WONDER DRUGS FOR VICTORY

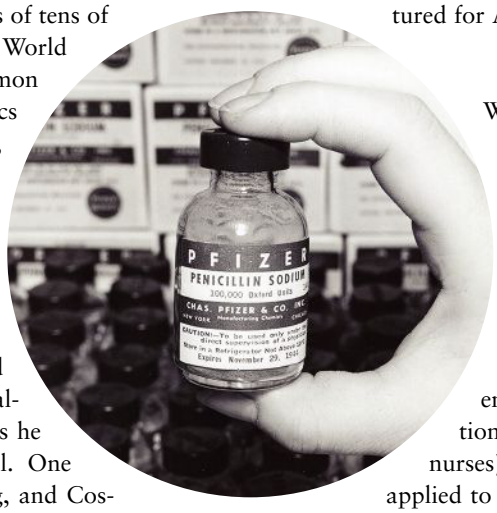
America's arsenal of democracy gave the Allies not only death-dealing weapons of war, but also cutting-edge, lifesaving antibiotics.

by Mark Weisenmiller

Soviet Premier Joseph Stalin was uncharacteristically generous toward the United States one evening during the November-December 1943 Tehran Conference at the Soviet embassy in Iran's capital. At dinner, he praised the Americans for their Lend-Lease program, which sent war supplies to nations battling the Axis powers. To President Franklin D. Roosevelt, British Prime Minister Winston Churchill, and the gathered staffs of the Soviet, American, and British heads of state, Stalin announced (optimistically, considering the war was not yet over), "Without American production, the United Nations [the Allies] could never have won the war."

Most of what Lend-Lease supplied was military hardware: tanks, ships, planes, and weapons. That was what Stalin had in mind. But there was another American product that not only helped secure Allied victory, but also changed the fate of countless people around the world for decades to come: antibiotics.

Antibiotics unquestionably saved the lives of tens of thousands of civilians and military during World War II. In an era when it was all too common for people to die from infections, antibiotics were wonder drugs. And, for the most part, they were American-made.



One reason for US dominance in the production of these new cutting-edge, germ-fighting drugs during World War II was government regulation. Roosevelt, whose polio and other health problems kept him on numerous medications, had taken a personal interest in assuring the quality of US pharmaceuticals, and in the 1930s he backed legislation to accomplish this goal. One such law was the 1938 Federal Food, Drug, and Cosmetic Act, which established federal oversight over drug quality and safety, and required drug companies to follow strict regulations in research and development.

Another reason for US leadership in antibiotic production was money. The United States was the only Allied country whose economy was robust enough to support R&D for the wonder drugs. If America ever had a pharmaceutical rival, it was, for a short time, Nazi Germany, whose massive nationwide militarization kicked its economy into overdrive—until the war brought it crumbling down. In the end, antibiotics developed in Germany would be appropriated by US pharmaceutical companies and manufactured for Allied use.

Antibiotics 101

What, precisely, is an antibiotic? It can be any of a variety of substances, usually derived from microorganisms, that slows or stops the growth of other microorganisms. Antibiotics can be classified in all sorts of ways, based on their active ingredients and the types of microorganisms against which they are most effective.

Most of us know from personal experience that antibiotics are administered by injection (the form often used by WWII medics and nurses), swallowed (think penicillin tablets), or applied to the skin via ointment. Many antibiotics are also powerful allergens. The most common example of this is penicillin, which can cause everything from a skin rash to life-threatening shock. If misused, antibiotics can cause superinfections by enabling harmful bacteria to develop resistance.

All of the above had to be taught to and learned by military doctors and nurses and the many thousands of airmen, sailors,

LEFT: NATIONAL ARCHIVES. OPPOSITE: MERCK AND COMPANY

Above: The drug that changed the world: penicillin, made by US pharmaceutical firm Pfizer in time for the June 1944 Normandy invasion. Penicillin was the most important of five antibiotics that saved thousands of Allied lives in World War II. Opposite: Lab worker Gertrude McAndrews tests streptomycin at Merck and Company in January 1945. First isolated in 1943, streptomycin worked against tuberculosis.

and soldiers who would serve as medics (marines medics were navy hospital corpsmen). The effort paid off in the form of increased chances of survival for wounded servicemen.

America's WWII Antibiotics

THE AMERICAN PHARMACEUTICAL INDUSTRY manufactured five antibiotics for use by the US forces during the Second World War. Here they are, in alphabetical order, with one postwar drug added because of its connections to war-era pharmaceutical development:

Atabrine: A synthetic antibiotic developed by the German pharmaceutical company Bayer in 1931, Atabrine (the trade name for mepacrine, also called quinacrine) was the first manmade substitute for quinine, the anti-malarial drug of choice at that time. It was a timely discovery, because Japanese conquest of the Philippines and Indonesia in late 1941 and early 1942 cut off the Allies' access to cinchona bark, essential to making quinine. American-made Atabrine was administered to US servicemen in North Africa and the South Pacific to protect them from the ever-present threat of malaria.

Author James Michener memorialized the drug with a fictional character named Atabrine Benny in his 1947 Pulitzer Prize–winning compendium of short stories, *Tales of the South Pacific*. A good-hearted scamp, Benny was a pharmacist's assistant during his civilian life in Texas, but while stationed in the New Hebrides Islands, he somehow convinces everyone that he is a doctor. He is loved by all because he gives Atabrine tablets to anyone who wants them.

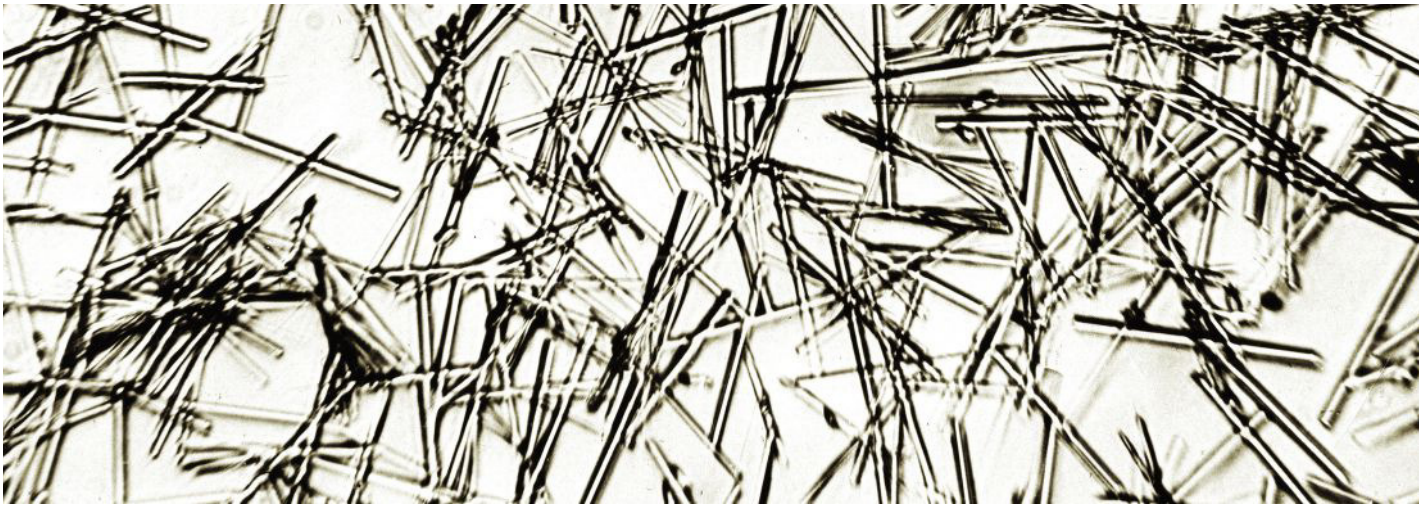
In reality, patients who took Atabrine had so many complaints about its many negative side effects that they found nothing funny about it. The yellow pills reportedly had a bitter taste, and it was not uncommon for patches of a patient's skin to turn yellow after ingestion of the drug. Other negative side effects were diarrhea, nausea, and vomiting.

"Yet Atabrine was effective, if only the men could be made to take it," notes author David Steinert in "The History of WWII Medicine," an article on his World War II Combat Medic website (www.mtaofnj.org/content/WWII Combat Medic - Dave Steinert/index.htm). "A great part of the problem was that the proper dosage had not yet been worked out. In an effort to ensure that the Atabrine was actually swallowed by the soldiers, medics or NCOs [noncommissioned officers] from the combat units stood at the head of mess lines to carefully watch marines and soldiers take their little yellow tablets."

Gramicidin: Many antibiotics originate from bacteria living in the soil, and gramicidin is one of them. It traces back to a bacillus found in things that rot in the ground, though the same organism can also be found in air, soil, and water. Gramicidin is one of World War II's less remembered antibiotics. Often used to treat eye infections, it is also found in most bacitracin-polymyxin antibiotic creams.

French-born microbiologist René J. Dubos, working with biochemist Rollin Hotchkiss, discovered gramicidin in the United States in 1939. The pair isolated both gramicidin and tyrothricin (a topical antibiotic) from *Bacillus brevis*. Both of these were among the first antibiotics to be mass-produced.

Penicillin: The most common and best known antibiotic of the Second World War was penicillin. Many people know the story of how Sir Alexander Fleming (a talented Scottish biologist, botanist, physician, and pharmacologist) went on vacation in 1928 and accidentally left a *staphylococcus* bacteria culture in an uncovered Petri dish. When Fleming returned, he noticed that mold was growing on the culture and that the *staphylococcus* had died all around the edges of the mold. Something in the mold—Fleming called it "mould juice"—had killed the bacteria.

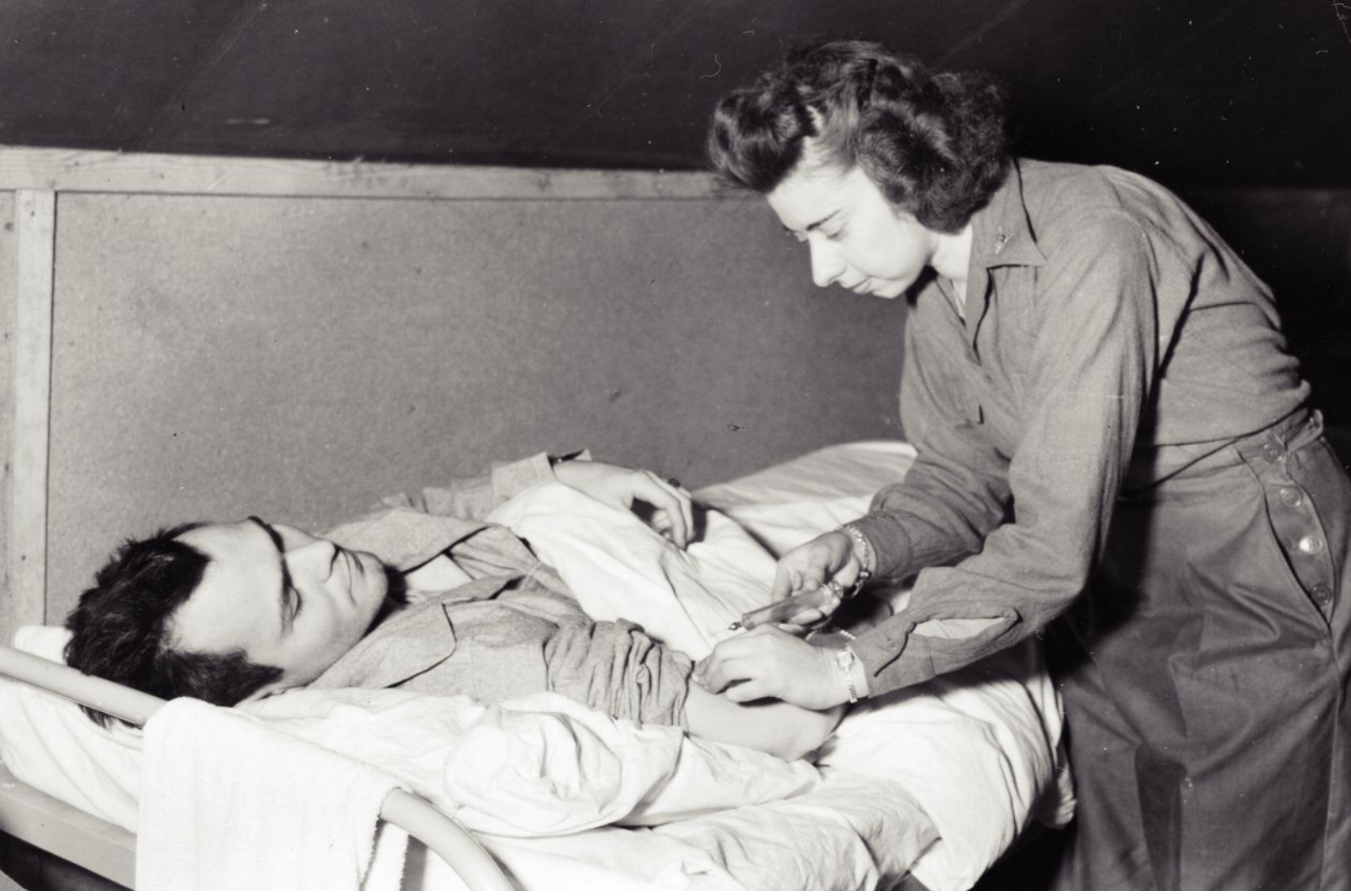


LEFT & OPPOSITE: NATIONAL ARCHIVES

Eventually, Fleming identified the mold as a *Penicillium* fungus. Renaming his "mould juice," he announced the discovery of penicillin in March 1929. His announcement garnered little interest at first. But little by little, experiments in treating various infections brought attention to the new drug.

By 1941, a team of biologists working in England, led by E.B. Chain and Sir H.W. Florey, developed a mass-production process for penicillin and set to work convincing US pharmaceutical companies to manufacture the new medicine. The drug-maker Merck and Company set to work. But by 1942 only enough penicillin to treat a handful of patients was available (especially because early penicillin left the body via urination within hours).

The military phased in penicillin as fast as it became available. Historian Andre Sobocinski of the US Navy Bureau of Medicine



and Surgery described for *America in WWII* how that process worked in the navy. "Penicillin first became available for use at selected naval hospitals in 1943 [Pearl Harbor, Hawaii; Mare Island, San Diego, and Oakland, California; St. Albans, New York; Philadelphia, Pennsylvania; Portsmouth, Virginia; and Seattle, Washington] and by the fall was available to naval forces in the Pacific and Atlantic theaters," he said. "Units deployed into theaters would also be supplied with requisite supplies."

By the time the Allies launched the Normandy invasion in France in June 1944, 2.3 million doses of penicillin from Merck, Pfizer, Lederle, Squibb, Abbott Laboratories, and 16 other US drug companies were available to treat casualties. At first, only a small amount of penicillin was allotted for non-military patients on the home front, but as production increased, the lifesaving medicine became a regular treatment for civilians, too.

Not surprisingly, Chain, Florey, and Fleming together received the 1945 Nobel Prize for Medicine for their work on this wonder drug. The discovery of benzylpenicillin (the chemical name for the 1928 original variety of penicillin) and its subsequent variants has saved the lives of millions of people. In World War II, it saved countless men from amputations or death resulting from infected combat wounds, illness, and accidents. For example, while bacterial pneumonia claimed the lives of 18 percent of servicemen who contracted it in World War I, it killed only 1 percent of its victims in World War II, thanks to penicillin. Penicillin also saved men from less honorable infections: venereal diseases. Sobocinski notes, "Beginning in 1944, penicillin therapy replaced sulfa drugs [see below] as the go-to treatment of venereal diseases (especially gonorrhea) at naval hospitals."

Streptomycin: Originally isolated by American biochemists Albert Schatz and Selman A. Waksman in 1943, streptomycin was "the first antibiotic effective against tuberculosis," as stated on the 1952 Nobel Prize notice. It was actually Schatz who isolated streptomycin while working in Waksman's laboratory, and just how much Waksman contributed has never been completely clear. As a result, the relationship between the two biochemists deteriorated until Schatz sued Waksman over royalties from the release of the drug. The lawsuit, though acrimonious, was settled out of court.

To this day, streptomycin is a major antibiotic used against tuberculosis. Streptomycin does its work by slowing protein synthesis and by destroying cell membranes in certain microorganisms. It isn't faultless: side effects can include kidney damage, nerve damage, and even deafness. The last of these would befall Corporal Desmond Doss, a conscientious objector who served as

Opposite: Under a microscope, a sample of streptomycin in a medically useful crystalline form looks like a glass sculpture. Above: Second Lieutenant Ella M. David, an army nurse, injects Staff Sergeant Willis Jenkins with penicillin at a field hospital in Normandy, France, in January 1945. The miracle drug had a shortcoming: it stayed in the body only a few hours before being flushed out in the patient's urine.

an army medic with the 77th Infantry Division in the Pacific and earned the Medal of Honor. In 1976, Doss was given too much streptomycin during a visit to a Veterans Administration facility in Atlanta and completely lost his hearing. Fortunately, in 1988 he received a cochlear implant that allowed him to hear again.

Sulfa drugs: From the first moments of World War II, the US military used sulfa drugs (short for sulfonamide) to help injured personnel beat infections. Sobocinski explains, "Following the attack on Pearl Harbor on December 7, 1941, naval medical personnel attached to the Naval Hospital Pearl Harbor and Mobile Hospital No. 2 and aboard the hospital ship USS *Solace [AH-5]* used sulfanilamide [the active ingredient in sulfa drugs] (powder form) to treat compound fractures, infections, and burns (using sulfa powder mixed with mineral oil). Sulfanilamide was also administered orally after initial treatment of infections."

The man who more or less discovered sulfa drugs was German chemist and pathologist Gerhard Domagk (1895–1964), director of research for I.G. Farben Industries at the Bayer lab in Wuppertal in the early 1930s. Domagk knew that dyes are quick to match up with bacterial cells, and his research led him to believe the right form of dye might be able to attach to undesirable bacteria and stop an infection. So he invented a red dye that became known by the trade name Prontosil and tested it on mice. When his daughter developed a life-threatening fever, he injected her with the dye, too. Her fever broke and she quickly recovered. Prontosil became the precursor to all sulfa drugs when a team of scientists discovered that the dye actually broke down inside the body, releasing a bacteria-fighting ingredient: sulfanilamide.

In 1939, the Nobel Prize in Physiology or Medicine went to Domagk, but Adolf Hitler refused to allow him to go to Sweden and claim it. Instead, the Nazis arrested and briefly jailed him. Two years after the war, in 1947, Domagk received his Nobel Prize gold medal, but the accompanying monetary award had expired.

Sulfa drugs proliferated, prescribed by physicians to stop meningitis as well as pneumonia. Author Thomas Hager, in his 2006 book about Domagk, *The Demon under the Microscope: From Battlefield Hospitals to Nazi Labs, One Doctor's Heroic Search for the World's First Miracle Drug*, notes that sulfa saved the lives of Franklin Roosevelt's son and Winston Churchill.

Churchill caught pneumonia while in Tunisia in 1943. Returning to England healthy due to sulfa treatments, he joked with reporters that he was happy to learn he could take sulfa with his favorite beverage: brandy.

If Churchill's press conference was a shot in the arm for the reputation of sulfa drugs, Franklin Roosevelt Jr.'s story was even better publicity. In November 1936, Roosevelt's 22-year-old son entered Boston's Massachusetts General Hospital with an acute streptococcus infection. When his condition dangerously worsened, his mother, Eleanor, authorized the physician to administer sulfa drugs. The young Roosevelt recovered, and on December 17, 1936, the *New York Times* announced, "Young Roosevelt Saved by New Drug." The news spread to other publications and was read by millions of people.

Tetracyclines: Tetracyclines arrived in America's pharmaceutical arsenal shortly after World War II, but were a product of the surge in antibiotics research in the 1930s and 1940s, and of the quest to find solutions to infections other antibiotics could not combat.

Created by bacteria of the genus *Streptomyces*, the tetracyclines are used to treat all sorts of maladies: acne; infections of the eye, intestinal, respiratory, or urinary tracts; and even Rocky Mountain spotted fever. Some are used to fight microorganisms that are resistant to penicillin. Today, some tetracyclines are losing their usefulness because certain strains of bacteria have developed resistance to them.

Ironically, the man who discovered the very first tetracycline antibiotic—chlortetracycline, known by the trade name Aureomycin—wasn't a medical researcher. Benjamin M. Duggar, better known for his work as a plant physiologist, uncovered chlortetracycline while working with the soil bacterium *Streptomyces aureofaciens*.

Another notable American scientist who did historic work on tetracyclines was Boston-born Robert B. Woodward. A founding father of research into synthesizing artificial laboratory versions of pharmaceutical substances found in nature, Woodward was an advisor to the US War Production Board on the development of penicillin. In 1944, with the help of a researcher, he synthesized manmade quinine for malaria treatment, bypassing the need for by-then-scarce cinchona bark. After the discovery of a second type of tetracycline, oxytetracycline, Woodward's research pinpointed the drug's molecular structure, allowing it to be made synthetically. For his lifetime work in synthesizing organic molecules, Woodward received the 1965 Nobel Prize for Chemistry.

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Opposite: Medics practice on a mock casualty at Camp Gruber, Oklahoma, in April 1943. They are using the state-of-the-art antibiotic of that time, sulfanilamide, pouring it on the fake wound. Above: Before penicillin, sulfa drugs were the best defense against bacteria at the front and on the home front.

JUST AS HUMANS HOPED the Great War of the early 1900s would be, as British author H.G. Wells wrote, "the war to end war," a later generation hoped the antibiotics developed in the 1930s and 1940s would eradicate many diseases once and for all. But time has proven that the quest for wonder drugs, like the quest for peace, will ever be a work in progress. ★

MARK WEISENMILLER *is an author-reporter living and working in Tampa, Florida.*

OPPOSITE: NATIONAL ARCHIVES