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HALLUCINOGENS AS HARD SCIENCE: The Adrenochrome Hypothesis for the Biogenesis of Schizophrenia

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Working in a psychiatrically innovative environment created by the Government of Saskatchewan, Canada, Abram Hoffer and Humphry F. Osmond enunciated the adrenochrome hypothesis for the biogenesis of schizophrenia in 1952, slightly later proposing and, apparently, demonstrating, in a double-blind study, that the symptoms of the illness could be reversed by administering large doses of niacin. After placing the hypothesis within its ideological framework, the author describes its emergence and elaboration and discusses the empirical evidence brought against it. Hoffer's idiosyncratic diagnostic procedures, especially his creation and use of a supposed biochemical marker for schizophrenia, are examined. The author argues that Hoffer's conceptualization of schizophrenia, as well as his treatment approach, depended on a tautology. Following David Healy, the author treats the adrenochrome hypothesis as a version of a transmethylation theory, thus incorporating it into mainstream psychopharmacology.

Keywords: adrenochrome theory, history of psychiatry, history of neuropharmacology, community psychiatry

Abram Hoffer's (1917–2009) and Humphry F. Osmond's (1917–2004) adrenochrome theory provided neuroscientists with what was, for a few years, the best available biochemical theory for the origin of schizophrenia.[1] Moreover, from the outset, Hoffer and Osmond claimed that they could control and even cure schizophrenia by administering nicotinic acid, thus exciting the interest of the medical community and the general public. Over the course of 6 years, Hoffer and Osmond obtained grants totaling about $500,000 (roughly $4 million in current dollars) from the Rockefeller Foundation, in addition to other grants from the Saskatchewan Provincial Treasury and the Government of Canada.[2]

John A. Mills, Professor Emeritus of Psychology in the University of Saskatchewan, devoted the early part of his career to the history of behaviorism. His major works in that area are *Control: A History of Psychological Behaviorism* (1998) and an article in the *Encyclopedia of the History of Psychology*, to be published by Springer-Verlag. The article concerns the adrenochrome theory, the first scientifically based treatment of an identifiable mental disease. Developed by Abram Hoffer and Humphrey Osmond, the theory is a topic about which Professor Mills has gained insight through his work on the history of psychopharmacology and community psychiatry in the province of Saskatchewan, Canada. Saskatchewan was the birthplace both of community psychiatry and the scientifically based treatment of schizophrenia, an area on which Professor Mills concentrates most of his attention.

I would like to thank Erika Dyck, Canada Professor of History in the University of Saskatchewan and author of *Psychedelic Psychiatry: LSD From Clinic to Campus* (2008), for her comradeship.

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The theory allowed the incorporation of the profession of psychiatry and the treatment of chronic psychotics into general medical practice and, above all, into the state funding of medical care. During the period when those diagnosed as suffering from chronic psychosis could be given only custodial care or ad hoc somatic therapy, neither the medical profession nor the state was willing to treat them as bona fide patients. Because the adrenochrome theory was derived from the neuropharmacological knowledge of its day and because it promised a scientific basis for treatment, it seemed to be both scientifically and medically respectable, thereby helping to enhance psychiatry's claim to be a part of scientific medicine.

Given the adrenochrome theory's role in providing a seemingly scientific basis for a biologically based psychiatry, it is, at first sight, surprising that the research supporting the theory was almost entirely performed in Saskatchewan, Canada. Saskatchewan became a leading center both for psychiatry (especially community psychiatry) and psychiatric research because, in 1944, the socialist Cooperative Commonwealth Federation government, which had a prior commitment to the introduction of medicare, was elected.[3] In addition, Premier Thomas ("Tommy") Clement Douglas (1904–1986), who had assigned himself the Portfolio for Public Health, was committed to enhancing the care of those suffering from mental illness and to scientific research into the causes of mental illness. Almost as soon as he was elected, he appointed Donald Griffith ("Griff") McKerracher (1909–1970) as Commissioner for Mental Health and then as director of the Psychiatric Services Branch (PSB) of the Department of Public Health. McKerracher created a program for psychiatric research, starting in 1950.[4] He reported that, "In July, 1950, with the assistance of Federal health grants, a research unit was established [at the Regina General Hospital] under the direction of Dr. A. Hoffer. A research biologist was added to the staff. Among the projects underway is an evaluation of training methods and results."[5] Until the end of 1958, no other provincial government in Canada supported psychiatric research by paying the salaries of research staff, even if Ontario, for example, had supported research indirectly.[6]

The Biochemical Basis for the Theory

The adrenochrome theory's ultimate basis resided in the discovery of the powerful hallucinatory properties of LSD-25.[7] In 1943, the Swiss pharmaceutical company Sandoz was working on derivatives of ergot and had synthesized a series of lysergic acid diethylamines; LSD-25 was so-named because it was the 25th derivative in the series. On April 16, 1943, one of Sandoz's chemists, Albert Hofmann, accidentally ingested a small amount and noted that he experienced restlessness and mild dizziness; after returning home, he experienced a minor and pleasant delirium. The following week, he deliberately took a dose of one quarter of a milligram (which he considered to be the lowest possible active dose) and cycled home, accompanied by his laboratory assistant. Despite suffering severe visual disturbances, he reached home safely and underwent a 6-hr period of hallucinations he described as follows:

> Vertigo, visual disturbances, the faces of those around me appeared as grotesque, colored masks; marked motor unrest, alternating with paralysis; an intermittent

> feeling in the head, limbs, and the entire body, as if they were filled with lead; dry, constricted sensation in the throat; feeling of choking; clear recognition of my condition, in which state I sometimes observed, in the manner of an independent neutral observer, that I shouted half insanely or babbled incoherent words. Occasionally I felt as if I were out of my body.[8]

Fairly soon after Hofmann's startling observations, it was discovered that a dose of 50 μg sufficed to produce prolonged and powerful hallucinatory effects (so that he had taken 500 times the required dose). The discovery that such minute amounts of a drug produced large-scale mental phenomena caused a radical reconception of the nature of drug-induced brain states. As far back as 1845, Jean Joseph Moreau de Tours had speculated that chronic mental illness could be caused by the endogenous release of chemicals in the brain.[9] However, until the discovery of the hallucinogenic properties of LSD, heavy doses of drugs such as opium were required to produce an effect. Because the doses were heavy enough to leave traces postmortem and because no such traces were found in the corpses of those who had suffered from chronic mental illness, psychiatric theorists such as Karl Jaspers discounted all psychopharmacogenic theories.[10] The discovery that amounts of a drug so minute as to leave no traces postmortem could have large-scale effects suggested to some psychiatrists that endogenously produced chemicals could have lifelong psychogenic consequences.

As early as 1915, Walter Cannon had discovered an endogenously produced chemical belonging to the catecholamine family, epinephrine (adrenaline). Epinephrine, Cannon found, was produced in the adrenal glands and mediated stress responses, including the psychological accompaniments and indicators of stress. Catecholamines are monamines, that is, they have only one amine (NH_2) group. All share the same nucleus (the catechol nucleus), which consists of a benzene ring with two hydroxy side chains; the nucleus also provides a site for the addition of the amine side chain. During the 1950s, Hans Selye's stress theories, which gave a central role to the hormones of the adrenal glands (epinephrine, norepinephrine, and the cortisones), were very influential.[11] Moreover, in 1950, Holtz demonstrated that norepinephrine occurred in mammalian brains and, in 1954, Marthe Louise Vogt identified it as a neurotransmitter.[12]

In 1951, John Smythies, then a registrar at St. George's Hospital in London, noted, like others, that epinephrine and mescaline were chemically similar. In the 1930s, both Henk de Jong and L. L. Noteboom had produced experimental catatonia using mescaline. Because, during that period, those diagnosed as schizophrenic frequently manifested catatonia, the findings were intriguing. Smythies questioned whether any of the catabolic products of epinephrine or norepinephrine could produce altered mental states. He consulted the Cambridge organic chemist John Harley-Mason, an expert on the catabolism of epinephrine and norepinephrine, who suggested that in an abnormal brain, there was a possibility that dopamine was *N*-methylated to dimethylphenylamine, a possible endogenous psychotogen. This led Smythies, with Osmond, who was then a senior psychiatric resident at St. George's, to formulate the first version of what later came to be known as transmethylation theories.

To recapture Smythies' insight, one has to know that catecholamines differ from one another in the presence or absence of methyl (CH_4) groups, either at

some point on the benzene ring or within the amine side chain. Furthermore, the methyl group can be attached to either an oxygen molecule (*O*-methylation) or a nitrogen molecule (*N*-methylation). Both the addition and subtraction of methyl groups and the site of the bonding alter a catecholamine's biochemical (and hence it is psychopharmacological) properties.

Following Harley-Mason's suggestions, Osmond and Smythies proposed that a chemical naturally synthesized in the body had the same effects as psychotomimetic chemicals like mescaline.[13] Furthermore, they reported a very close relationship between the symptoms that followed the ingestion of mescaline and those presented in cases of schizophrenia. Osmond could not succeed in persuading British granting agencies to fund the biochemical research needed to refine and explore the hypothesis. As a result, he decided to emigrate, going to Canada almost by chance. In 1951, he arrived for an interview with McKerracher at Saskatchewan House, London, even though it was late in the day and he had not placed himself on the interview schedule. The secretary who had set up the interview schedule succumbed to Osmond's blandishments and persuaded McKerracher to interview him. McKerracher was equally susceptible to Osmond's charm and offered him the post of clinical director at the Saskatchewan Hospital, Weyburn.[14]

Osmond arrived in Saskatchewan in July 1951. In the fall of that year, McKerracher arranged a meeting between Osmond and Hoffer, and the two became lifelong friends. Soon after, Smythies joined them at Weyburn, and the three published an article in which they claimed that schizophrenia was caused by faulty metabolism of adrenaline (epinephrine) and postulated that the chemical causing schizophrenia could be the presence in the brain of a breakdown product of adrenaline (the product was known as "pink adrenaline" at the time).[15]

Early in 1952, Hoffer and Osmond received the first of several research grants from the federal government of Canada. In March of that year, Hoffer came to believe that the brain chemical that he and Osmond were endeavoring to discover was an *indole*. An indole is a variant of a catecholamine formed by the abutting of a five-carbon ring against a benzene ring; the characteristic amine group is attached to the five-carbon grouping. As a result, the number of possible chemicals shrank from several thousand to fewer than 12. To facilitate the search for their suggested compound, Hoffer and Osmond created the Saskatchewan Committee on Schizophrenia Research, with Hoffer as the committee chair. The committee held its first meeting, in Saskatoon, on April 25 and 26, 1952.[16] Committee member Duncan Hutcheon, a British-trained pharmacologist who had research experience with catecholamines, suggested that pink adrenalin could be adrenochrome, then a little known chemical.[17] Hutcheon and one of his graduate students synthesized adrenochrome. In a heroic study, initially using themselves, their wives, and the psychologist Neil Agnew as subjects, Hoffer and Osmond satisfied themselves that adrenochrome was not just a hallucinogen but was a psychotomimetic. As a result, they formulated what they called "the adrenochrome hypothesis," presenting it for the first time at a meeting in New York in 1952.[18]

Structurally, the adrenochrome hypothesis appeared to satisfy the canons of science. It stated that certain naturally occurring substances (e.g., mescaline, peyote) and their synthetic analogues (e.g., LSD) produce symptoms well nigh

identical to those manifested in schizophrenia. Chemicals produced in the body, which are structurally analogous to LSD, when isolated and then injected, produce similar symptoms. Therefore, those same compounds produce schizophrenia. Finally, chemical antagonists of schizophrenia will at least ameliorate the symptoms of those diagnosed as schizophrenic. Crucially, the hypothesis was open to disproof at various points. For example, one could demonstrate that the symptoms seen in artificially induced delusional or hallucinatory states were not identical to those observed in those diagnosed as schizophrenic or that the proposed drug therapy was ineffective.

So far, I have not discussed Hoffer and Osmond's work with the best known of the indoles, LSD. That is because speculation about the structure and psychopharmacological role of LSD played no direct part in the formulation of the adrenochrome theory. Hoffer and Osmond shared the fundamental conviction that all mental states were brain states. That conviction manifested itself most strongly in their concept of malvaria, which had its origins in the work of Hoffer and his biochemists. They discovered that the urine of some people produced a mauve spot on chromatograph paper when treated with Ehrlich's reagent. Hoffer claimed that the mauve spot was "[an] excellent marker of oxidative stress and the possible presence of mental illness."[19] He also claimed that a majority of those diagnosed as schizophrenic, but untreated, produced the mauve spot. Hoffer called those who produced a mauve spot "malvarians" and wrote, "A malvarian is any human who excretes the mauve factor." He continued, "Since malvarians (no matter what they are clinically) resemble the majority of schizophrenics biochemically, we hypothesized they would react badly to LSD." Hoffer found, in a sample of 20 malvarians, none of whom had been diagnosed as schizophrenic, that 20% had adverse reactions, the same proportion found in the relatives of those diagnosed as schizophrenic.

Hoffer was not alone in believing that, in schizophrenia, severe stress produced psychological as well as physical symptoms and that adrenal hormones played a crucial role in producing those symptoms. Other well-known researchers, such as Hudson Hoagland and Mark Altschule, were also attempting to find relationships between disorders in steroid metabolism and schizophrenia.[20] At about the same time, norepinephrine was discovered in the brain, with the result that the Hoffer–Osmond theory had a great deal of contextual support.

Hoffer did not rely only on a biochemical test when diagnosing schizophrenia. He and Osmond developed a card-sorting diagnostic test, the Hoffer–Osmond Diagnostic test (the HOD). He created the test after becoming dissatisfied with standard personality inventories. Such tests showed little correspondence with the clinical judgments. Hoffer therefore designed his own test. He had a set of questions printed on cards and asked patients to place the cards in either a "Yes" or a "No" box. To be classified as schizophrenic on the HOD, the patient's score had to exceed a predetermined cutoff.[21] Hoffer employed the Saskatchewan psychologist Harold Kelm, later a professor of psychology at the University of Saskatchewan, to refine his own early version in order to produce the published form of the test.[22]

So far, it is clear that the adrenochrome theory (or adrenochrome hypothesis, as Hoffer insisted on calling it) was a conceptually distinctive variant of a transmethylation theory. Perhaps more important, however, Hoffer and Osmond

used the theory not merely as a means of understanding, explaining, and diagnosing schizophrenia but to provide the rationale for curing the disease. Hoffer began to speculate about possible treatments at the same time as he and Osmond were beginning to formulate the adrenochrome theory. As a physician, Hoffer knew that histamine causes flushing because it opens the peripheral blood capillaries, thereby causing a drop in blood pressure. The flushing and the fall in blood pressure can be countered by injecting adrenaline. Because, like Osmond, Hoffer was already beginning to speculate that some adrenaline-like chemical caused the symptoms of schizophrenia, he began to review other chemicals that caused flushing (i.e., one of the bodily functions incompatible with the presence of adrenaline). On the basis of his work with the B vitamins, Hoffer knew that high doses of B_3 (in the form of either niacin or niacinamide) caused vasodilatation and thereby flushing. Moreover, extreme deficiency of B_3 causes pellagra, a disease that, in its late stages, presents as dementia, with symptoms that are very difficult to differentiate from those of schizophrenia. Even in its late stages, the symptoms (and the disease) will disappear if very high doses of B_3 (up to 600 mg per day, which is far greater than the dose required to prevent the disease from occurring) are administered. Finally, by 1950, it was widely known that B_3 is a methyl group acceptor.[23]

Hoffer inferred that massive doses of B_3 would be required. He persuaded Merck, a pharmaceutical company, to donate several drums of the vitamin. Hospital pharmacists then made the material into pills. A trial with three schizophrenic patients produced a favorable outcome. Using those results as justification, Hoffer and Osmond obtained funds from the Canadian Mental Health Association (CMHA) and carried out one of the earliest double-blind clinical trials in the history of psychiatry.[24] Using Eugen Bleuler's criteria, they assigned 30 patients suffering from schizophrenia to three groups (placebo, niacinamide, and niacin).[25] The results strongly supported the theory; of the nine patients on the placebo, only three improved, whereas of the 21 on either niacin or nicotinamide, 17 improved. It is intriguing that McKerracher did not find the study convincing. When it was first presented (presumably at a meeting of PSB staff and members of the Department of Psychiatry, University of Saskatchewan), he said that, were the results true, Hoffer and Osmond should be awarded the Nobel Prize (a tactful way of saying they were false or the result of some artifact).

So, Hoffer and his group carried out a much larger double-blind study, using 89 patients drawn from the psychiatric ward at the Regina General Hospital and the University Hospital in Saskatoon.[26] This time, they used the Lewis and Piotrowski factors, a list of 10 signs, such as physical sensation with dissociation or feeling of physical isolation and personal unreality, to identify schizophrenia.[27] Hoffer stated that five signs were required for a positive diagnosis of schizophrenia.[28] There were only two groups, placebo or nicotinic acid (even though those in the treatment group could be identified because they flushed, Hoffer did not explain why he did not use a nonflush control). The 82 patients providing the data were those who remained in the study for its full duration (33 days). An unstated number of patients were rejected from the study if, following the 33-day period, they were unimproved, deemed to be in need of further treatment, or if the therapist wished to know which treatment (i.e., drug or placebo) the patient had received. Of the patients in the study, 18 in the placebo group improved and 25

did not. Of the 39 patients in the nicotinic acid group, 31 improved and eight did not. The results, Hoffer and Osmond believed, resoundingly supported the theory. However, one cannot say that the patients for whom we have data constituted a randomly selected group because they were those members of the original participants in the study who survived a fairly stringent set of selection criteria. Moreover, the second study, unlike the first, did not have a treated, nonflush group, so those receiving treatment would have been easily recognizable. Possibly, therapists could have responded differently to those in the two groups and, consequently, the outcome could be attributed to differential responses on the part of the therapists rather than to treatment with nicotinic acid. Finally, and bafflingly, the mean Lewis–Piotrowski scores for neither the treatment group (4.2) nor the control group (4.8) met Hoffer's criterion for schizophrenia.

Hoffer and Osmond also ran additional long-term clinical studies, all with outcomes supporting the theory.[29] In addition, they asserted that nicotinic acid therapy, when combined with chlorpromazine, produced better outcomes than did the use of chlorpromazine alone. Furthermore, they claimed that the administration of nicotinic acid had no side effects, apart from skin rashes early in a course of treatment. Chlorpromazine, in contrast, had serious side effects. David Healy reported that "a flurry of confirmatory reports of the benefits of nicotinic acid came from researchers around the world."[30] But, perhaps more crucially, Hoffer and Osmond had provided a coherent rationale for the use of B_3, so that, unlike all previous attempts to treat mental illness pharmaceutically, their treatment was not merely empirical. Healy comments,

> The work of Hoffer, Osmond, and Smythies was important for three reasons. They had produced a coherent theory of schizophrenogenesis, along with a treatment that appeared to produce some benefits and certainly provoked considerable interest. In addition, their ideas tapped straight into an increasing public awareness of the hallucinogens, which as a group were referred to as the psychedelic drugs, a term coined by Osmond. The heady buzz that resulted made Saskatchewan in the 1950s one of the focal points of the psychiatric universe.[31]

Hoffer's laboratory was one of many examining the serum and urine of those suffering from mental illness (and normal controls) in the search for the metabolites of chemicals active in the brain and potential biochemical markers of various mental illnesses. However, despite their successes, the research techniques of Hoffer and his collaborators faced a fundamental problem, which they never overcame. They tried to explain the human brain's neurochemistry by analyzing the end products of brain metabolites in plasma and urine. Because they did not use animal models, they could not study metabolism within the nerve cells of the brain and so, effectively, deprived themselves of the opportunity to offer convincing causal accounts of the biochemical origins of schizophrenia. They faced an additional difficulty in that those diagnosed as "schizophrenic" are so aberrant in so many ways that their urine is certain to be biochemically different from that of normal people. Thus, some of the causes of those differences might have had nothing to do with their brain chemistry, and others might have been the consequence of drug treatments. So, Hoffer was reduced to claiming that he could diagnose schizophrenia by using the presence of the mauve spot in combination with a cutoff score on the HOD. But, despite at least 7 years of

heroic and sustained effort, the group never did succeed in identifying the unknown substance.[32]

Ideological Considerations

Although, from the 1930s onward, psychiatrists had used a range of physical treatments for severe mental illness, it still remained the case that the medical community and the general public believed that mental states had mental causes. Furthermore, in the 1950s, psychosomatic medicine had a much larger scope than it has today; peptic ulcers and rheumatism, for example, were both said to have psychological origins. In addition, within American psychiatry, psychoanalysis reigned supreme in the 3 decades following World War II. To enhance the credibility of their claims, therefore, Hoffer, in particular, disavowed psychogenic explanations of illness, and both Hoffer and Osmond were opposed to psychoanalysis.[33]

Hoffer frequently expressed his distaste for the post hoc explanations proffered by psychoanalysts. For example, he described a visit to the clinic of the well-known psychoanalyst Franz Alexander in Chicago. Hoffer was present for a training exercise in which a group of residents had to diagnose a selected group of illnesses (e.g., ulcerative colitis, asthma, peptic ulcer, arthritis, hyperthyroidism, hypertension) solely on the basis of a transcript of an interview (with any mention of the physically based diagnoses removed). None of the residents could make the correct diagnosis (even though the probability of being correct by chance was 14%). However, once given the diagnosis, they could proffer retroactive explanations for the symptoms.[34]

For his part, Osmond did not believe that psychiatrists should neglect the study of mental states and the relationship of such states to mental illness. He claimed that, by using LSD under controlled circumstances, one could discover the physical causes of both normal and abnormal states of consciousness and perception. The historian Erika Dyck goes so far as to maintain that Hoffer and Osmond advanced a version of psychiatry ("psychedelic psychiatry") combining biochemical models of mental illness with scientific observation of subjective states.[35]

Psychopharmacology proved to be a much more redoubtable foe to the adrenochrome hypothesis than did psychoanalysis. In particular, in the early 1950s, it became evident that chlorpromazine dramatically attenuated the symptoms of schizophrenia, as shown by Henri Laborit and his associates in a clinical study and by Jean Delay, Pierre Deniker, and J. M. Harl in what amounted to a set of clinical trials, the results of which they published in 1952.[36] Even more threateningly for Hoffer and Osmond, a salesman for Rhône-Poulenc, the company then marketing the drug, left a sample and a document extolling its effectiveness in the office of Heinz Lehmann of the Hôpital Sainte Anne, Montreal.[37] Lehmann read Delay, Deniker, and Harl's article (then available only in French and thus inaccessible to most North American psychiatrists) and was especially struck because it reported a dissociation between initiative, alertness, and vigilance (which were depressed) and intellectual and motor performance (which were unaffected). Convinced that he was dealing with a then unique drug,

in May 1953 Lehmann and his associate Gorman Hanrahan administered it to 74 patients, with largely beneficent outcomes.[38]

From a purely pharmacological point of view, chlorpromazine had an advantage in that it acted much more rapidly than did nicotinic acid. But chlorpromazine alone was by no means the adrenochrome hypothesis's sole rival. Other psychopharmacologists were just as active as Hoffer and Osmond. In the constraint-free atmosphere of early psychopharmacology, researchers produced chlorpromazine, haloperidol, the selective serotonin reuptake inhibitors, and rediscovered the psychotropic effects of lithium, thereby laying the complete foundation for contemporary pharmacological treatments of mental illness.[39] The pharmaceutical industry rapidly exploited the financial advantages of those drugs. To give a germane example, once Smith, Kline, and French had acquired the patent for chlorpromazine (which they marketed as Thorazine), the company went beyond promotion of the drug's merits in a lobbying campaign directed at every state legislature in the United States to the establishment of programs in which company representatives worked with health officials and psychiatrists to organize therapeutic regimens and programs of aftercare.[40]

Most of those familiar with Hoffer and Osmond's work would say that they were eager to promote the merits of their approach and were therefore ideologically rather than medically or scientifically driven. Hoffer, in particular, eventually became a member of the orthomolecular psychiatry movement, thus placing himself outside the medical establishment.[41] Even while he was an employee of the PSB, Hoffer saw to it that his research received wide publicity.[42] In particular, he exploited his contacts with the Saskatchewan branch of the CMHA to promote the merits of niacin therapy (his sister Fanny was an active member and her husband, Irvin Kahan, was the association's executive secretary). The CMHA, in turn, could use the theory as a propaganda device both to rally its membership and to persuade the federal government and the Government of Saskatchewan to further their cause. Hoffer used other avenues to publicize his work. His efforts were facilitated, in part, because it was easy to portray the adrenochrome hypothesis and the rationale for niacin therapy in commonsensical ways. Hoffer's remorseless advocacy of niacin therapy eventually alienated him from his psychiatric colleagues in Saskatchewan, as well as his colleagues in the medical profession.[43] To Hoffer's credit, there are no signs that he wished to benefit financially from what he believed were his "objective" and "scientifically based" discoveries.

The Demise of the Adrenochrome Hypothesis

Hoffer first ran into difficulties in 1958. He claimed that he had found adrenochrome in blood.[44] Laboratories funded by the American National Institute of Mental Health (NIMH) had never detected adrenochrome in blood. The NIMH sent an investigatory team to Saskatoon; the team concluded that Hoffer's data were an artifact of the presence of ascorbic acid. Hoffer refused to retract. Because the medicoscientific world accepted the validity of the NIMH report, organizers of the meetings of leading medicoscientific organizations stopped inviting Hoffer or members of his research team to present their work at conferences.[45] Within 3 years, research articles published by other investigators had the effect of blocking

Hoffer's access to leading medical and scientific journals. Theodore L. Sourkes, a biochemist at the Department of Psychiatry, McGill University, wrote a review article on the biochemistry of mental illness in which he cited several articles reporting evidence fatal to the adrenochrome theory.[46] As a consequence of Sourkes's review article and the accumulating evidence from other researchers, Hoffer's research funds were greatly reduced. His peak levels of funding were never restored.

To evaluate the evidence that Sourkes cited, one has to know how Hoffer's biochemists, A. N. Payza and M. E. Mahon, attempted to measure the amounts of adrenochrome in the human body. They extracted erythrocytes (red blood cells) from their subjects, centrifuged them, dissolved the product in acetone, and subjected it to a fluorescent analysis. Using such analyses, they obtained activation and fluorescence peaks that, they claimed, were characteristic of adrenochrome.[47] However, as Payza and Mahon admitted,

> Because neither adrenochrome nor any of its derivatives have yet been isolated from blood or urine, there is no absolute proof that this method measures adrenochrome. However, the method is accurate when adrenochrome is added to plasma or injected intravenously into blood. Plasma contains fluorescent factors which behave as if they were adrenochrome. Therefore it is a working assumption that adrenochrome is being measured. However, proof must await isolation studies.[48]

The chief biochemist of the Saskatchewan laboratory sent plasma to which adrenochrome had been added to Donald S. Layne and Sourkes, who failed to find such a proof. They could find adrenochrome neither in blood drawn from normal people nor in that drawn from those diagnosed as schizophrenic.[49] Other investigators reported that they could not verify the assertions of Hoffer and his group.[50] Even before the publication of the studies failing to verify the Saskatchewan method for the detection of adrenochrome, Aaron Feldstein had pinpointed the problem. He wrote,

> [a]drenochrome in acetone does not fluoresce. The maxima observed were probably due to scatter light. The conclusion that adrenochrome is present in the erythrocytes of schizophrenic patients is therefore not justified by the evidence. Our investigations have led us to believe that the fluorimetric procedure does not measure adrenochrome endogenously found in plasma, but that the procedure measures instead an artifact due to the reaction of zinc acetate and ascorbic acid. Our evidence is based upon a study of activation maxima which were not investigated in the published procedure.[51]

But Smythies, whose insights provided the basis for the adrenochrome theory, delivered the unkindest cut of all. He thrust his dagger into the theory's heart—the supposed psychotomimetic properties of adrenochrome and adrenolutin. He wrote,

> Unfortunately the experiments which are supposed to show that [adrenochrome and adrenolutin] are psychomimetic are unconvincing, because, in most cases, no double-blind controls were used. The results may well have been due to placebo effects, the extraordinary range of which was not fully realized at the time.[52]

The CMHA acted as the theory's mortician. Because of the demands from the general public for the use of nicotinic acid, they funded a comprehensive evaluation by a team of biochemists, led by Thomas A. Ban.[53] Ban planned 12 studies involving 320 subjects. A large body of work on the possible biochemical origins of schizophrenia was discussed comprehensively, and alternatives to the adrenochrome theory were suggested. Despite Ban and his colleagues' failure to find any previous studies, other than those conducted by Hoffer and his group, demonstrating that nicotinic acid was a therapeutic agent, Hoffer and Osmond's theory and their suggested therapy were treated seriously. Above all, transmethylation theories were not discounted. Instead, the authors of the study tried to determine what sort of role such theories might have played in increasing our understanding of the neurochemical origins of schizophrenia.

The assessment of nicotinic acid's possible role as a therapeutic agent was equally thorough. The authors displayed a complete grasp of the principles of experimental design, a good appreciation of the shortcomings of those principles in medical settings, and made praiseworthy efforts to modify the applications of the principles accordingly. They explored four general hypotheses, breaking them down into subhypotheses, each of which controlled a particular project. The general hypotheses were as follows: (1) Does nicotinic acid have a therapeutic effect larger than that exerted by standard drug treatments? (2) If nicotinic acid were therapeutically effective, would its effects be enhanced by ascorbic acid, pyroxidine, or d-penicillamine?[54] (3) Does the presence of the mauve spot or the pink factor predict a favorable outcome from drug therapy?[55] (4) If a methyl donor and monoamine oxidase inhibitor were administered, could the resultant exacerbation of the psychosis be overcome with nicotinic acid?[56]

I discuss only Hypotheses 1 and 4 and refer briefly to Hypothesis 3. Hypothesis 1 provided the most direct test of the efficacy of niacin therapy. In their first test of the hypothesis (a study with a duration of 6 months), Ban and his colleagues assigned 30 people suffering from schizophrenia, all of whom received chlorpromazine, to three 10-member groups (a nicotinic acid, a nicotinamide, and a placebo group) matched in terms of age, sex, and level of symptoms on the Brief Psychiatric Rating Scale (BPRS). Those subjected to the treatments came from the Douglas Hospital, Verdun, Quebec. The adrenochrome theory received only limited support (administration of nicotinamide was associated with a significant decrease in symptoms on the BPRS). However, the combined mean scores of the nicotinamide and nicotinic acid groups did not differ from the mean score of the placebo group. Moreover, the placebo group required a lower level of chlorpromazine than did either of the treatment groups.

Given that only limited evidence had been found for assigning nicotinic acid a therapeutic role, Ban and his group explored Hypothesis 1 further in a study of the same design but of longer duration (2 years) than the first, involving people diagnosed with schizophrenia from the Hôpital St. Jean de Dieu, Montreal, the Hôpital des Laurentides, Montreal, and the Douglas Hospital. Unfortunately, the study was inconclusive because only six people remained in the study for its full duration. Even so, for those originally assigned to the study, the mean days spent in hospital were lowest for the placebo group and the mean dosage of chlorpromazine was lower in both the placebo and nicotinic acid groups. There was limited

support for the Hoffer–Osmond theory in that the mean improvement in BPRS scores in the two treatment groups exceeded that of the placebo group.

The results of testing the fourth hypothesis, in a study designed by J. V. Ananth, also produced an outcome unfavorable to the adrenochrome theory.[57] Psychopathology was artificially induced in a group suffering from chronic schizophrenia by administering either methionine or tranylcypromine. Ananth found that administering nicotinic acid did not result in an improved psychological state.

Ban concluded that schizophrenia might well be a family of illnesses, each one caused by a different chemical disorder, but with all members of the family displaying similar behavioral manifestations or clinical presentations. Overall, he stated, "[t]hat there is sufficient evidence to suggest strongly that nicotinic acid or nicotinamide is not the treatment of choice for every schizophrenic patient, under all possible conditions and without any further considerations."[58] Moreover, and disturbingly, Ban presented convincing evidence that, contrary to Hoffer's assertions and in a high proportion of cases, the massive doses of nicotinic acid required in therapy yielded side effects, some of which were serious. Moreover, he cited animal studies from the 1930s showing postmortem evidence of severe lesions following administration of B_3 at dosage levels comparable to those used in nicotinic acid therapy.

However, the most damning parts of Ban's articles were those that dealt with the structure of and evidence for the adrenochrome theory. Ban stated, "It has been over 18 years since the first patients were successfully treated with high dosage nicotinic acid administration. The clinical information which has accumulated during this period compares unfavorably with the scientific progress made in this area of research."[59] In his report, Ban took transmethylation theories seriously. However, he concluded that the evidence indicated that metabolic pathways different from those that Hoffer and Osmond had adduced could be responsible. As a result of his tests of Hypothesis 3, Ban finally brought the theory to earth by citing evidence showing that "[t]he 'mauve factor' was eliminated as one of the possible stimulant metabolites producing overarousal in the schizophrenic patient."[60]

Hoffer, to the end of his life, refused to accept the findings of the CMHA study.[61] He believed that it was improperly carried out. At the time of the study, he and Osmond were claiming a therapeutic effect for nicotinic acid only in cases of freshly diagnosed schizophrenia (although subsequently Hoffer claimed an effect in chronic schizophrenia). Ban stated that, in his 6-month study, all the experimental subjects were patients freshly admitted to Douglas Hospital. However, after the study had been published, Ban told Hoffer that the study's subjects had all spent several years in other institutions. Apparently, Hoffer missed the point of the study, which was that it provided a thorough review and assessment of the status and role of a particular form of transmethylation theory. Moreover, consistency in the results of several independent studies counted for more than supposed imperfections in a single study.

We therefore have to ask why Hoffer continued to promote the merits of nicotinic acid therapy or, rather, ask what constituted the basis for his convictions. Hoffer and Osmond appear to have been misled on two grounds. First, they

characterized schizophrenia as an illness, conceptually no different from aphasia or diabetes. Second, they defined schizophrenia idiosyncratically. With respect to the first error, we have to appreciate that Hoffer and Osmond were fully committed biological psychiatrists. Because they looked on all forms of mental illness as physical illness, it followed that each form of mental illness would have had its distinctive signs and symptoms. Mental illness, then, was to be classified biochemically and not clinically. In the case of schizophrenia, the mauve spot on chromatography paper was the crucial sign, indicating that the patient was malvaric. They treated malvaria as a disease caused by the improper metabolism of adrenaline, resulting in the formation of the natural hallucinogens adrenochrome and adrenolutin. Thus, Hoffer or other psychiatrists who shared his views would observe a set of symptoms that they believed were characteristic of schizophrenia. They would then submit the patient to a malvaria test. If the test was positive, they would prescribe biochemical treatment (the ingestion of massive doses of niacin or nicotinic acid). If the patient improved or recovered, they would say that they had cured his or her disease (schizophrenia). None of them ever discovered the cause of the mauve spot (they merely presumed that it was a consequence of the retention of adrenochrome or adrenolutin within the body). Even if the mauve spot had some specific and constant biochemical cause, it does not follow that the relationship to schizophrenia was perfect. It would then follow that some schizophrenics are malvaric, but that many nonschizophrenics are also malvaric. Furthermore, let us assume that the malvaric nonschizophrenics display nonpermanent features of mental illness (e.g., depression). Such people are likely to recover spontaneously while undergoing nicotinic acid therapy and will be counted among those who were cured, thereby spuriously inflating the recovery rate for schizophrenia. Because the cause of malvaria was unknown, its purported role in mental illness could be assessed only via rates of improvement.

As for Hoffer's idiosyncratic diagnoses, it was apparently widely known among the Western Canadian medical profession that he followed faulty diagnostic procedures. For example, it was usually said that Hoffer treated all forms of delusional thinking as psychotic, even though many neurotics display delusions. Even though it was known that neurotics have high rates of spontaneous recovery, Hoffer still included them in his cured groups.[62] Certainly, Hoffer's diagnosis of schizophrenia was idiosyncratic. Based on their belief that LSD was a psychotomimetic, Hoffer and Osmond overemphasized the role of perceptual disorders in schizophrenia, believing that such disorders were the driving force behind other symptoms, such as social withdrawal. Hoffer, especially, believed that, by using the Lewis–Piotrowski signs, clinicians could make the diagnosis of schizophrenia infallibly and that they could reliably differentiate between schizophrenia and manic–depressive disorder.[63] Crucially, he noted that five of the Lewis–Piotrowski signs referred to perceptual distortions (such as hearing voices or having visions). So, in assembling items for the HOD, he allowed himself to be guided by the Lewis–Piotrowski criteria. As a result, 72 of the 150 items on the HOD ask questions about perception. As with the diagnostic use of the mauve spot, this overemphasis on perceptual distortion may well have resulted in misidentification or miscategorization of individuals suffering from some sort of mental illness.

Conclusion

The adrenochrome hypothesis was, in many respects, unique, but otherwise it sat comfortably within psychopharmacology's institutional and ideological framework. Hoffer's background was certainly unusual (he had a PhD in biochemistry, specializing in the B vitamins, and took up medicine as a second career choice). In England, Osmond was the victim of the prejudices of the day (the belief that psychological symptoms must have exclusively psychological causes, combined with suspicion of anyone who chose to work with powerful hallucinogens) so that the British funding agencies would not support his and Smythies' research. But, conceptually, Osmond's work ran with the main stream, as I have shown earlier in this article.

Because the adrenochrome theory's rationale ultimately lay in the supposed equality between hallucinations produced by the ingestion of particular chemical compounds and the symptoms manifested in schizophrenia, the theory, according to Dyck, promised to provide both a pharmacological treatment and, via experimentation with LSD, insights into the mental world of schizophrenia. In my research for this article, I was unable to find evidence that the Saskatchewan researchers used those insights to open ways of talking to those suffering from schizophrenia. Instead, the researchers would take LSD themselves in order to understand schizophrenia from an external perspective. Hoffer's and Osmond's approaches to schizophrenia remained resolutely medical and biological: Whether naturally or artificially induced, the delusions and perceptual distortions they and their researchers observed were chemically induced.

Hoffer and Osmond believed that to follow the path of understanding rather than taking the road of explanation committed psychiatrists to the errors of psychoanalysis (using a theory to assign a cause to a phenomenon rather than to discover that cause). But, presumably without realizing it, Hoffer and his associates were, even so, trapped within a closed ideological circle because they guaranteed themselves beforehand the very proof that they needed. But that proof was acceptable only if one agreed to grant truth to all their assumptions.

Endnotes

1. For biographical information on Hoffer, see his *Adventures in Psychiatry: The Scientific Memoirs of Dr. Abram Hoffer* (Caledon, ON, Canada: KOS Publishing, 2005); and Erika Dyck, *Psychedelic Psychiatry: LSD From Clinic to Campus* (Baltimore: Johns Hopkins University Press, 2008), 26. For biographical information on Osmond, see Dyck, *Psychedelic Psychiatry*, 15–19.

2. Abram Hoffer, e-mail message to the author, December 13, 2004.

3. For a review of the history of psychiatry in Saskatchewan under the Cooperative Commonwealth Federation government, see John A. Mills, "Lessons From the Periphery: Psychiatry in Saskatchewan, Canada, 1944–1968," *History of Psychiatry* 18 (2007): 179–202.

4. According to Hoffer, McKerracher was prompted to create a research program because, while Hoffer was working as a medical intern at City Hospital, Saskatoon, he asked McKerracher whether he could work for the government as a research psychiatrist. McKerracher agreed, on the proviso that Hoffer should start his psychiatric training immediately after completing his medical residency. Hoffer trained under McKerracher's supervision, acquiring his Specialty in Psychiatry, the forerunner of the current Fellowship

(Hoffer, Memorandum to McKerracher, January 1960, Department of Psychiatry Papers, Archives of the University of Saskatchewan; and Hoffer, interview with the author, Victoria, July 28, 2000).

5. Government of Saskatchewan, Department of Public Health, Psychiatric Services Branch, Annual Report, 1950–51, 72. Hoffer told the author (e-mail message, February 2007) that McKerracher appointed him Director of Research for the PSB. I have no documentary record of the appointment.

6. Canadian Mental Health Association, Saskatchewan Division, Submission to the Government of Saskatchewan, 1959, 3. For accounts of psychiatric research in Saskatchewan in the 1950s and 1960s, see Dyck, *Psychedelic Psychiatry*; Dyck, "Flashback: Psychiatric Experimentation With LSD in Historical Perspective," *The Canadian Journal of Psychiatry* 50 (2005): 381–88; Dyck, "'Hitting Highs at Rock Bottom': LSD Treatment for Alcoholism, 1950–1970," *Social History of Medicine* 19 (2006): 319–29; Mills, "Lessons From the Periphery"; Mills and Dyck, "Trust Amply Recompensed: Psychological Research at Weyburn, Saskatchewan, 1958–1961," *Journal of the History of the Behavioral Sciences* 44 (2008): 199–217.

7. The following account is based on David Healy, *The Creation of Psychopharmacology* (Cambridge, MA: Harvard University Press, 2002), 176–82; and on Edward M. Brecher and the editors of *Consumer Reports, Licit and Illicit Drugs: The Consumers' Union Report on Narcotics, Stimulants, Depressants, Inhalants, Hallucinogens, and Marijuana—Including Caffeine, Nicotine, and Alcohol* (New York: Little, Brown, 1972).

8. Quoted in Brecher et al., *Licit and Illicit Drugs*, 347. Brecher et al. comment that Hofmann's was the only true LSD "trip" in history because he was the only person who had no preconceptions about its probable effects.

9. de Tours discussed his speculations in his *Hashish and Mental Alienation* (see Healy, *The Creation of Psychopharmacology*, 180). Healy points out that de Tours's suggestions made sense at the time because insanity was seen as primarily a delirium so that the delirious states produced by hashish provided a model for comprehending psychosis.

10. Healy, *The Creation of Psychopharmacology*, 178–82.

11. Healy, *The Creation of Psychopharmacology*, 184–85.

12. Robert S. Feldman and Linda F. Quenzer, *Fundamentals of Neuropsychopharmacology* (Sunderland, MA: Sinauer Associates, 1984), 152.

13. Humphry Osmond and John Smythies, "Schizophrenia: A New Approach," *Journal of Mental Science* 98 (1952): 309–15.

14. The author heard that story from the Saskatchewan psychiatrist Frank Coburn in an interview in Saskatoon, October 1999.

15. Hoffer, Osmond, and Smythies, "Schizophrenia: A New Approach. II. Result of a Year's Research," *Journal of Mental Science* 100 (1954): 29–45.

16. Hoffer, *Adventures in Psychiatry*, 61. The committee members were Osmond, Professor Charles McArthur (head of the Department of Biochemistry at the University of Saskatchewan), Vernon Woodford (also of the Department of Biochemistry), Duncan Hutcheon (a professor of pharmacology in the Department of Physiology), Professor Louis Jacques (head of the Department of Physiology), and McKerracher.

17. Hoffer, interview with the author, Victoria, July 28, 2000.

18. Hoffer, e-mail message to the author, February 2007. In the same e-mail message, Hoffer denied that the adrenochrome theory was a variant of transmethylation theory. I, however, accept Healey's view that it is. The meeting was of the Dementia Praecox Committee of the Scottish Rites Masons.

19. This quotation and those following it are from Hoffer, *Adventures in Psychiatry*, 107; and Hoffer and Osmond, *The Hallucinogens* (New York: Academic Press, 1967), 102.

20. See Healy, *The Creation of Psychopharmacology*, 184–85; and Hoffer, *Adventures in Psychiatry*, 38.

21. For the first version of the HOD, see Hoffer and Osmond, "A Card-Sorting Test Useful in Making Psychiatric Diagnoses," *Journal of Neurophysiology* 2 (1961): 306–30.

22. The first version of the test was psychometrically defective. The standardization sample was small and idiosyncratic. It consisted of 105 patients (of whom half had been diagnosed as schizophrenic) from Weyburn and 174 from the University Hospital, for a total of 279. The diagnoses in the hospital sample were made by a psychiatric resident in consultation with a senior psychiatrist while the hospital records were used for the Weyburn sample. It would appear that Hoffer and Osmond established validity indirectly. Having established that the diagnoses in their major criterion group (schizophrenics) were reliable, they reported that the mean HOD score in that group differentiated it from other groups in the study. No major psychological journal would have accepted such a procedure.

23. Hoffer, *Adventures in Psychiatry*, 72–73. Healy gives the rationale for Hoffer's therapy as follows: "The B_3 vitamin, nicotinic acid, is methylated in the body to nicotinamide. Conceivably, then, giving large doses of nicotinic acid could mop up all the methyl donors in the body that could be used to convert norepinephrine to epinephrine, and if epinephrine were produced in smaller amounts, its potentially toxic by-product, adrenochrome, would also be produced in smaller amounts" (Healy, *The Creation of Psychopharmacology*, 184).

24. Hoffer described the study in his *Vitamin B-3, Schizophrenia: Discovery, Recovery, Controversy* (Marquis, Quebec: Quarry Health Books, 1998), 45–51. In a double-blind study, all subjects are assigned randomly to a placebo and a treatment group and the identity of the participating subjects is concealed from those assessing the subjects' progress. Hoffer stated (*Adventures in Psychiatry*, 92) that his and Osmond's double-blind study was the first to be carried out in psychiatry. That may be because the Hoffer–Osmond study was undertaken in 1952, but the results were not published until 1954. However, Hoffer did not know that the British psychiatrist W. Linford Rees carried out a double-blind study to evaluate the effectiveness of some of the current treatments for schizophrenia in the same year. Because the results were negative, Rees did not publish them; see W. Linford Rees and David Healy, "The Place of Clinical Trials in the Development of Psychopharmacology," *History of Psychiatry* 8 (1997): 1–20. Hoffer soon became disenchanted with double-blind studies for moral reasons (he considered it wrong to deny treatment to people who were ill, while misleading them at the same time). See Hoffer, *Adventures in Psychiatry*; and Dyck, *Psychedelic Psychiatry*, 92–95.

25. Niacin causes flushing, whereas niacinamide does not, so that evaluating psychiatrists would have known which patients were receiving that treatment. Hoffer and his fellow researchers would have liked to use a nonflush form of niacin, but no such preparation was available.

26. Hoffer described the study in his *Niacin Therapy in Psychiatry* (Springfield, IL: Thomas, 1962), Chap. 5.

27. See Nolan D. C. Lewis and Zygmunt A Piotrowski, "Clinical Diagnosis of Manic-Depressive Psychosis," in *Depression*, ed. Paul H. Hoch and Joseph Zubin (New York: Grune & Stratton, 1954), 25–38. I am most grateful to Steve Foley, who e-mailed me a copy of Lewis and Piotrowski's chapter. It would seem that Lewis and Piotrowski believed that the presence of even one sign was taken as sufficient to make a diagnosis of schizophrenia because they wrote, "Even a trace of schizophrenia is schizophrenia and has very important prognostic as well as diagnostic significance" (38).

28. Hoffer, *Adventures in Psychiatry*, 41–43.

29. Hoffer, *Niacin Therapy in Psychiatry*, 49–67.

30. *The Creation of Psychopharmacology*, 186. Healy cites Thomas Ban's study

(which I review in detail below). I find Healy's statement puzzling because not only did Ban's own work conclusively demonstrate that nicotinic acid therapy had, at best, limited effects but the only other studies he cited were negative.

31. Healy, *The Creation of Psychopharmacology*, 185–86.

32. Hoffer claimed that the mauve spot is either kryptopyrrole or some similar chemical (e-mail message to the author, December 13, 2004). It has been shown to be 2, 4 dimethyl-3-ethylpyrrole (Arnold Sohler, Raymond Beck, and Joseph. J. Noval, "Mauve Factor Re-identified as 2, 4 Dimethyl-3-Ethylpyrrole and Its Sedative Effect on the CNS," *Nature* 228 [1970]: 1318–20).

33. Hoffer, *Adventures in Psychiatry*, 109.

34. Hoffer, *Adventures in Psychiatry*, 44–45.

35. Dyck, *Psychedelic Psychiatry*, 29–30.

36. Jean Delay, Pierre Deniker, and J. M. Harl, "Utilisation en thérapeutique psychiatrique d'une phenothiazine d'action centrale élective," *Annales Médicale Psychologie* 110 (1952): 112–31. For an overall account of the introduction of chlorpromazine, see Healy, *The Creation of Psychopharmacology*, 77–101.

37. See Heinz Lehmann, "The Introduction of Chlorpromazine to North America," *Psychiatric Journal of the University of Ottawa* 14 (1989): 263–65.

38. Heinz E. Lehmann and Gorman E. Hanrahan, "Chlorpromazine: New Inhibiting Agent for Psychomotor Excitement and Manic States," *Archives of Neurology and Psychiatry* 71 (1954): 227–37. For a general account of Lehmann's discovery of the effects of chlorpromazine, see Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (New York: Wiley, 1997), 250–53.

39. Healy, *The Discovery of Psychopharmacology;* and Healy, *The Anti-Depressant Era* (Cambridge, MA: Harvard University Press, 1997).

40. Judith P. Swazey, *Chlorpromazine in Psychiatry: A Study in Therapeutic Innovation* (Cambridge, MA: Harvard University Press, 1974), 201–07. For a brief account of Smith, Kline, and French's acquisition of the right to market chlorpromazine, see Shorter, *The History of Psychiatry*, 253–55.

41. Hoffer defined *orthomolecular psychiatry* as follows: "By orthomolecular psychiatry I mean the use of optimum (often large) doses of molecules naturally present in the body to treat poor health and promote good health, specifically mental health" (Hoffer, *Vitamin B-3 Schizophrenia*, 10.) For a similar definition, see Healy, *The Creation of Psychopharmacology*, 190.

42. For example in February 1966, the *Regina Leader Post* published an article based on an interview with Hoffer in which he promoted the use of a yeast extract containing large amounts of niacin. The publication of the article caused heated interchanges between R. W. Begg (dean of the College of Medicine, University of Saskatchewan), the registrar of the College of Physicians and Surgeons of Saskatchewan, and the director of the PSB F. S. Lawson. All disapproved of what they saw as Hoffer's relentless search for publicity. See Department of Psychiatry, Correspondence, Archives of the University of Saskatchewan.

43. In the correspondence cited above, Lawson reported that Hoffer resigned from the Psychiatric Association of Saskatchewan.

44. Hoffer, "Adrenochrome in Blood Plasma," *American Journal of Psychiatry* 114 (1958): 752.

45. Healy, *The Creation of Psychopharmacology*, 190. Hoffer pointed out to the author that he and his associates continued to be invited to speak at some universities (e-mail message to the author, November 2007).

46. Theodore L. Sourkes, "The Biochemistry of Mental Disease," *Canadian Medical Association Journal* 85 (1961): 487–90.

47. For a description of the method, see A. N. Payza and M. E. Mahon, "Spec-

trofluorometric Estimation of Adrenochrome in Human Plasma," *Analytical Chemistry* 31 (1959): 1170–75.

48. Payza and Mahon, "Spectrofluorometric Estimation," 1174.

49. Donald S. Layne and Sourkes, letter to the editor, *Journal of Nervous and Mental Diseases* 130 (1960): 93.

50. Axel Randrup and Ib Munkvad, "On the Measurement of Adrenochrome in Blood," *American Journal of Psychiatry* 117 (1960): 153. Stephen Szara, Julius Axelrod, and Seymour Perlin, "Is Adrenochrome Present in the Blood?" *American Journal of Psychiatry* 115 (1958): 163.

51. Aaron Felstein, "On the Relationship of Adrenaline and Its Oxidation Products to Schizophrenia," *American Journal of Psychiatry* 116 (1959): 455–56.

52. J. R. Smythies, "Recent Advances in the Biochemistry of Psychosis," *The Lancet* (June 11, 1960), 1287. Smythies goes on to state, "Hoffer's only experiment using such controls produced negative results. . . . Thus whether these agents produce a condition resembling psychosis remains uncertain. The only properly designed trial so far conducted has yielded negative results, and the balance of evidence suggests that these agents are not psychotomimetic, at least when given by ordinary routes. We have, of course, no means of knowing what such chemically reactive compounds might do if released by some metabolic fault in the brain, but there is as yet no evidence that this happens."

53. Thomas A. Ban, *Nicotinic Acid in the Treatment of Schizophrenias: Introduction*; Ban and Heinz E. Lehmann. *Nicotinic Acid in the Treatment of Schizophrenias: Progress Report I*; Ban, *Nicotinic Acid in the Treatment of Schizophrenias: Complementary Report A* (Toronto: Canadian Mental Health Association, 1971). I am most grateful to John Court and Erika Dyck, who located and photocopied those reports for me.

54. Pyroxidine blocks the action of compounds antagonistic to the action of chemicals similar to the B vitamins. Hoffer asserted that penicillamine, in combination with niacin, could be used to treat schizophrenia (Hoffer, *Adventures in Psychiatry*, 139).

55. The pink spot is caused by the presence of 3, 4 dimethyoxyphenylethylamine in the urine. The chemical can be of dietary origin or else occurs as a result of treatment with chlorpromazine.

56. Monoamine oxidase inhibitors, such as iproniazid, inhibit the action of an enzyme controlling the breakdown of norepinephrine, with resultant increases in its level and an elevation of mood (thus, if one assumes that schizophrenic symptoms are largely perceptual, exacerbating those symptoms).

57. Ban, *Progress Report I*, 12–13.

58. Ban, *Progress Report I*, 12.

59. Ban, *Progress Report I*, 13.

60. Ban, *Complementary Report*, 8.

61. See especially, Hoffer, *Adventures in Psychiatry*, 158–60.

62. Conversation between the author and Dr. Mike Parrish, a former general practitioner from Alberta (Hornby Island Co-Op Store, November 27, 2004.) As a specific instance, Frank Coburn, in his interview with the author, said that one of his former patients, whom he did not diagnose as schizophrenic, had previously been treated by Hoffer and, so Hoffer claimed, had been cured. During the course of his psychotherapy, the patient told Coburn that he had not taken the prescribed nicotinic acid because he could not tolerate the unpleasant side effects. Nevertheless, he recovered spontaneously.

63. Hoffer, *Adventures in Psychiatry*, 41–43.

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