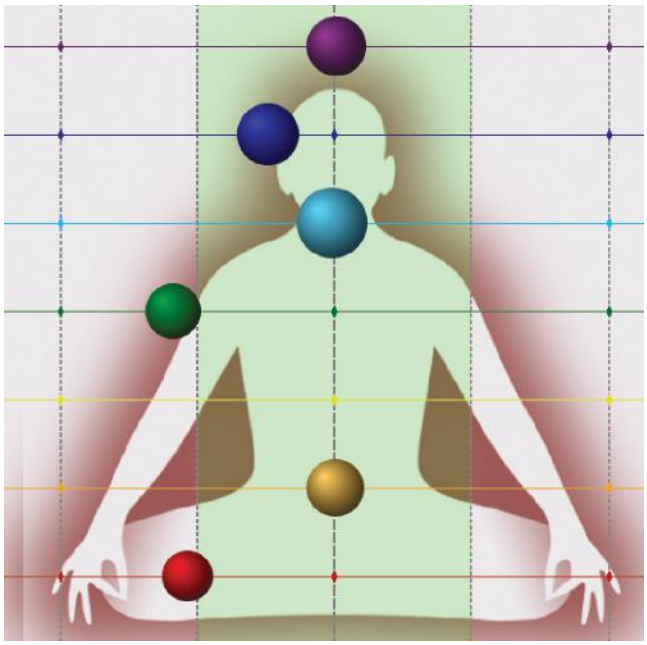

FIGURE 12.7 Chakras distribution of a person.

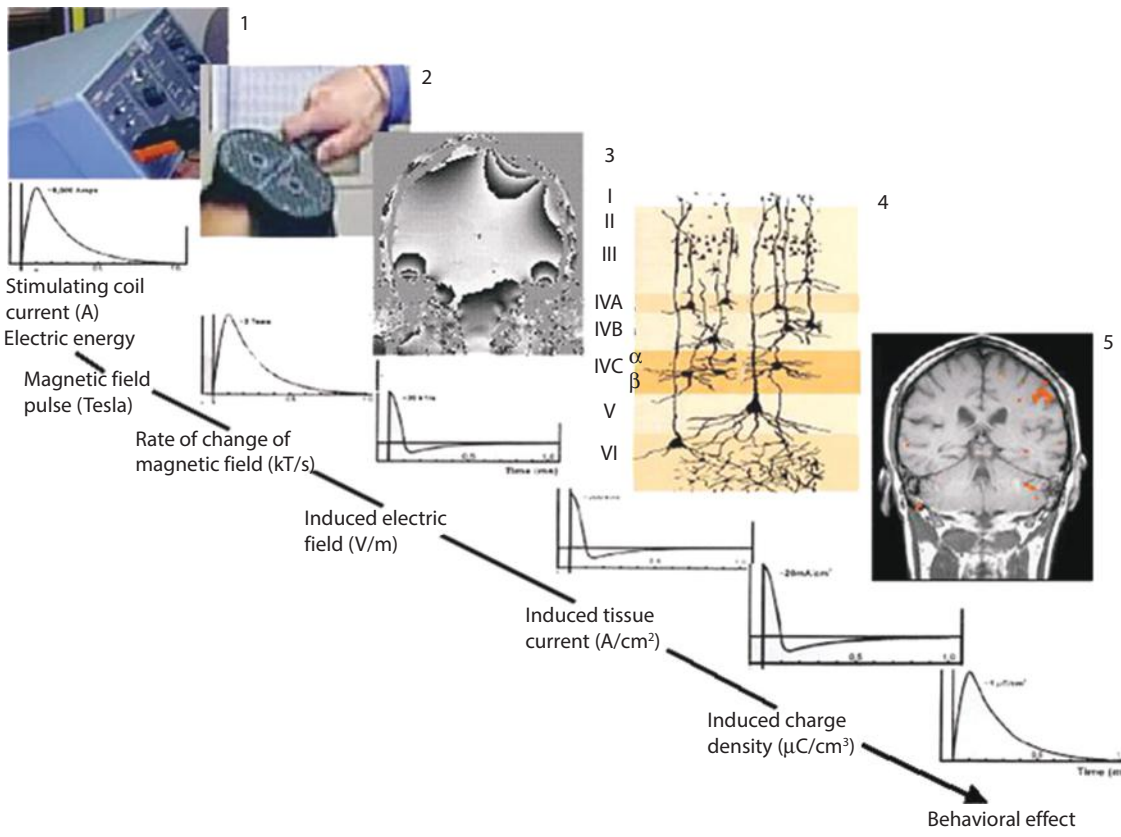

FIGURE 18.1 This diagram shows the cascade of events that occur following a transcranial magnetic stimulation pulse. It was initially thought that almost all of the biological effects of TMS come from the electrical induced current in the brain, at the end of the cascade. The studies and discussion of the rest of this book, however, reveal that there may be biological effects of the magnetic field itself, or any of the other steps in the TMS cascade.

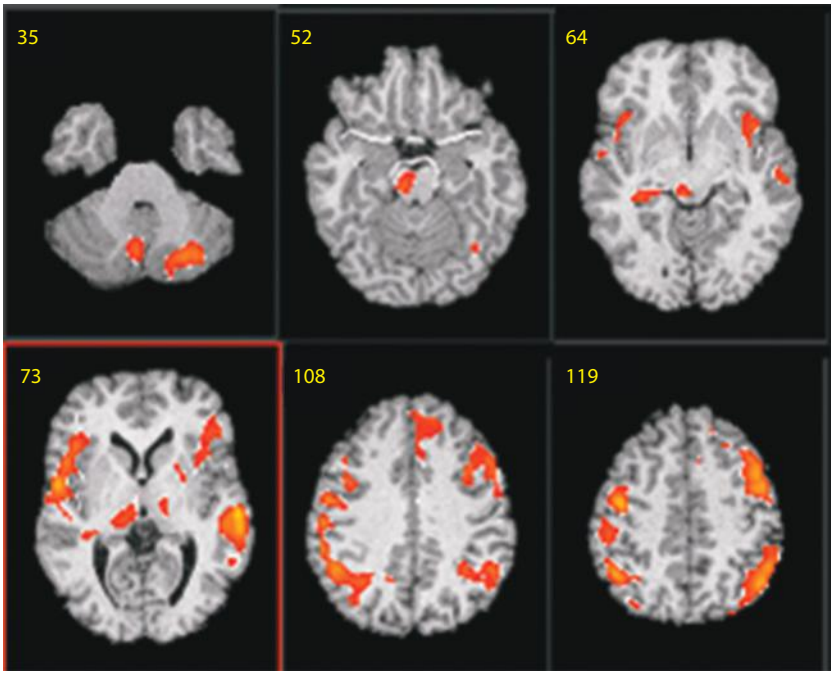

FIGURE 18.2 fMRI demonstrates the secondary brain effects of prefrontal transcranial magnetic stimulation (TMS). Shown in color are the brain regions that are significantly activated compared to rest ($p < 0.01$, extent $p < 0.05$) in six adults with clinical depression during left prefrontal TMS at 1 s. The differences are projected on a common brain (Talairach). The arrow depicts the TMS coil position, which follows the algorithm developed in 1994 for probabilistically finding the prefrontal cortex based on relative distance from the motor cortex. TMS was originally used over the prefrontal cortex to treat depression because of the potential for activating cortical-limbic loops. Imaging studies such as this one show that this assumption was likely correct and that the prefrontal cortex is a window to stimulating subcortical and limbic sites. Future work is needed to determine the optimum cortical sites for maximal clinical effectiveness, and whether there are general rules for finding this across individuals or should be individually guided based on structural or functional imaging.[209] (From MUSC Brain Stimulation Laboratory and Center for Advanced Imaging Research, Dr. Li.)

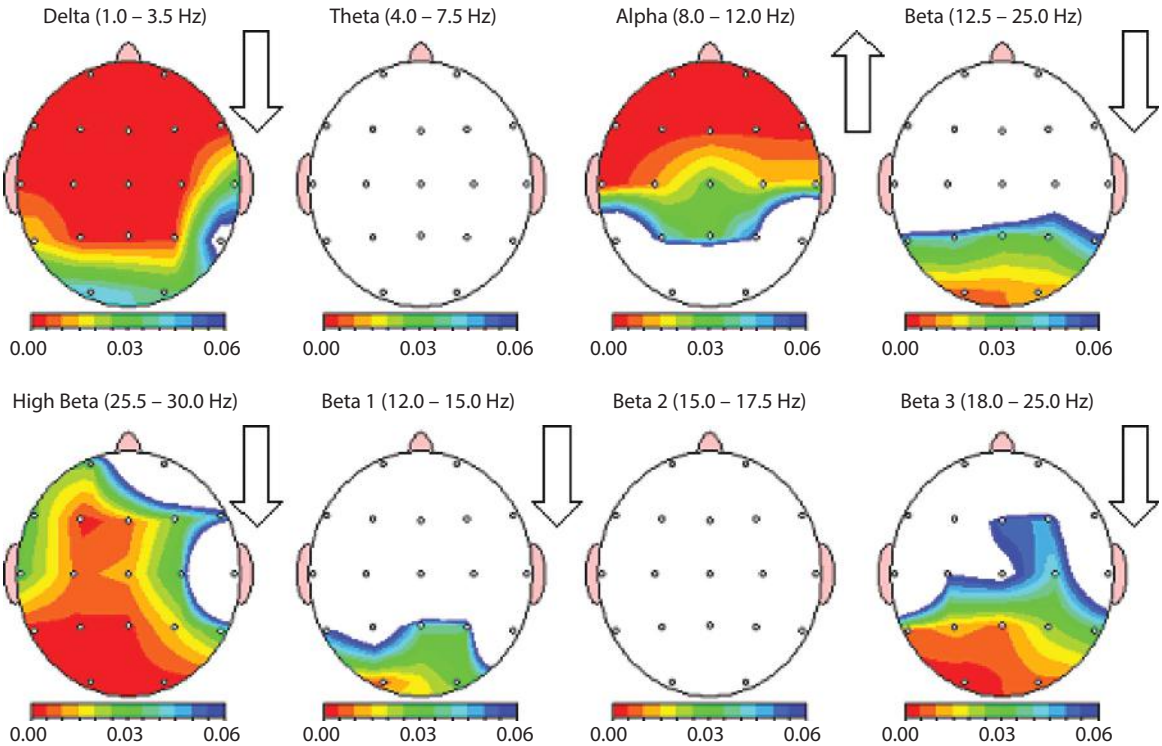

FIGURE 19.1 Relative power p-value topographical map for 0.5 Hz cranial electrotherapy stimulation (CES). Statistically significant changes ($p < 0.05$ or better) after a single 0.5 Hz CES session are indicated by color; white indicates no significant change. The arrows indicate the direction of change. Statistically significant decreases were seen in delta and beta with statistically significant increases in alpha.

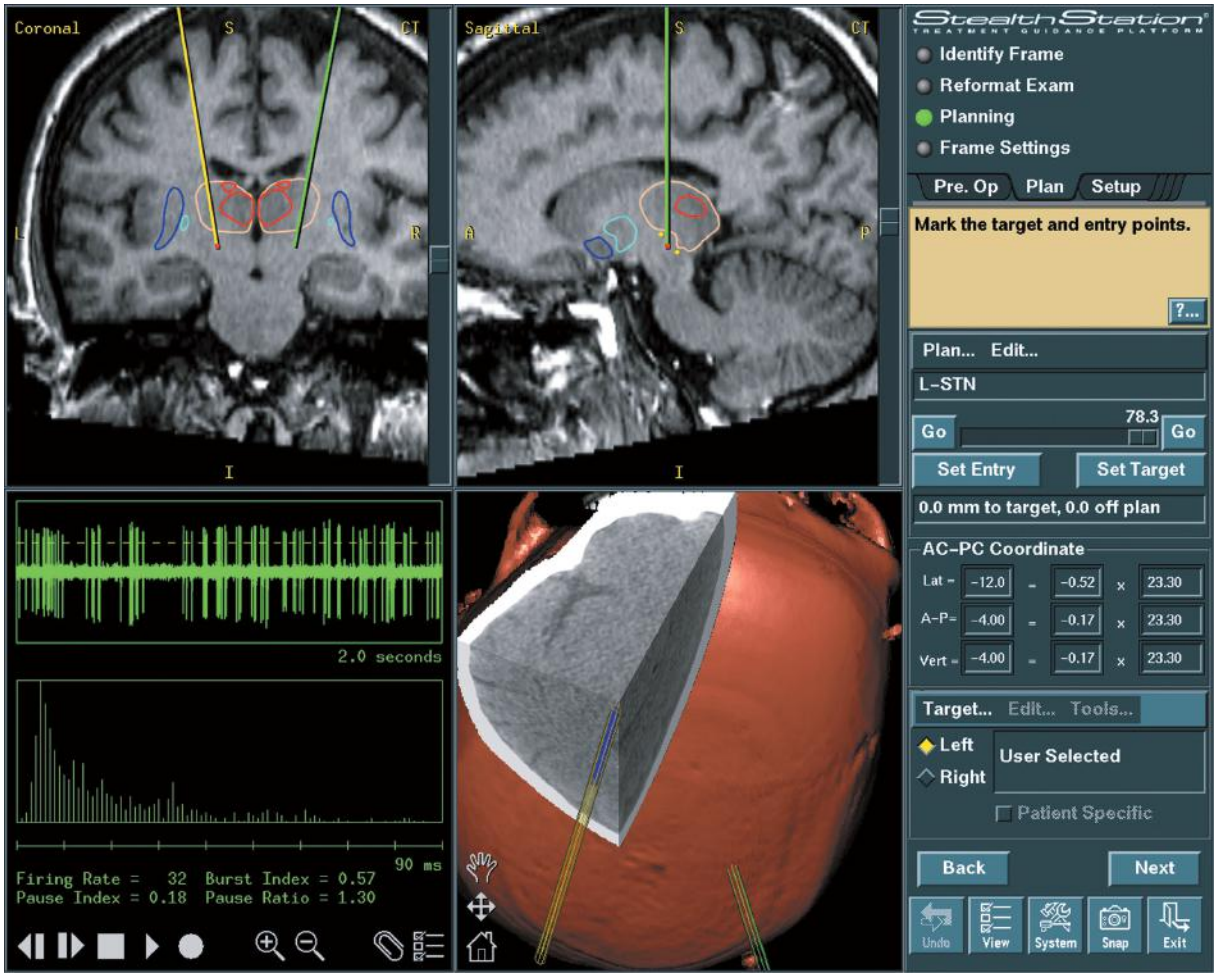

FIGURE 20.3 Computer-guided brain targeting and navigation. Operative computers combine different imaging modalities such as computed tomography and various magnetic resonance imaging (MRI) sequences, along with brain and patient-specific atlases, to provide the target and best trajectory of approach to that target. In this case, an actual path in the brain is shown in the axial, sagittal, coronal, and three-dimensional planes, toward the target—the subthalamic nucleus.

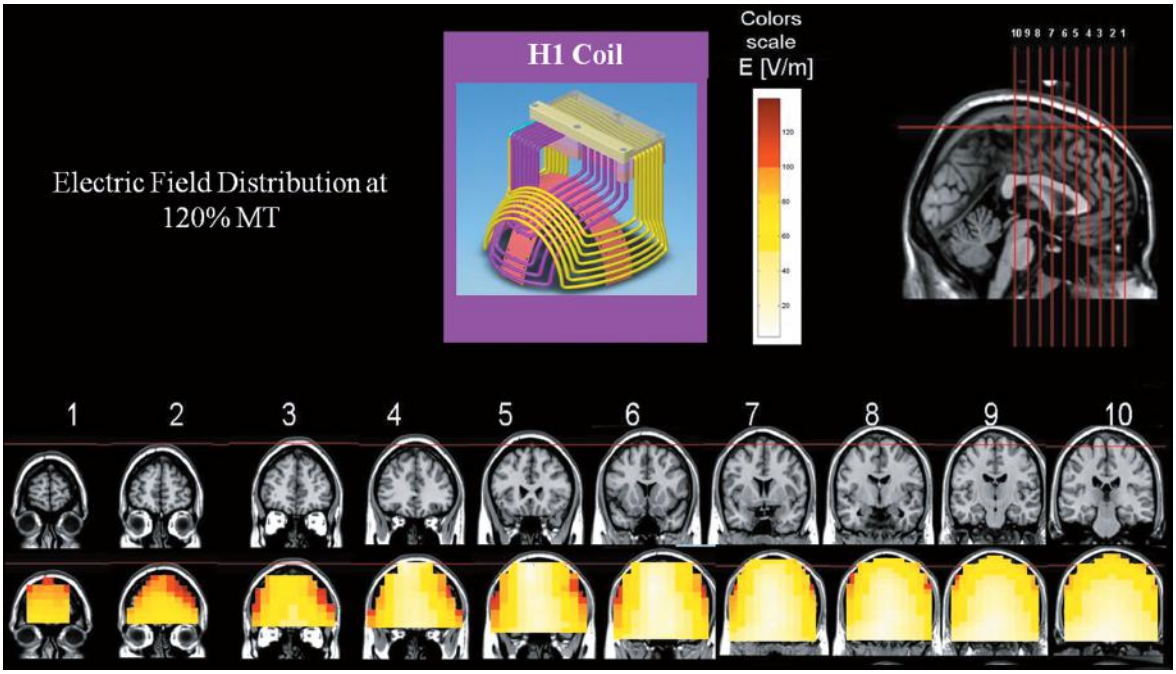

FIGURE 21.1 Colored field maps for the H1 coil indicating the electric field absolute magnitude in each pixel over 10 coronal slices 1 cm apart. The red pixels indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output level required to obtain 120% of the hand motor threshold, at a depth of 1.5 cm.

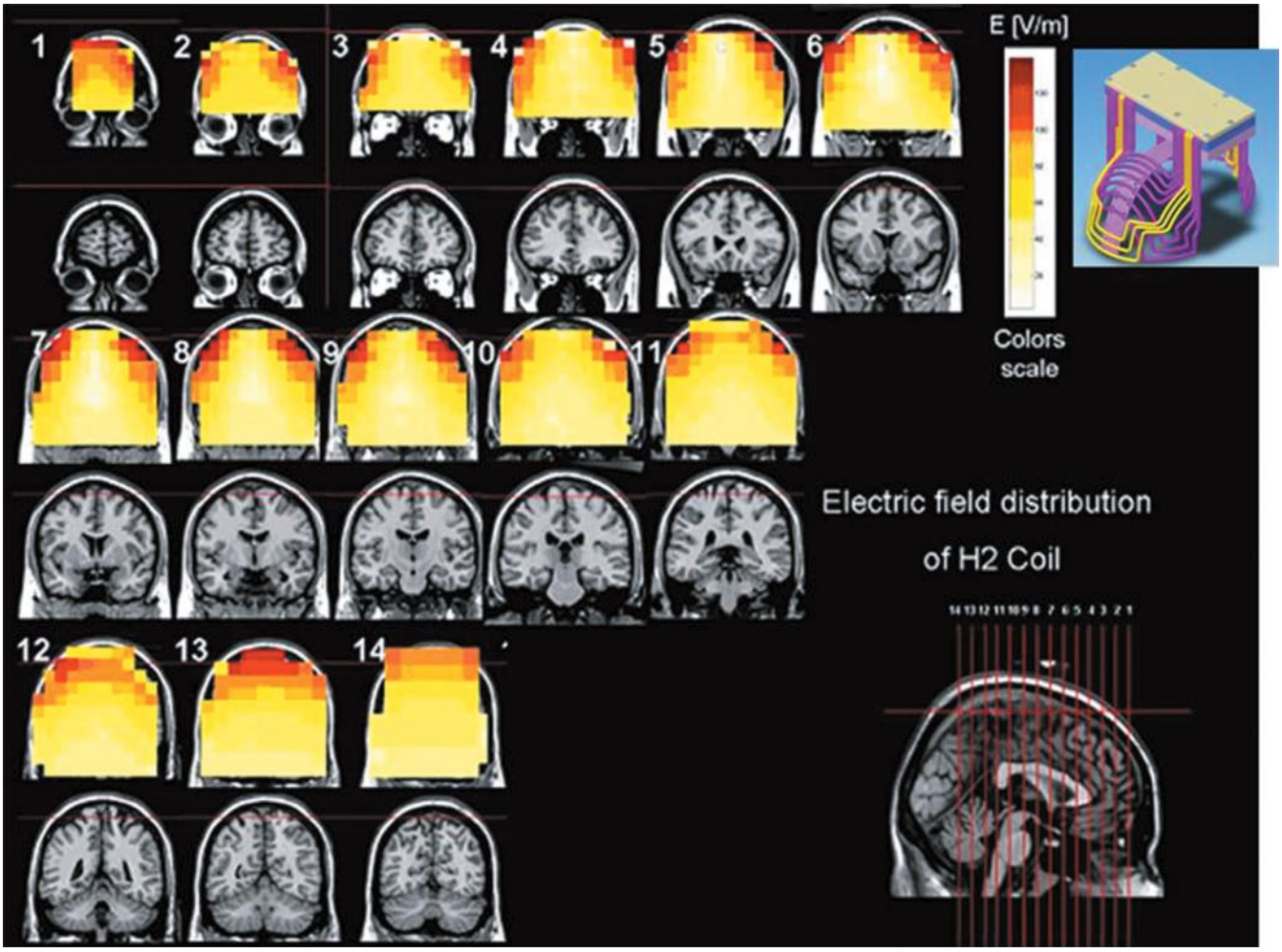

FIGURE 21.2 Colored field maps for the H2 coil indicating the electric field absolute magnitude in each pixel at 120% of hand motor threshold, for 14 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

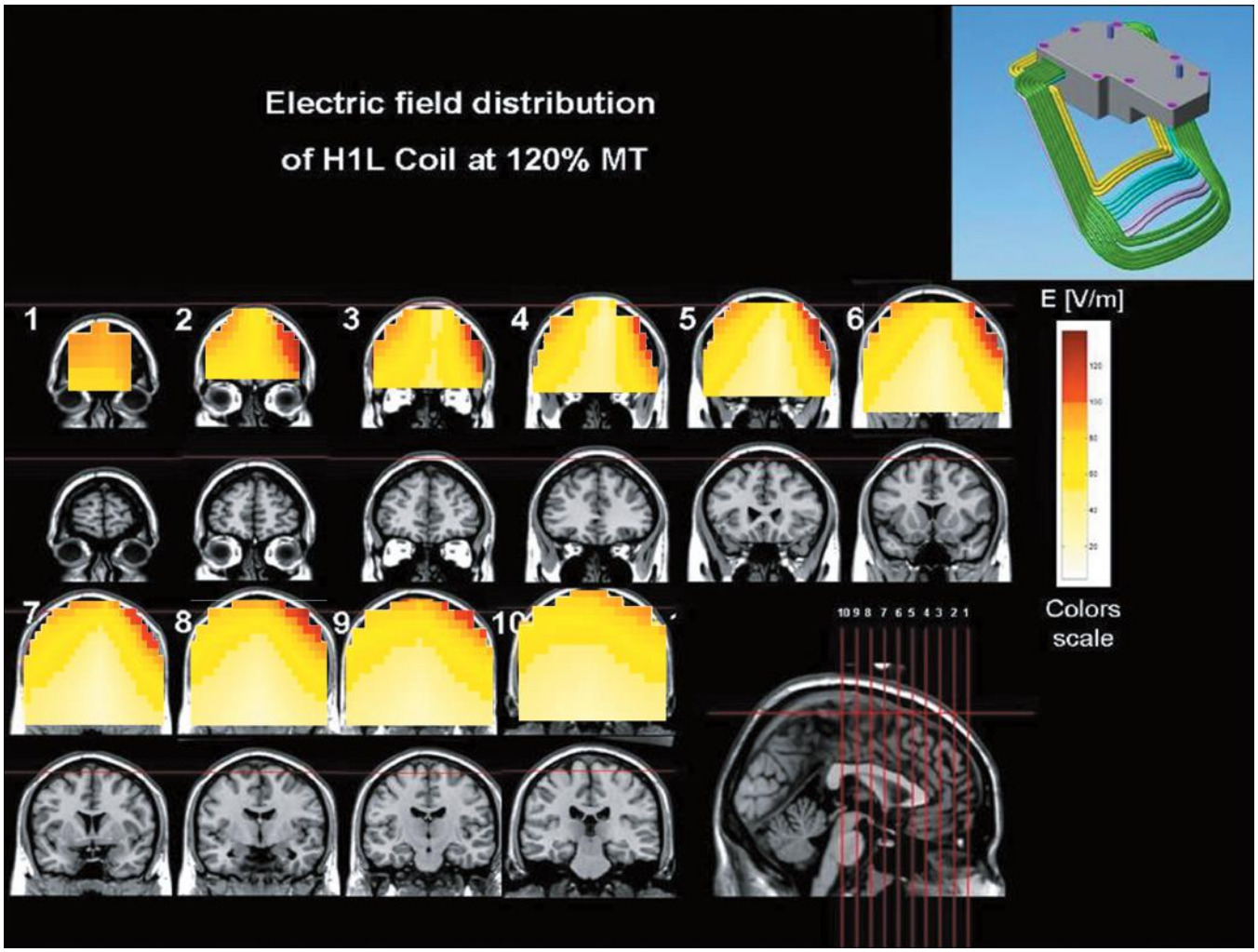

FIGURE 21.3 Colored field maps for the H1L coil indicating the electric field absolute magnitude in each pixel at 120% of hand motor threshold, for 10 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

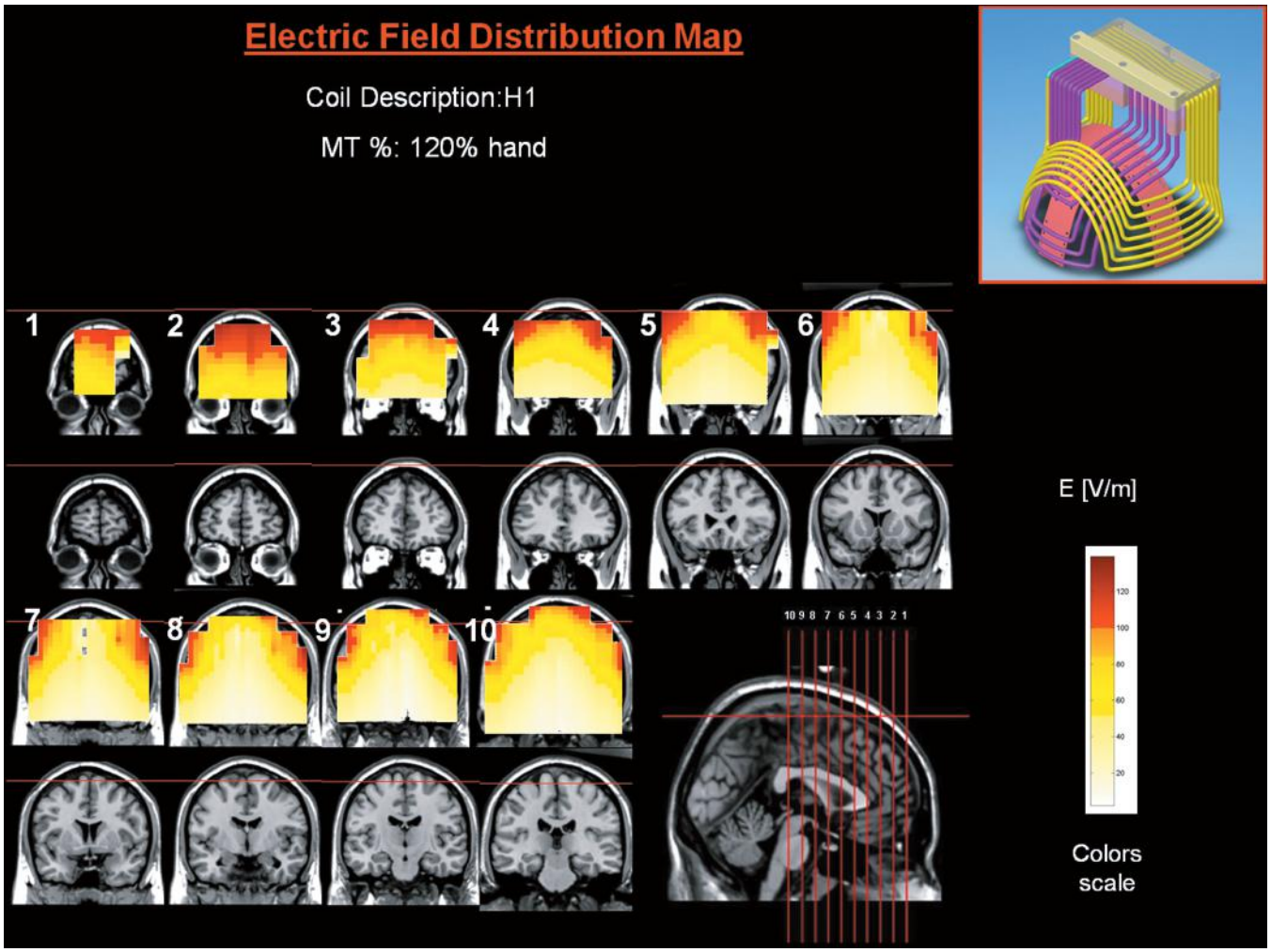

FIGURE 21.4 Colored field maps for the H1 coil positioned above the medial frontal cortex for the treatment of posttraumatic stress disorder patients, indicating the electric field absolute magnitude in each pixel at 120% of hand motor threshold, for ten coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

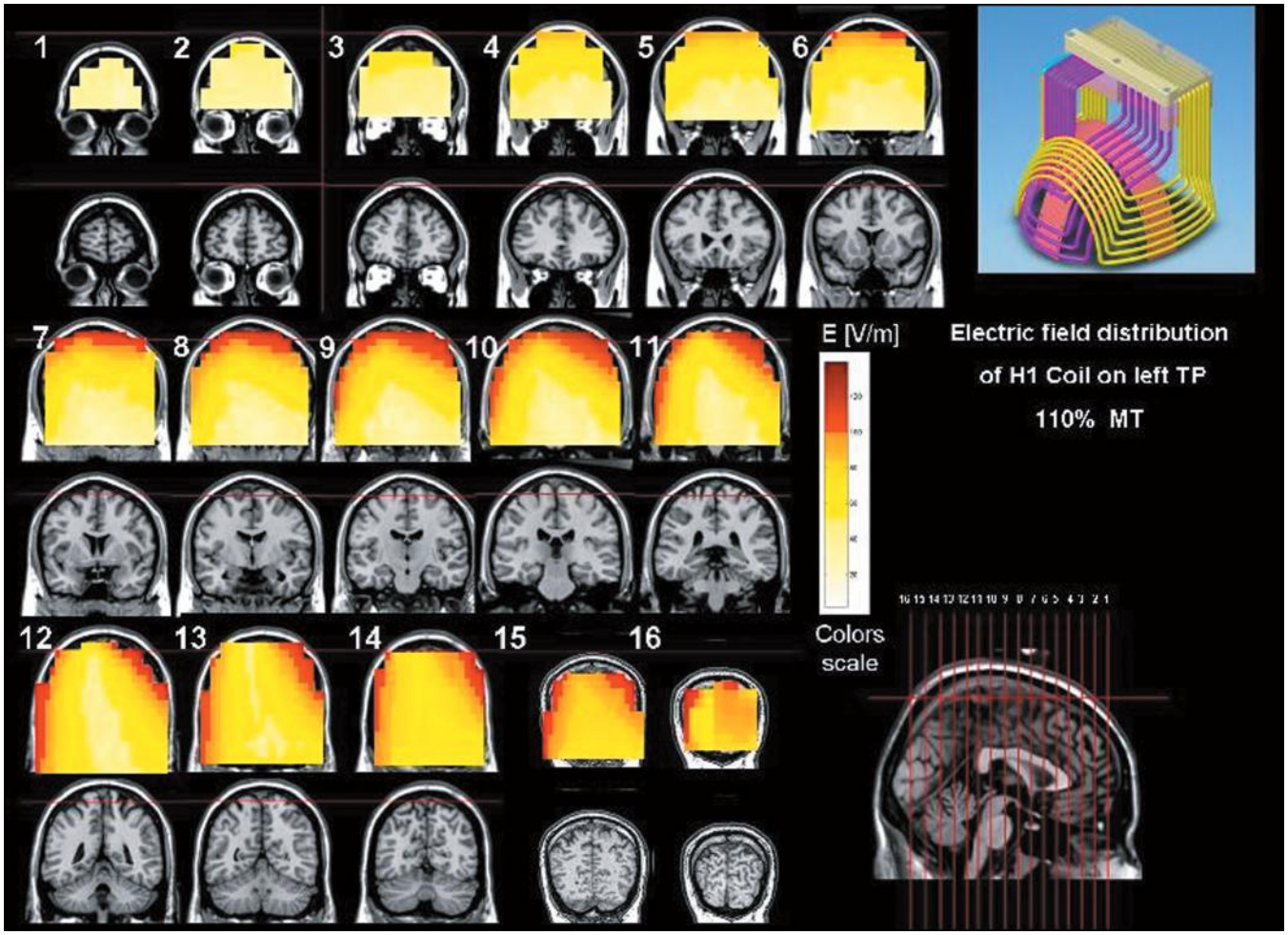

FIGURE 21.5 Colored field maps for the H1 coil positioned above the left temporoparietal cortex for the treatment of auditory hallucinations in schizophrenic patients, indicating the electric field absolute magnitude in each pixel at 110% of hand motor threshold, for 16 coronal slices 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set to 100 V/m.

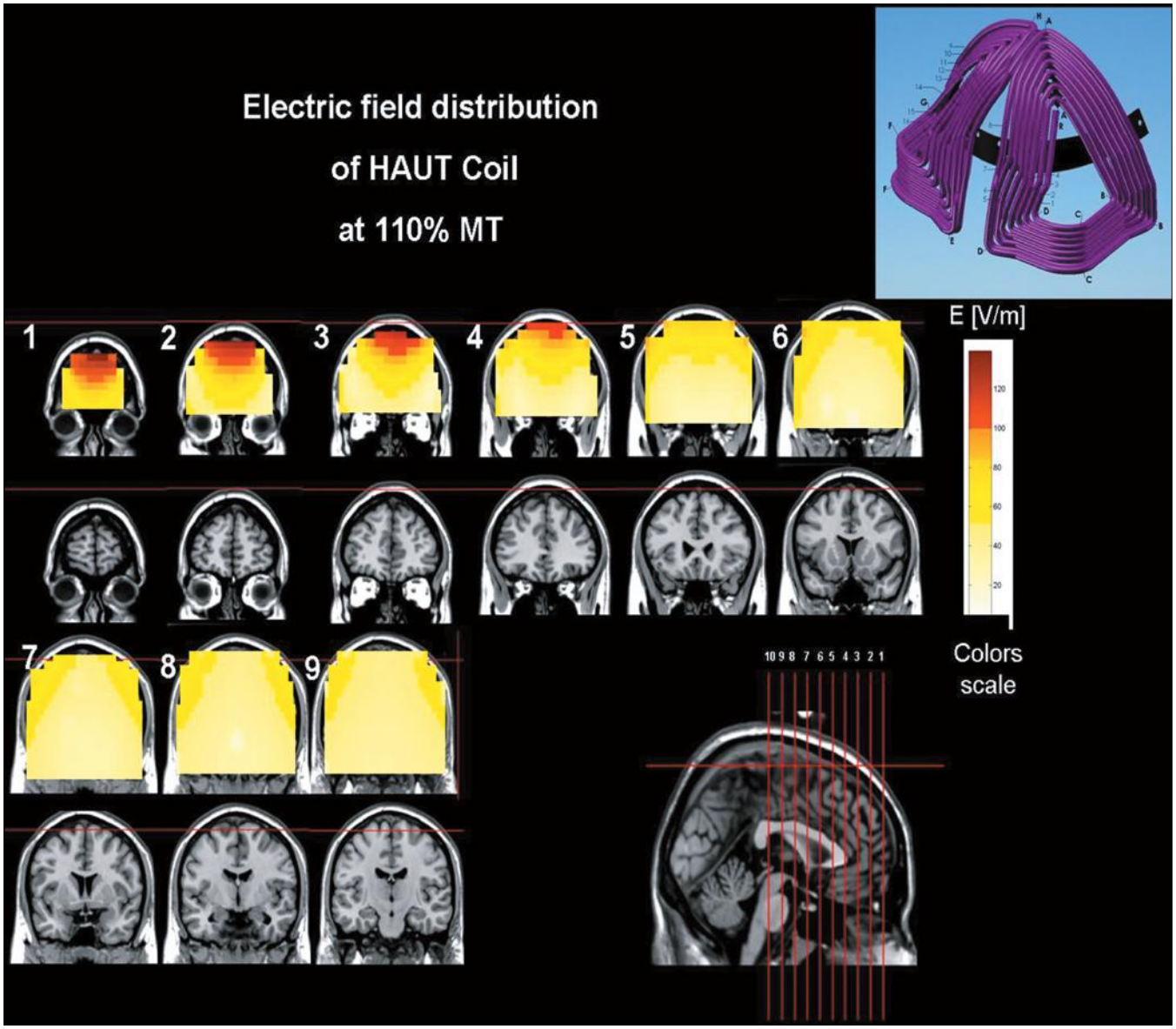

FIGURE 21.6 Colored field maps for the HAUT coil indicating the electrical field absolute magnitude in each pixel at 110% of hand motor threshold, for nine coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

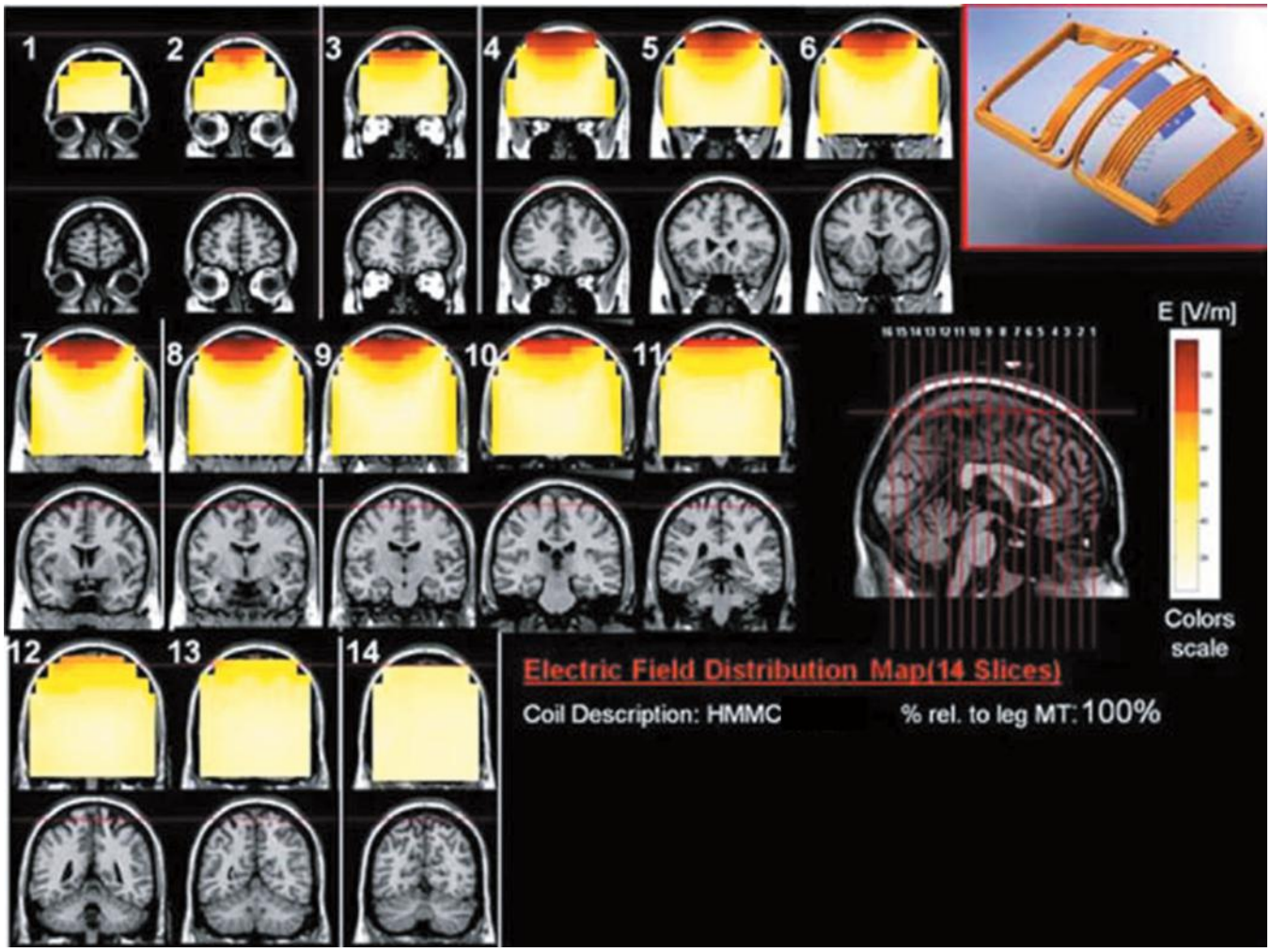

FIGURE 21.7 Colored field maps for the HMMC coil indicating the electrical field absolute magnitude in each pixel at 100% of leg motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

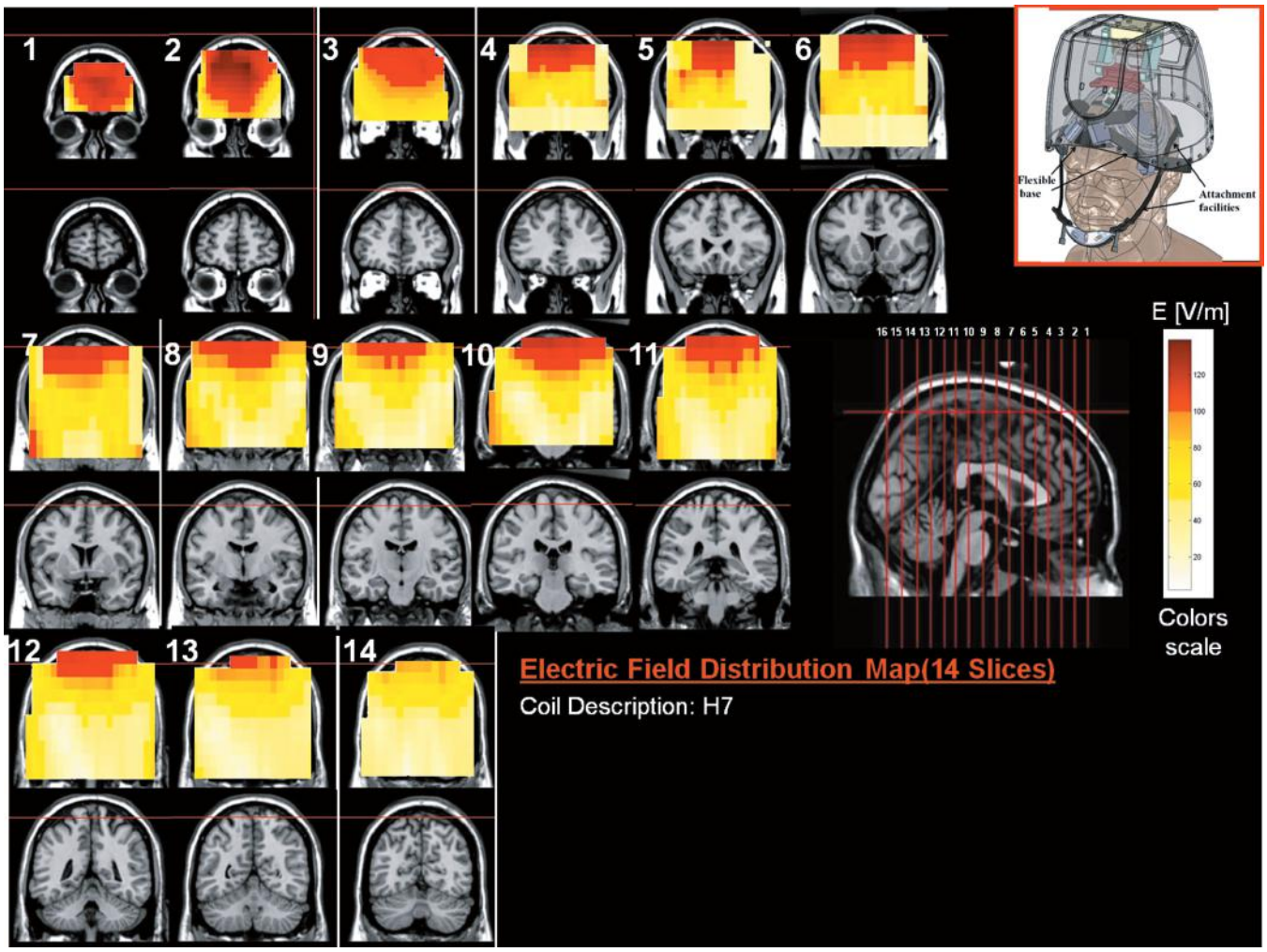

FIGURE 21.8 Colored field maps for the H7 coil indicating the electrical field absolute magnitude in each pixel at 110% of motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

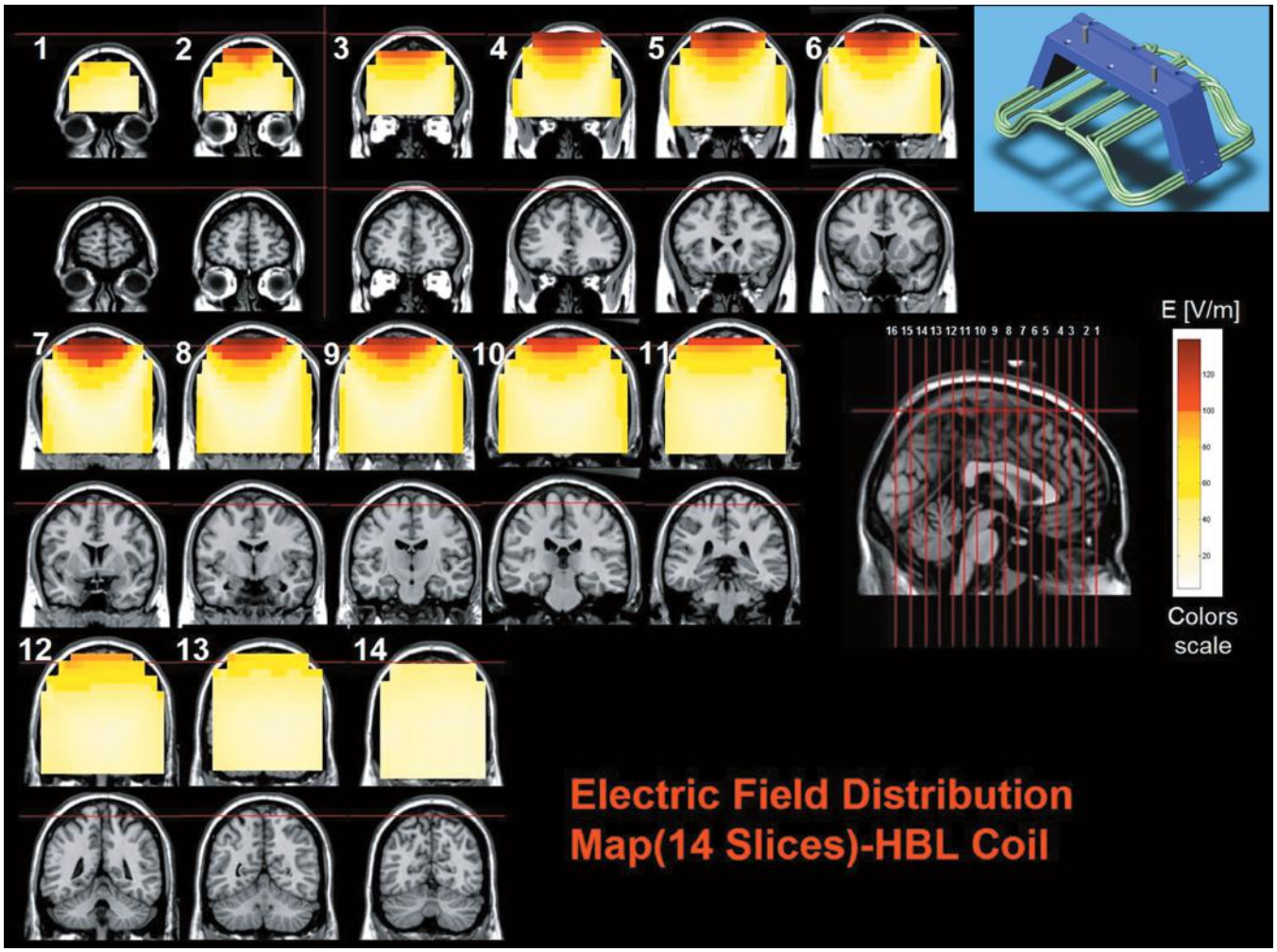

FIGURE 21.9 Colored field maps for the HBL coil indicating the electrical field absolute magnitude in each pixel at 100% of active leg motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

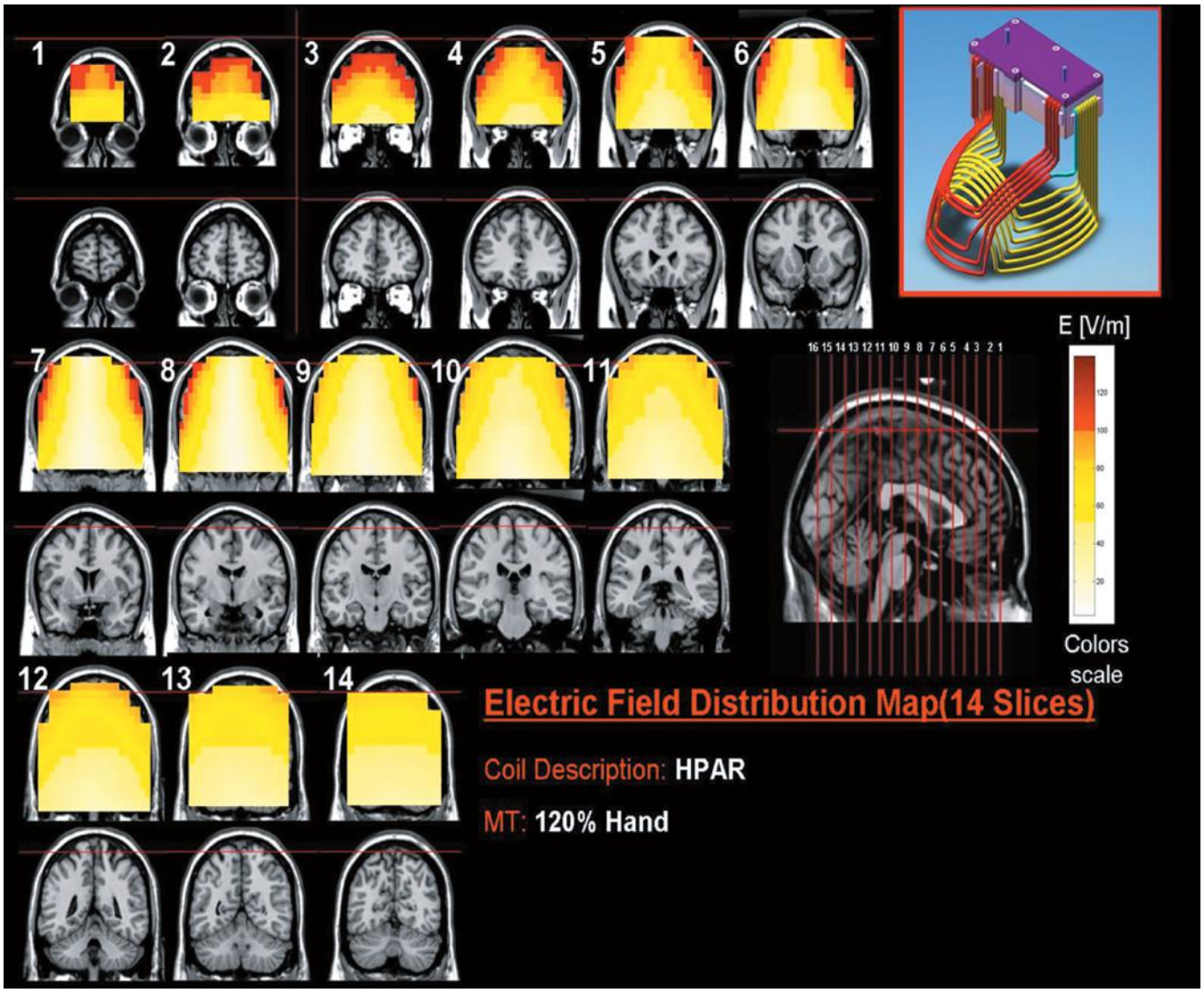

FIGURE 21.10 Colored field maps for the HPAR coil indicating the electrical field absolute magnitude in each pixel at 120% of active hand motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

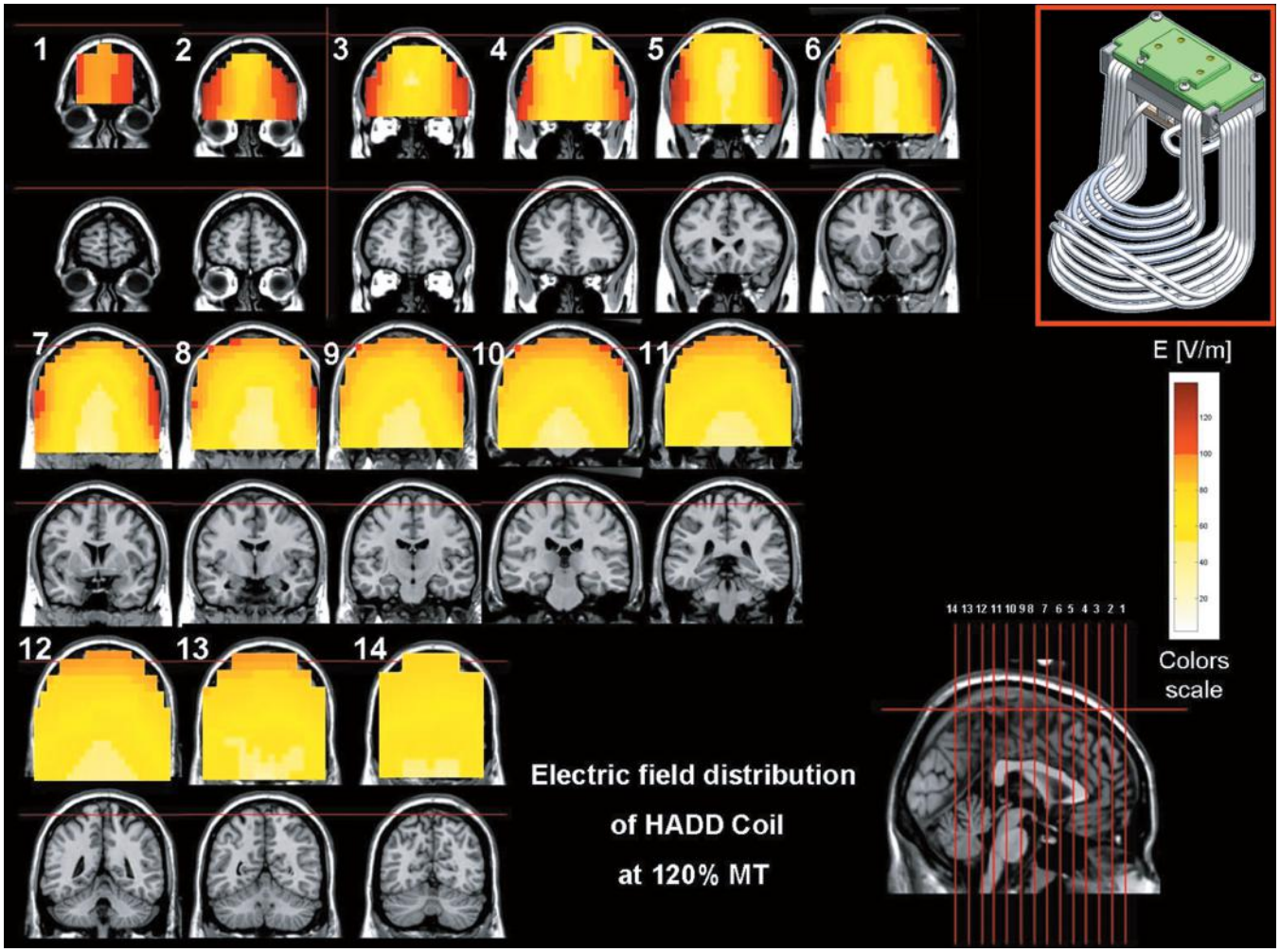

FIGURE 21.11 Colored field maps for the HADD coil indicating the electrical field absolute magnitude in each pixel at 120% of active hand motor threshold, for 14 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m.

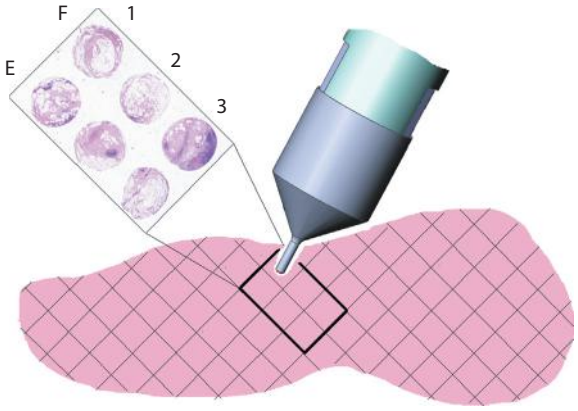

FIGURE 25.4 Open-ended coaxial probe configuration. Measurements are performed in reflection mode. Inset illustrates pathology slide used to analyze measured tissue sites.

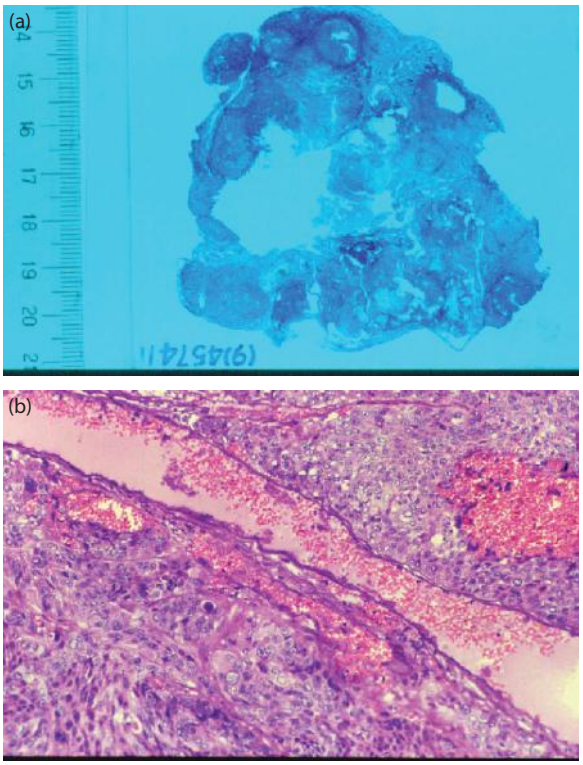

FIGURE 26.3 Cancer cells were dissolved and underwent "breakdown," congestion and edema of tissue were represented in the area of the cathode. (a) Low power lens, (b) high power lens.

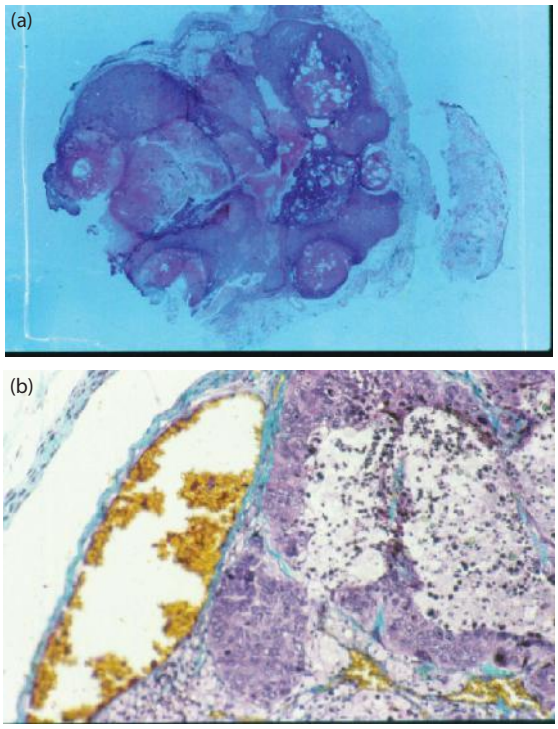

FIGURE 26.2 Tumor tissue dehydration and carbonized, protein coagulated, and necrosis by the anode. (a) Low power lens, (b) high power lens.

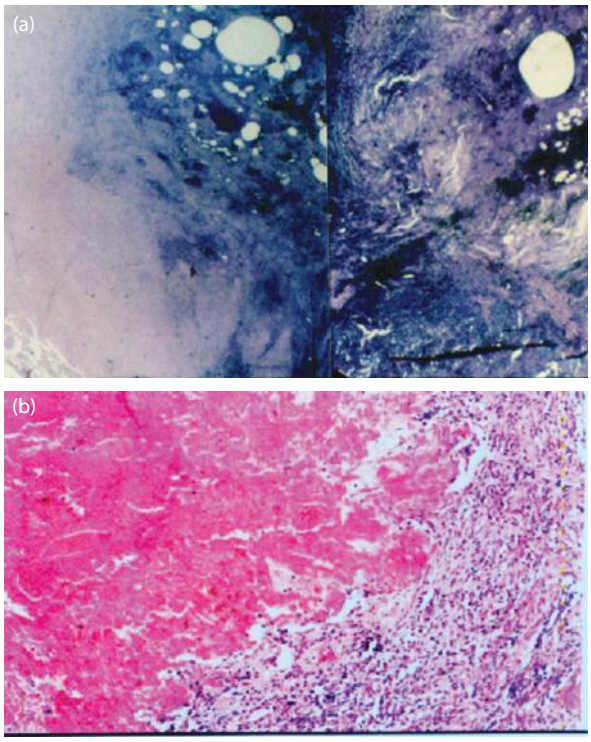

FIGURE 26.5 (a, b) No cancer cells remained when the distance of the electrodes was shorter than 2 cm.

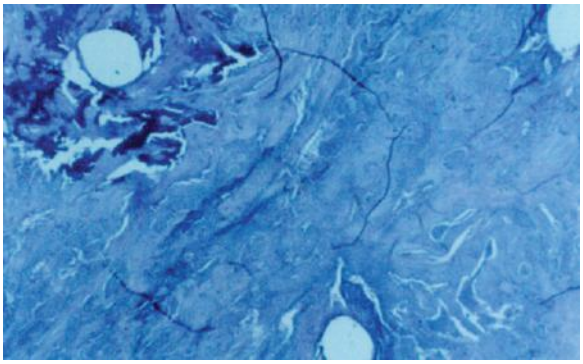

FIGURE 26.6 The distance of the electrodes is over 3 cm, cancer cells can be found in the remaining area.

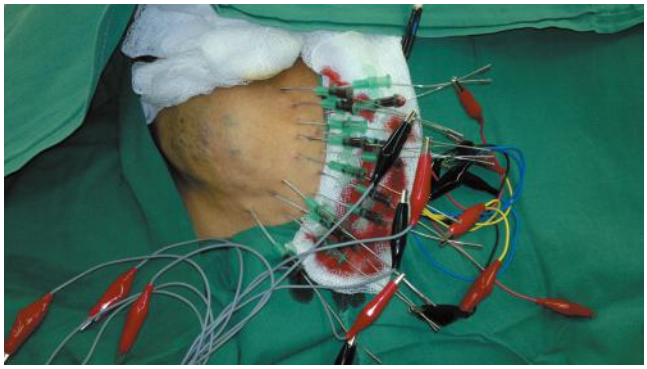

FIGURE 26.7 Electrochemotherapy on a patient suffering from venous malformations in his right hip.

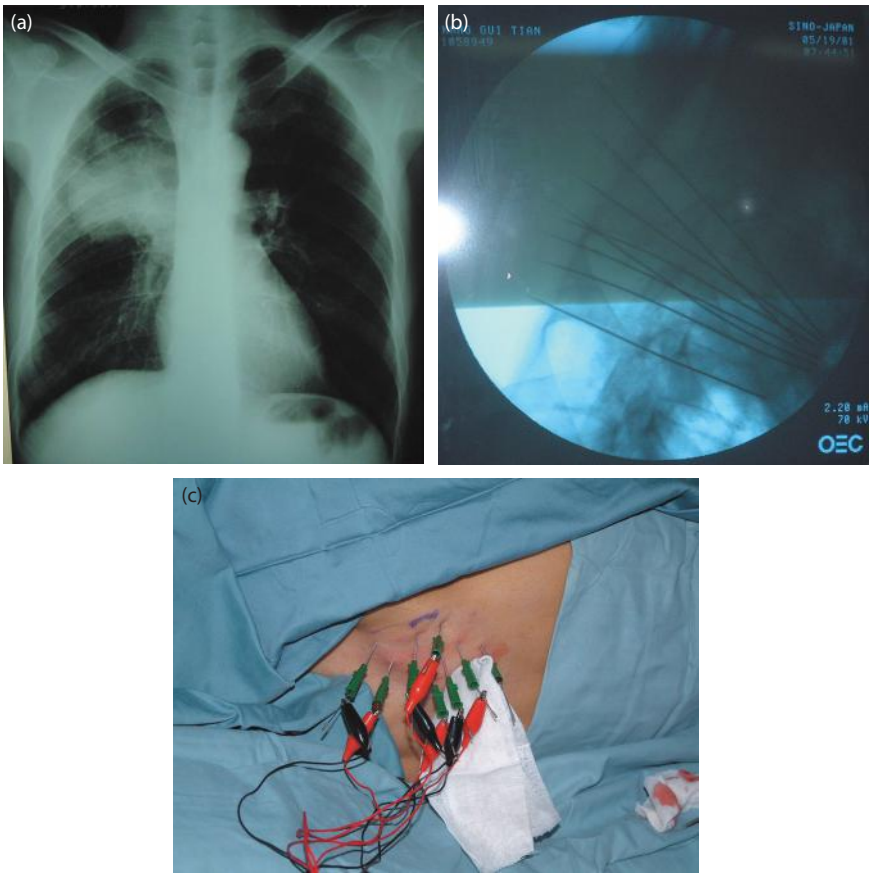

FIGURE 26.8 Male, 67 years old. (a) Right: lung cancer. (b) Electrodes inserted into the tumor. (c) During electrochemical therapy.

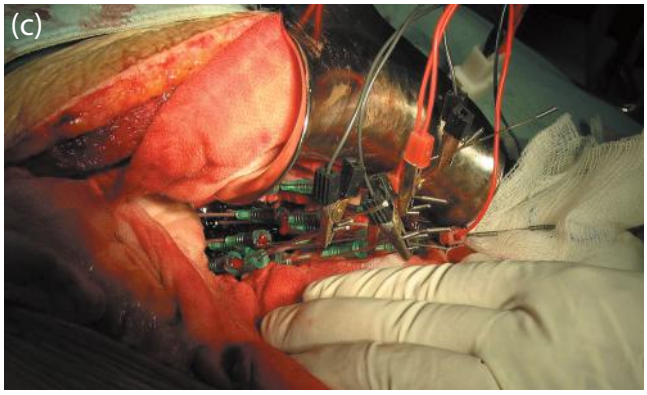

FIGURE 26.9 Male, 53 years old. He suffered from a left thoracic and abdominal tumor, $14 \times 8 \times 4$ cm^3. The thoracic cavity and abdominal cavity was opened but the tumor could not be resected. Pathologic diagnosis: neurofibroma. Electrochemical therapy (EChT) was performed. The patient was followed up for 5 years and recovered well. (c) during EChT.

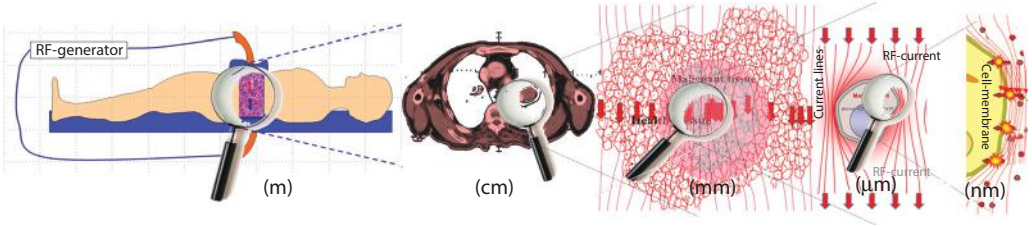

FIGURE 29.2 The concept of the automatic focus of current density on the malignant cellular membrane.

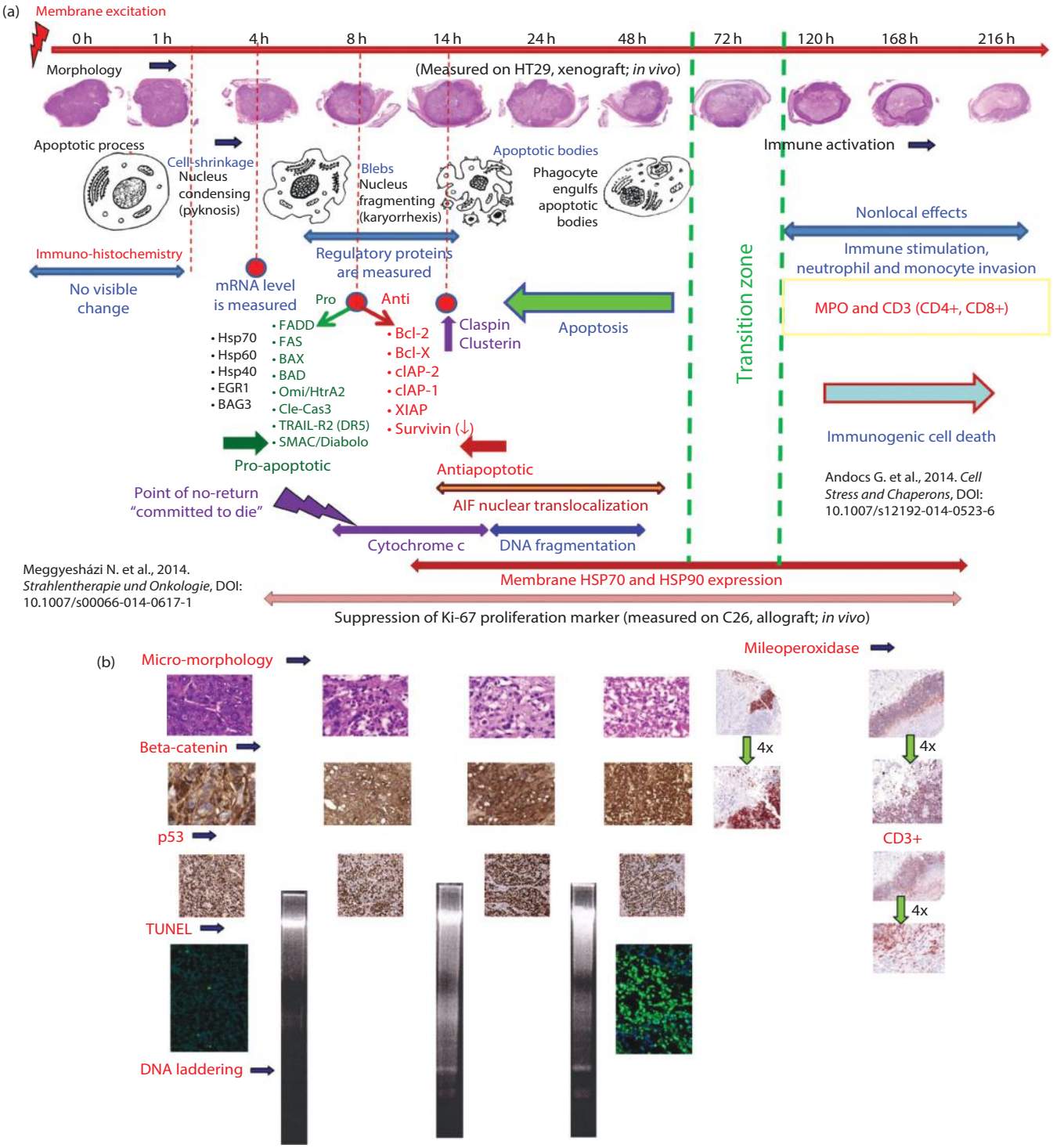

FIGURE 29.7 Developments after oncothermia treatment *in vivo* by elapsed time (h) after a single shot treatment (30 min, 42°) HT29 xenograft model on nude mice.

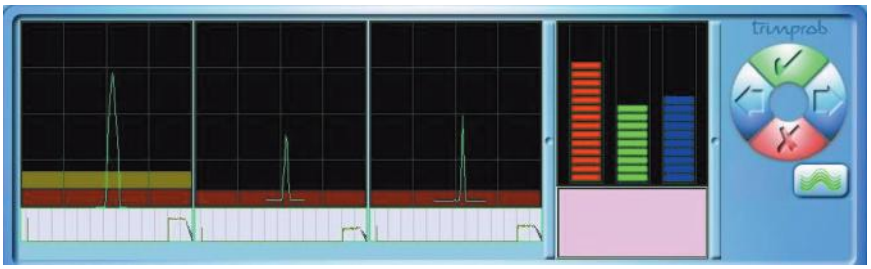

FIGURE 30.4 Visualization of the three spectral lines on the display.

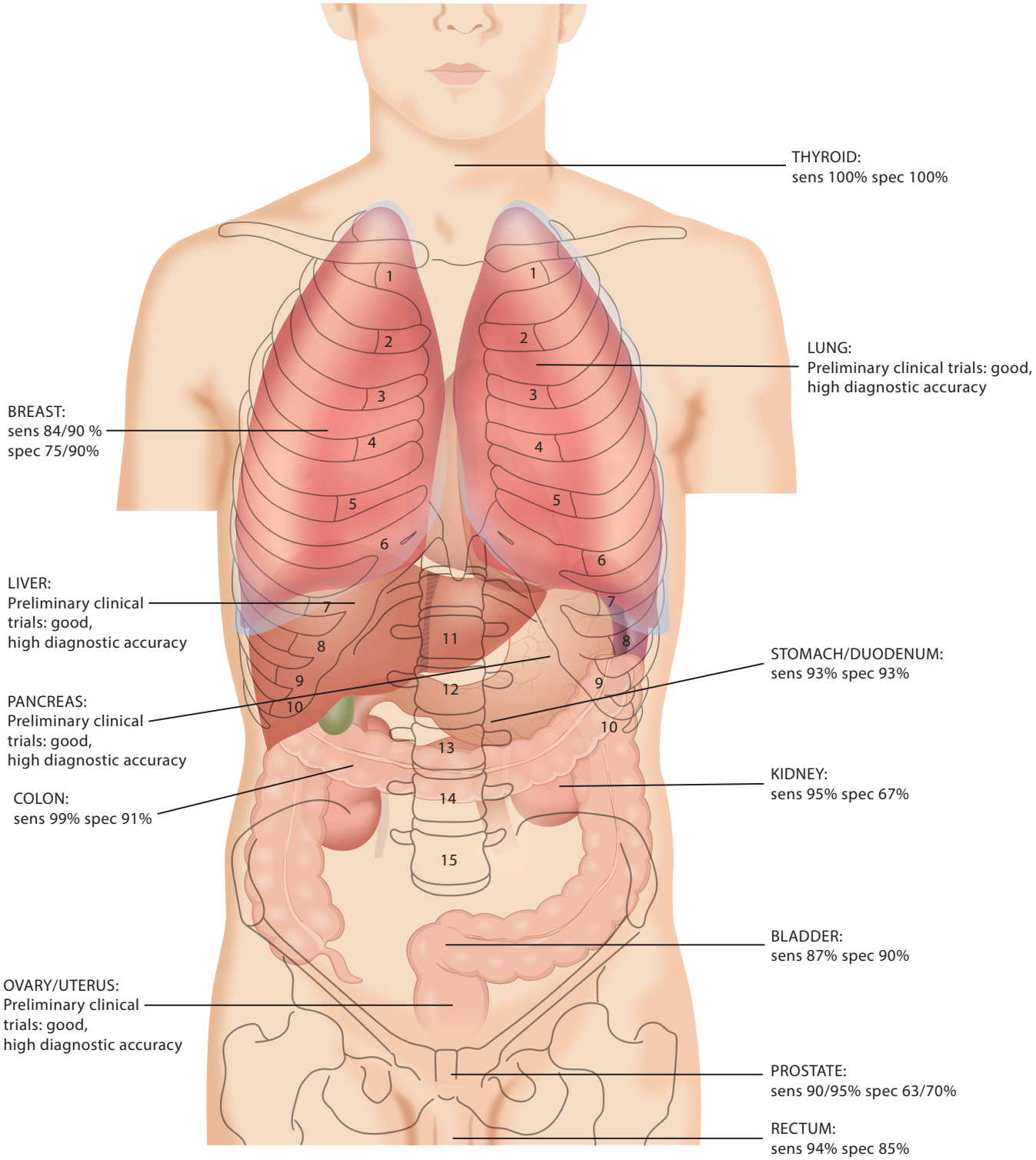

FIGURE 30.8 Clinical trials in several body organs.

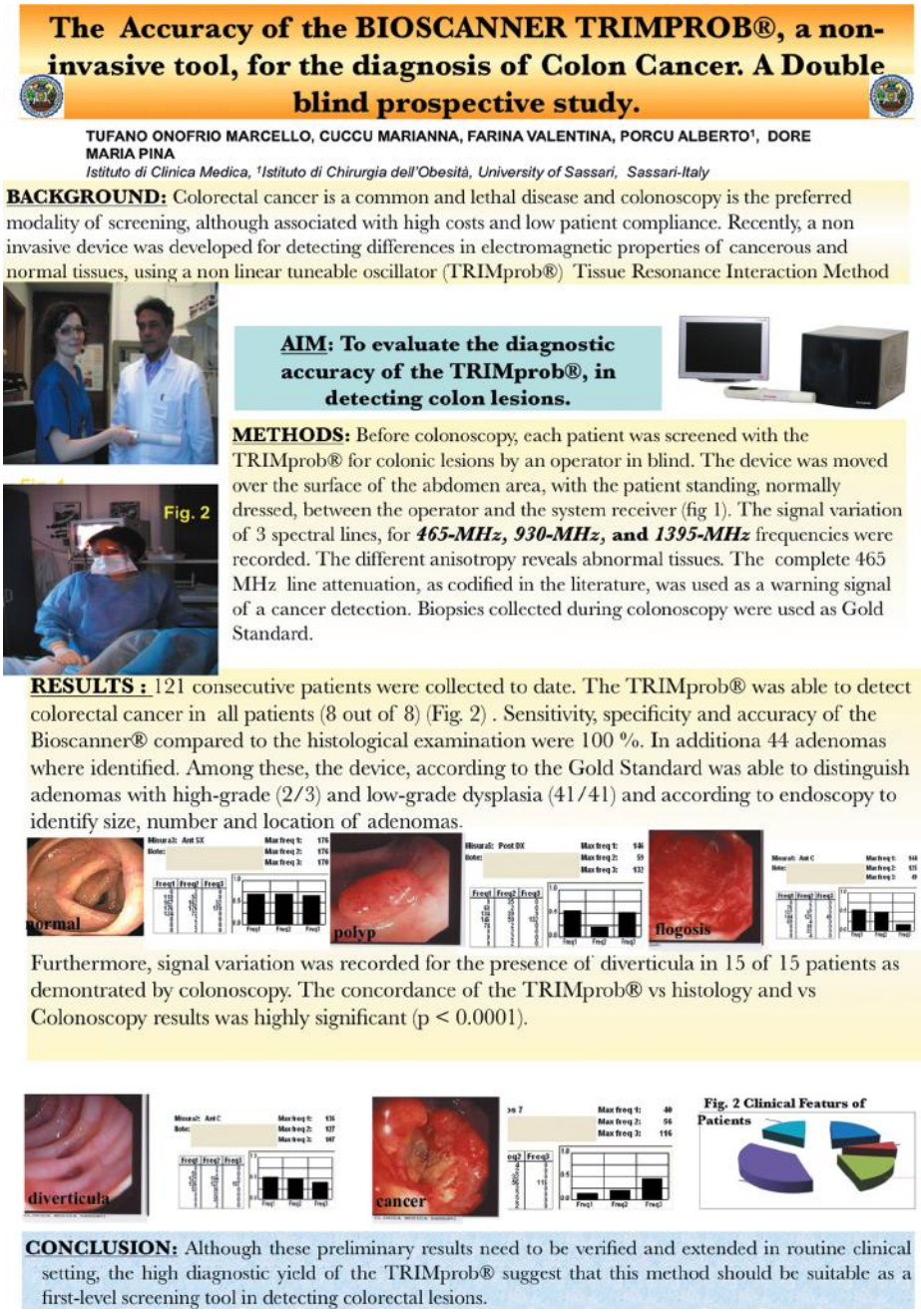

FIGURE 30.9 Clinical trial for the diagnosis of colon cancer.

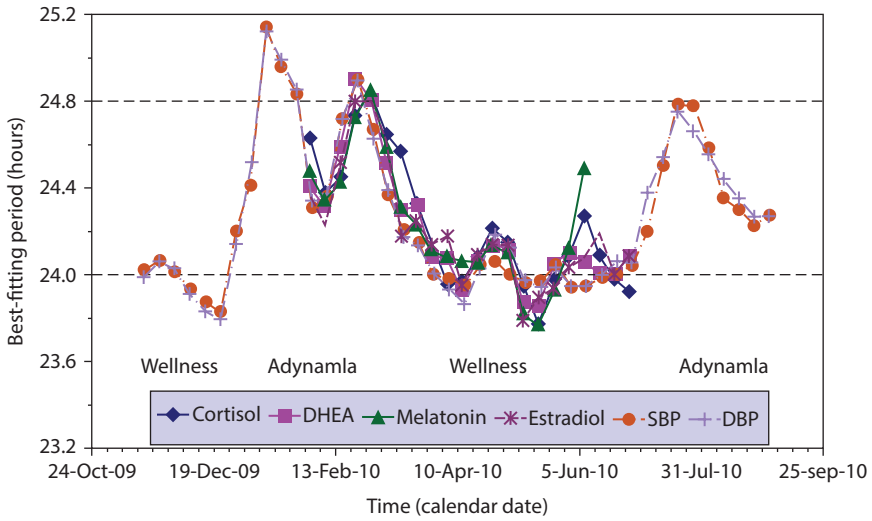

FIGURE 35.4 A 61-year old selenosensitive woman who experienced half-yearly recurrent episodes of adynamia lasting about 2 months for the past 20 years monitored her mood, vigor, urine volume, wrist activity, blood pressure, heart rate, and several salivary hormones around the clock for over a year. A 24-h synchronized circadian rhythm and an about 24.8-h (double tidal) component coexist, alternating in prominence between spans of wellness and adynamia.

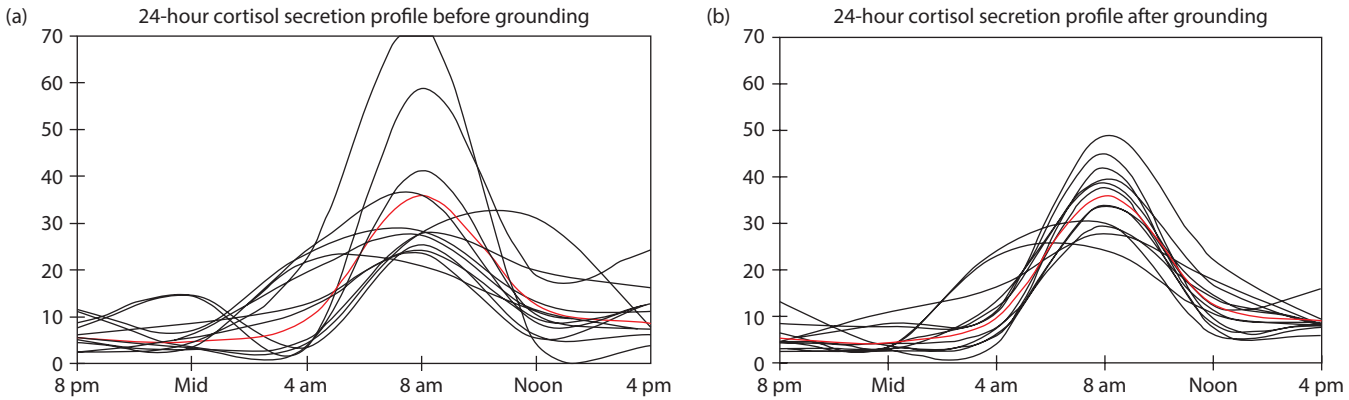

FIGURE 38.5 Cortisol levels before and after grounding. In unstressed individuals, the normal 24 h cortisol secretion profile follows a predictable pattern: lowest around midnight and highest around 8 a.m. Graph (a) illustrates the wide variation of patterns among study participants prior to grounding, while (b) shows a realignment and normalization trend of patterns after six weeks of sleeping grounded. (From Ghaly M, Teplitz D. *J Alternat ComplMed* 2004;10:767–76.)

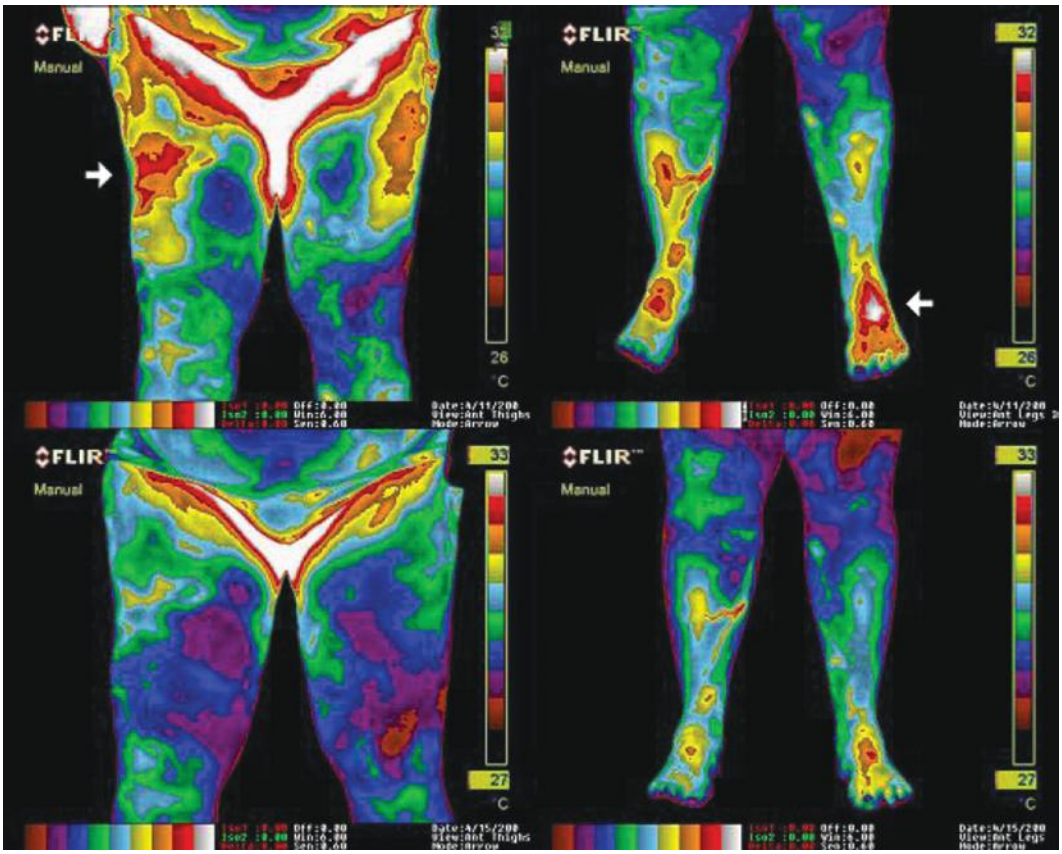

FIGURE 38.10 Reduction in inflammation and pain after sleeping grounded for four nights. Medical infrared imaging shows warm and painful areas (arrows). Sleeping grounded for four nights resolved the pain and the hot areas cooled. (From Amalu W. Medical Thermography case studies. Clinical earthing application in 20 case studies. Available online from http://74.63.154.231/here/wp-content/uploads/2013/06/Amalu_thermographic_case_studies_2004.pdf.)

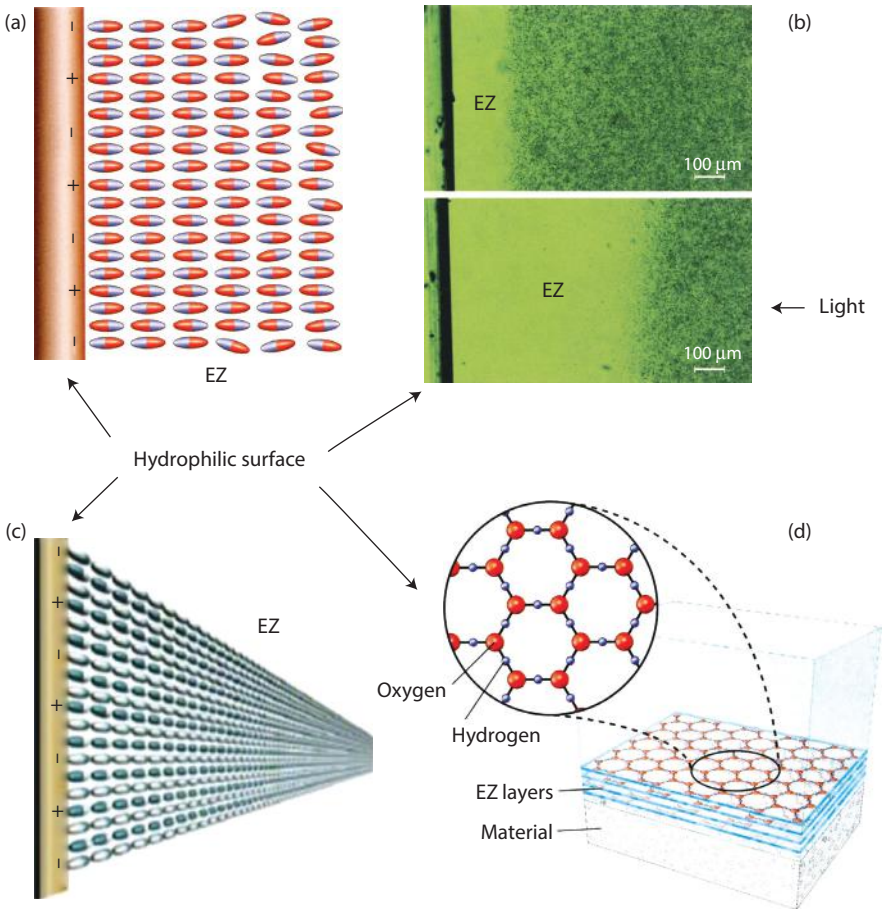

FIGURE 38.19 (a) Dipolar water molecules (electronegative region shown in red) line up adjacent to a hydrophilic (water-loving) surface. (b) The region close to the surface excludes solutes, demonstrated here with the use of microspheres. The lower picture shows how the exclusion zone is expanded in the presence of light. (c) The exclusion zone is extends far from the hydrophilic surface. (d) The water molecules form honeycomb sheets. (From Pollack G. *The Fourth Phase of Water: Beyond Solid, Liquid and Vapor.* Seattle, WA; Ebner & Sons; 2013.)

HEALTHCARE

BIOELECTROMAGNETIC AND SUBTLE ENERGY MEDICINE

SECOND EDITION

Bioelectromagnetic and Subtle Energy Medicine focuses on a wide variety of evidence-based bioelectromagnetic and subtle energy therapies for disorders ranging from cancer, cardiomyopathy, and Parkinson's disease to depression, anxiety, and pain. Since publication of the first edition more than a decade ago, there have been so many advances in these and other diseases that a thorough revision is required for this resource to remain the gold standard in a burgeoning field.

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