SPECIAL ARTICLE

Neurosyphilis, Malaria, and the Discovery of Antipsychotic Agents

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Four of the most disabling human diseases are syphilis, malaria, schizophrenia, and manic-depressive illness. The history of the development of treatments for these seemingly unrelated disorders intersects at several points. Treatment of tertiary cerebral syphilis (general paresis) by inducing fever with malaria led to a Nobel Prize. Although attempts to synthesize quinine, a plant product effective against malaria, failed, these efforts encouraged industrial organic chemists to synthesize many useful substances, including dyes, antibiotics, and antihistamines. The aniline-derived dye methylene blue was a member of a new class of polycyclic chemicals, the phenothiazines. Efforts to modify phenothiazines to find an antimalarial agent also failed but led to novel antiemetic-sedative antihistamines, including promethazine, promazine, and eventually chlorpromazine—the first effective treatment for schizophrenia and mania. Chlorpromazine has antipsychotic and antimanic properties, and it revolutionized the therapeutics of psychotic illnesses. (HARV REV PSYCHIATRY 2008;16:299–307.)

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Despite their diverse etiologies, syphilis, malaria, and psychotic illnesses have been intertwined with each other and with phenothiazines for over a century. Syphilis is caused by the spirochete *Treponema pallidum*, and malaria by a protozoön, usually *Plasmodium falciparum*, carried by a principal insect vector, the *Anopheles gambiae* mosquito; the etiology of psychotic disorders, including schizophrenia and manic-depressive (bipolar) disorder, is unknown. A century ago, patients with neurosyphilis often developed psychotic symptoms, occupied a high proportion of psychiatric hospital beds, and were sometimes treated with malaria-induced fever. This treatment was widely celebrated as a breakthrough but may not have been clinically effective. The first treatment with clear efficacy in schizophrenia and mania was, instead, the phenothiazine drug chlorpromazine. Its development is considered serendipitous because it emerged unexpectedly in a search for safer preoperative sedatives for use with surgical anesthesia, but its discovery was even more serendipitous than that; the identification and development of chlorpromazine and other phenothiazines arose out of the hunt for safe and tolerable treatments for malaria.

The material considered here involves a series of interconnected discoveries and developments important for the development of the antipsychotic-antimanic drugs that led to a revolution in modern psychiatric theory and practice over the past half-century. The key figures and events are summarized in Table 1. More generally, this brief historical overview considers topics that continue to be of interest and

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TABLE 1. Summary of Events Leading to Discovery of Chlorpromazine

Year	Place	Persons	Discovery
1820	École de Pharmacie, University of Paris	Pierre-Joseph Pelletier (1788–1842) and Joseph Caventou (1795–1877)	Isolate quinine from *cinchona* bark
1856	Royal College of Chemistry, London	William Perkin (1838–1907)	Synthesis of mauve, the first aniline dye
1865	London	Charles Ledger (1818–1905) and Manuel Mamani	Ledger sells *cinchona* seeds found by Mamani in Bolivia to the Dutch consul, leading to a Dutch monopoly on quinine based on plantations in Java
1878	BASF, Germany	Heinrich Caro (1834–1910)	Synthesis of methylene blue, the first phenothiazine dye
1882	University of Berlin	Paul Ehrlich (1854–1915)	Uses methylene blue to stain the tuberculosis bacillus
1883	University of Heidelberg	August Bernthsen (1855–1931)	Characterizes the structure and synthesizes the phenothiazine molecule
1891	University of Berlin	Paul Ehrlich (1854–1915)	Uses methylene blue to treat sailors with malaria
1917	Psychiatric Clinic, University of Vienna	Julius Wagner-Jauregg (1857–1940)	Treats neurosyphilis with malaria fever therapy (receives Nobel Prize in Medicine in 1927)
1944	Harvard University, Cambridge	Robert Woodward (1917–79)	Partial synthesis of quinine
1950	Rhône-Poulenc, Paris	Paul Charpentier	Synthesis of chlorpromazine, the first effective antipsychotic drug
1952	Hôpitals Val-de-Grâce and Ste. Anne, Paris	Henri Laborit, J. Hamon, Jean Delay, and Pierre Deniker	Initial clinical studies of chlorpromazine: Laborit in surgical pre-anesthesia; Hamon, and later Delay and Deniker, in psychiatry
2001	Columbia University, New York	Gilbert Stork (1921–)	Stereoselective, total synthesis of quinine

importance, including the recent emergence of chloroquine-resistant malaria, the difficulty in finding new antimalarials and antibiotics for treatment-resistant organisms, and the emergence of innovative psychotropic medicines. These topics have implications for drug development and clinical psychiatry, and malaria itself remains a leading international cause of death and disability, including neurocognitive deficits in children.

MALARIA AS A TREATMENT FOR ONE FORM OF PSYCHOSIS

An historically important connection between psychotic illnesses and malaria is the use of malaria-induced fever to treat neurosyphilis—a treatment that led to a Nobel Prize for a psychiatrist. The form of neurosyphilis of particular psychiatric relevance is general paresis of the insane (GPI), which can develop 10 to 25 years after initial infection, during the "tertiary" stage of syphilis. Patients with GPI experience disturbances in memory and judgment, and megalomania and delusions also were prevalent in the past. Although there are other manifestations of neurosyphilis, including spinal cord damage and ataxia (tabes dorsalis), the terms GPI and neurosyphilis are often used interchangeably.

Neurosyphilis was a common cause of psychosis and psychiatric hospitalization in the nineteenth century. In the United States, as recently as the mid-twentieth century, GPI continued as the basis for about 10% of all first admissions to psychiatric hospitals, and accounted for more than 20% of all patients in mental hospitals.[1] Without modern antibiotics, the outcome of neurosyphilis is often fatal. In a representative study, 80% of 1500 patients with untreated tertiary syphilis died within four years of the onset of the illness.[2]

Julius Wagner-Jauregg (1857–1940), a Viennese neuropsychiatrist, addressed the seemingly intractable challenge of finding an effective treatment for GPI. In 1887 he began attempts to treat GPI by inducing fever, because fevers seemed to be associated with improvement in the illness. Physicians had tried various ways of inducing fever, such as injections of turpentine, tuberculin, mercury, and the typhoid fever bacterium *Salmonella typhi*. In 1917, after nearly three decades of failed attempts, Wagner-Jauregg tried malaria because of its well-known association with episodic high fevers. He injected or rubbed malarial

blood from patients with benign tertian malaria caused by *Plasmodium vivax* into the skin of patients with GPI. Within a few days they developed high fevers lasting five or six hours, returning to normal about 48 hours later. Wagner-Jauregg allowed patients to go through this two-day cycle three or four times, and then used quinine to treat the malaria. He reported clinical success in six of the first nine patients he treated.[3]

Malaria was used to treat neurosyphilis throughout Europe and the United States until the early 1950s, when the use of penicillin became widespread.[2] Whether malaria therapy was effective is difficult to determine, in part because it was reserved for less seriously ill patients who were more likely to tolerate infection with malaria, and because neurosyphilis typically varies in severity over time. When malaria therapy was introduced, the concept of controlled clinical trials that might have addressed the question of effectiveness had not yet become a standard of experimental therapeutics. Moreover, the mechanisms by which malaria therapy might have been useful—if it was at all—remain unclear.

Wagner-Jauregg received the Nobel Prize for physiology or medicine in 1927 for his work on fever therapy for general paresis. In his memoirs, he noted that a long-standing member of the Nobel Prize committee rejected the idea that a physician who inoculated people with malaria deserved a Nobel Prize; only after this member retired from the committee was the prize awarded.[4] Braslow[5,6] has described how malaria fever-therapy, although not necessarily effective, gave physicians and patients a sense of hope, and also encouraged more positive and optimistic general clinical care of patients with GPI.

THE HUNT FOR EFFECTIVE TREATMENT FOR MALARIA LEADS TO THE PHENOTHIAZINE MOLECULE

Although malaria now is mainly a tropical disease, it existed in the past in countries with temperate climates. For example, malaria was prevalent in the marshlands of coastal southern England and the Netherlands, and it may have led to the death of King James I (1566–1625) of England. Malaria also flourished in the United States for centuries, particularly in the southeast.

Until the mid-nineteenth century, malaria patients were treated with a variety of remedies, including bloodletting, brandy, or mercury.[7] None of these treatments was effective, and mercury and bloodletting probably further weakened the patients. The one fairly safe and effective remedy for malaria, known since the seventeenth century, was the ground bark from *Cinchona calisaya* trees, native to South America. *Cinchona* is a genus of tropical evergreen trees and shrubs, which belongs to the family Rubiaceae. The major active antimalarial substance in the bark was quinine, an alkaloid (see Figure 1).

The first Europeans to use *Cinchona* were Jesuit missionaries working in South America. They were well aware of malaria because it was endemic to the swamps and marshes

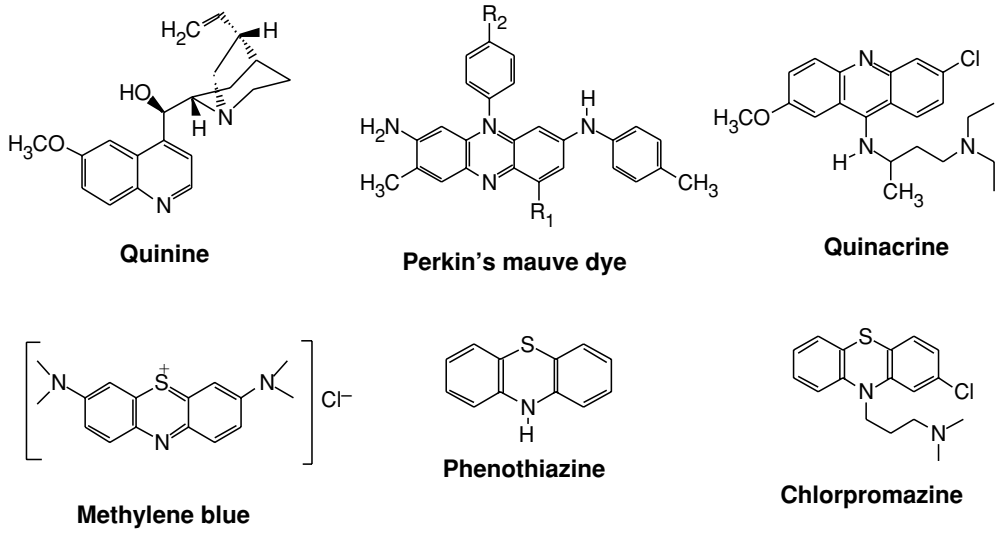

FIGURE 1. Chemical structures of compounds related to the discovery of chlorpromazine, the first successful antipsychotic agent: *quinine* (natural product for malaria); Perkin's *mauve dye* (one of the first synthetic dyes derived from aniline, a mixture of four mauveines with R_1 and R_2 either H or CH_3; most prevalent is mauveine-B2, with R1 = H and $R_2 = CH_3$); *quinacrine* (important synthetic antimalarial); *methylene blue* (an early phenothiazine dye); *phenothiazine* (the core structure of many dyes, antihistamines, and, eventually, antipsychotic agents); and *chlorpromazine* (a phenothiazine, the first successful antimanic-antipsychotic agent).

surrounding Rome, and had caused the deaths of popes and cardinals in previous centuries. Beginning in the 1600s, the use of *Cinchona* spread throughout Europe. Oliver Cromwell (1599–1658), lord protector of England, became ill with malaria but, suspicious of anything to do with the Catholics, died of the illness after refusing to use the "Jesuits' bark."

Like other colonial powers, the British were intent on controlling malaria, which was common in the fens of England and interfered with its imperial ambitions in India and in other areas. Finally convinced of the value of *Cinchona*, the British sponsored major efforts by various explorers to obtain *Cinchona* seeds and plants from South America.[8] This effort involved dangerous and difficult travel into the densely forested highlands of Bolivia, Peru, and Ecuador—where there were no roads but many tropical diseases and hostile, indigenous tribes. *Cinchona* trees were difficult to find. They grow best at 4,000- to 10,000-foot elevations, and exist in many varieties, only some of which produce quinine. For years, quantities of various types and quality of *Cinchona* seeds were taken from the South American jungles and shipped to London. The seeds were planted in the Royal Botanical Gardens at Kew or in large, climatically more appropriate plantations in India, largely without success. Neither site had the right conditions for *Cinchona*, and most of the seeds probably were from varieties with low concentrations of quinine-like alkaloids.

Working together, the British explorer Charles Ledger (1818–1905) and the Bolivian *cascarillero* (bark cutter) Manuel Incra Mamani (dates unknown) discovered a grove of 50 *Cinchona calisaya* trees whose bark produced high concentrations of quinine. Mamani spent five years gathering seeds from these trees. This species was later renamed *Cinchona ledgeriana* after the British explorer. Mamani was beaten to death by Bolivian police because of his role in letting *Cinchona* be taken out of the country and his refusal to give Ledger's name to local authorities. Ledger himself had a great deal of difficulty in selling his *Cinchona* seeds, though he is known to have sold one pound of them to the Dutch consul in London in 1865.[8] Ledger died in poverty in Australia before the significance of this sale was appreciated.

The Dutch East India Company, chartered in 1602—and then the Netherlands itself during the nineteenth century—colonized parts of Southeast Asia and also were interested in therapies for malaria. The Dutch were experienced in agricultural colonialism in Java and had already successfully converted large tracts of Java to plantations to grow coffee. The coffee plant belongs to the family Rubiaceae, so it was natural that another Rubiaceae member, *Cinchona*, would flourish in Java. The Dutch successfully planted the *Cinchona ledgeriana* seeds obtained by Ledger and Mamani. The bark of *Cinchona ledgeriana* contained up to 13% quinine by weight, whereas bark of other related species rarely contained more than 2%. By the 1930s, 97% of the world's supply of quinine came from Java.[8]

Meanwhile, scientists searched for quinine in a very different venue—the laboratory. In 1820, the French chemist-pharmacists Pierre-Joseph Pelletier (1788–1842) and Joseph Bienaimé Caventou (1795–1877) had isolated quinine, which is named for an old Peruvian name for *Cinchona* bark: *quinqina*. Having fared badly in their horticultural adventures, the English also directed their attention to synthesizing quinine.

In London, William Perkin (1838–1907), an 18-year-old chemistry student with a flair for organic chemistry, was working with coal tar residue, a rich source of organic molecules. August Hofmann (1818–92), the German director of the Royal College of Chemistry, where Perkin was enrolled, gave him the task of synthesizing quinine ($C_{20}H_{24}N_2O_2$) by oxidizing allyltoluidine ($C_{10}H_{13}N$), an aminobenzene (aniline) derivative. While trying to accomplish this feat, Perkin produced some "sludge" in 1856 that turned out to stain silk effectively. The color was brilliant and did not fade with time, washing, or exposure to sunlight. This material, the first of many synthetic aniline dyes to come, was known as mauve (see Figure 1).[7] Perkin put aside the search for synthetic quinine and pursued the manufacturing and economic opportunities that this aniline dye opened up.

Perkin was wise to abandon his search for synthetic quinine, which is an especially difficult molecule to synthesize. He and Hofmann could never have produced biologically active quinine by oxidizing allyltoluidine. Perkin synthesized mauve dye at a time when the textile industry was thriving, and there was a great demand for cheap and durable dyes. Perkin became wealthy, and the synthetic organic chemical industry was born.

Despite Perkin's discovery of mauve, much of the subsequent leadership in the synthetic dye industry came not from English companies, but from German corporations, such as I.G. Farben (Interessen-Gemeinschaft Farbenindustrie AG, or Syndicate of Dye Manufacturers) and the Hoechst and Bayer corporations. These companies generously supported scientists making important experimental and conceptual advances in synthetic organic chemistry. A great variety of useful substances from coal tar, including explosives, poisons, agricultural chemicals, and medicines, poured out of their laboratories.

Hoechst also supported the work of Nobel laureate Paul Ehrlich (1854–1915), a physician-scientist who was quick to realize the biological significance of aniline dyes.[9,10] He suggested that the chemical dyes obtained from coal tar combined via selective chemical reactions with substances within animal tissues and cells. The specific staining that resulted was of fundamental importance for the development of modern histology. For example, Ehrlich used dye stains to

differentiate various types of white blood cells (e.g., staining eosinophils with the brominated fluorescein dye eosin). He wrote his doctoral dissertation in 1878 about the theory and practice of staining animal tissues.

In 1876, Heinrich Caro (1834–1910) at the Badische Anilin und Soda Fabrik (Baden Aniline and Soda Factory; BASF) chemical company, had synthesized another aniline dye, methylene blue ($C_{16}H_{18}ClN_3S$; see Figure 1). This substance would prove to be important as a dye, as a medicinal agent, and as a starting point for the synthesis of other molecules of psychiatric interest. In 1882, Ehrlich used it to stain the tuberculosis bacillus and to facilitate its detection in sputum samples as a means of supporting the diagnosis of tuberculosis.[10] He also realized that, in addition to being used as dyes to identify microorganisms, cells, and tissues, such compounds were potentially valuable for therapeutic purposes.

Ehrlich became increasingly interested in *chemotherapy* (a word he coined) as he realized that the ability to stain differentially in the laboratory could be paralleled by the ability to kill differentially in the clinic. Some dyes could kill bacteria without harming the host or damaging its tissues. Many dyes, including congo red, scarlet red, acridine yellow, and, perhaps best known of all, the sulfonamide prontosil red, have such selective antibiotic properties. Prontosil combated streptococcal infections and was the first of a long series of sulfa drugs used as antibiotics. In 1891 Ehrlich discovered the therapeutic activity of methylene blue by using it successfully to treat two sailors with malaria.[8] Other investigators later confirmed this finding and modified the structure of methylene blue to form other antimalarial agents.[11] The connection between the chemistry of dyes and of antibiotics soon became widely appreciated. In 1917 the *Manchester Guardian* reported that "dyes and drugs must be thought of together. Whatever serves the modern dye-maker directly serves national health."[7]

In 1883 August H. Bernthsen (1855–1931), an academic chemist working with Caro at BASF, reported on the structure of the important nucleus in methylene blue—thiodiphenylamine ($C_{12}H_9NS$; see Figure 1)—and patented a method of synthesizing it.[11] Thiodiphenylamine is also known as phenothiazine. The term refers to compounds containing a tricyclic nucleus consisting of two benzene rings (*pheno*) joined by a central ring containing a sulfur (*thio*) and a nitrogen (*azo*) atom. A straight (aliphatic) or cyclic carbon-side chain can be connected to the nitrogen atom, leading to a variety of pharmacological activities.[12] Phenothiazines are a large class of drugs and dyes comprising hundreds of derivatives.

In summary, because of the inability of British explorers in South America and horticulturists at Kew Gardens to "anglicize" *Cinchona*, August Hofmann and William Perkin attempted unsuccessfully to synthesize quinine. Arising out of these failures was the synthetic dye industry and, with it, the synthesis of many chemicals, including antibiotics and—especially of interest to psychiatrists—phenothiazines.

THE HUNT FOR ANTIMALARIALS LEADS TO THE SYNTHESIS OF CHLORPROMAZINE

In the twentieth century the need for antimalarial drugs was growing since quinine was not always available. Moreover, prolonged use of quinine at high doses causes a syndrome, *cinchonism*, marked by headache, nausea, vomiting, tinnitus, or deafness. During World War II, America needed quinine for its military forces in the Pacific Islands, Asia, and North Africa. Quinine became unavailable to the Allies when the Japanese occupied Java in March 1942 and choked off the supply; just as many troops in these areas died of malaria as in combat. In 1943, General Douglas MacArthur said, "This will be a long war if for every division I have facing the enemy, I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease."[8]

During World War II, Robert Woodward (1917–79), one of the leading organic chemists of the twentieth century, worked on the synthesis of quinine. With the help of Harvard University chemist-colleague William von Eggers Doering (1917–), Woodward announced the "synthesis of quinine" in April 1944. Woodward's claim was widely celebrated in the international press. While doubtless good for wartime morale, the celebration was hasty. Woodward and Doering did not actually synthesize quinine, but instead prepared a precursor, homomeroquinene, which supposedly could be converted into quinotoxine and then quinine, using a technique that was devised by the German chemist Paul Rabe (1869–1952) in 1918 but never actually replicated.[13] Moreover, there are four asymmetric carbon atoms in the quinine molecule, so there are 16 stereoisomers (see Figure 1), including the pseudo-enantiomeric pair (–)-quinine and the anti-arrhythmia cardiac depressant (+)-quinidine (which is also antimalarial and is one of many natural alkaloids found in *Cinchona* bark). This complex stereochemistry was to prove very challenging. Indeed, Belgian-born Gilbert Stork (1921–) and his collaborators at Columbia University did not achieve the first stereoselective total synthesis of quinine until 2001, after a 55-year quest.[14,15] Despite the efforts of Perkin in England, Rabe in Germany, and Woodward, Doering, and Stork in the United States, synthetic quinine is still unlikely to be produced commercially, as the process would be prohibitively expensive.

The United States also coordinated a massive effort during World War II to find South American *Cinchona* trees that produced quinine and to cultivate plantations of these crops. In two years of work, over 12 million pounds of *Cinchona*

bark was shipped from South America, but the preferred plant, *Cinchona ledgeriana*, remained elusive.[16] As an alternative to the natural product, in partnership with the American company Winthrop Chemicals, I.G. Farben chemists had developed another antimalarial, quinacrine (Atabrine®) in the 1930s (see Figure 1). This agent contains a planar tricyclic core with a nitrogen-containing central ring—and so bears some resemblance to methylene blue and phenothiazine. In the 1940s Winthrop greatly increased production of quinacrine and licensed it to other American manufacturers to increase availability and to support the war effort. Nevertheless, while quinacrine was an effective antimalarial, it led to gastrointestinal distress, yellow discoloration of the skin, and adverse psychiatric effects. The Japanese also circulated propaganda that it caused impotence. The result was that much of the military refused to take quinacrine, thus limiting its usefulness.[16,17]

Stimulated by war needs, more work on antimalarials was carried out in the United States and in other countries. Henry Gilman and David A. Shirley at Iowa State College knew that Paul Ehrlich had found some antimalarial activity in methylene blue, but in examining a series of phenothiazines to see if they, too, had antimalarial activity, these two American scientists had little success. Because of disruption in international scientific communication during World War II, however, chemists at the Rhône-Poulenc Laboratories in Vitry-sur-Seine near Paris did not learn of those negative results and consequently continued their own studies of phenothiazines in search of a replacement for quinine. Like the Iowans, these French scientists concluded that phenothiazines were not antimalarial. Although, as discussed below, both the American and the French chemists may have reached this conclusion prematurely, the French continued their study of phenothiazines because of their antihistaminic properties.[11]

DEVELOPMENT OF CHLORPROMAZINE

Anesthesiologists hoped that antihistamines might modify autonomic responses associated with surgical shock. Early phenothiazine antihistamines developed at Rhône-Poulenc included promethazine and promazine. In 1950, Paul Charpentier at Rhône-Poulenc synthesized chlorpromazine (see Figure 1) from the sedative agent promazine.[11] He gave this molecule to naval surgeon-anesthesiologist Henri Laborit to test as a preoperative sedative and "autonomic stabilizing agent" for use before major surgery. Laborit found that this phenothiazine was an effective sedative and that it greatly reduced preoperative anxiety in surgical patients at Val-de-Grâce military hospital in Paris.[18] Pierre Hamon and his colleagues at the same military hospital took advantage of the sedative and apparent anti-anxiety effects of the new drug to potentiate the effects of a barbiturate to treat a young man diagnosed with acute mania.[19] Soon thereafter, Jean Delay and Pierre Deniker at Hôpital Sainte Anne near Paris were the first psychiatrists to use chlorpromazine as a monotherapy for mania and other "excited" states. The new treatment calmed the excitement of mania and diminished delusions and hallucinations, but it did not alleviate the "negative" symptoms of schizophrenia, including emotional withdrawal, lack of motivation, social isolation, and cognitive deficits.[20–22]

Jean Thuillier,[23] a psychiatrist and pharmacologist working at Sainte Anne in the early 1950s, describes remarkable changes in the inpatient units directed by Pierre Deniker:

> [T]he fury and violence had given way to calmness and peace, the most evident sign of this extraordinary therapeutic result could be appreciated even from the outside of the building of the men's clinic—there was silence . . . the results obtained with chlorpromazine could be measured in the psychiatric hospital in decibels . . . recorded before and after this drug. In fact, Deniker's department was a small island of silence in Sainte-Anne, [often filled with] the cries of rage of the mentally ill patients . . .

Delay and Deniker understood the implications of their findings and in 1952 published a series of clinical reports on initial experiences with chlorpromazine in treating manic and psychotic patients (see, e.g., Delay et al. (1952)).[20] These observations led to rapid acceptance of chlorpromazine in Europe and soon throughout the world, as has been detailed elsewhere.[11,23–25] The antipsychotic properties of chlorpromazine perhaps should not have been so surprising, since methylene blue, the original phenothiazine, had been used to treat psychotic illnesses in the 1890s and was tried again in the 1920s and 1930s,[11] as well as in more recent studies of psychotic and manic patients.[24,26–28]

Early clinical observations with chlorpromazine in France also established the close association of antipsychotic-antimanic effects of chlorpromazine with extrapyramidal abnormalities of posture and movement. The term "neuroleptic" was coined in an attempt to capture the range of actions of this agent and of the others that were developed in its wake—not only phenothiazines, but thioxanthenes (lacking a central-ring nitrogen atom) and butyrophenones (discovered in the late 1950s by Paul Janssen [1926–2003] as structural modifications of phenylpiperidine analgesics such as meperidine), with haloperidol being of particular significance.[25] Chlorpromazine treatment was sufficiently effective clinically that it strongly stimulated academic and industrial research into other pharmacological treatments for psychotic, mood, and other disorders—indeed, opening the era of modern psychiatric chemotherapy.[12,25]

WHAT HAS HAPPENED TO NEUROSYPHILIS?

Neurosyphilis, or GPI, a common illness in asylums a century ago, is diagnosed less often now. In the past, general paresis often was marked by dramatic and grandiose delusions. Today, neurosyphilis is more often asymptomatic or may present with dementia and apathy. This change in the clinical manifestations of the disease is not understood but may be due to organism- and illness-altering effects of the widespread use of penicillin and other antibiotics.[1,29]

Co-occurrence of human immunodeficiency virus/acquired immunodeficiency disease (HIV/AIDS) also affects the prevalence, diagnosis, and treatment of syphilis. HIV can increase susceptibility, make serological testing more difficult to interpret, limit cell-mediated immune response, and make adequate treatment of syphilis more difficult to achieve.[30] Even in the twenty-first century, neurosyphilis remains in the differential diagnosis of illnesses presenting with dementia, psychosis, and other neuropsychiatric or behavioral symptoms.[1]

SURPRISING ROLE FOR PHENOTHIAZINES IN THE TREATMENT OF MALARIA

Although quinine is an effective malarial agent, it is short-acting, ineffective in preventing recurrences of malaria, difficult to acquire, impractical to synthesize, and associated with cinchonism when used long-term. In 1934, chemists at I.G. Farben Laboratories synthesized chloroquine, and British and U.S. clinicians began to use it in the 1940s. Chloroquine is safe, inexpensive, and effective in both the treatment and prophylaxis of malaria. Some countries added it to table salt in endemic areas to assure wide exposure.[31,32] In the 1950s, broad application of both the antimalarial chloroquine and the insecticide dichlorodiphenyltrichloroethane (DDT) virtually eradicated malaria in some parts of the world. This widespread use of chloroquine inevitably led to enormous selection pressure on malaria parasites. Chloroquine-resistant *Plasmodium falciparum* strains are now found throughout much of the world.[33]

Researchers continue to investigate phenothiazines as possible antimalarials. Despite the earlier negative findings of Gilman and Shirley in Iowa and of chemists at Rhône-Poulenc, some studies suggest that there may be a role for chlorpromazine in the treatment of malaria. Chlorpromazine modulates chloroquine resistance, and phenothiazines inhibit growth of chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*.[34]

Paul Ehrlich's methylene blue also is being reconsidered as an antimalarial. It is relatively inexpensive and has effects similar to those of chloroquine, although its combination with chloroquine has proved largely ineffective.[35,36] Methylene blue produces blue-green urine, blue sclera, and stained clothing, and might induce hemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency. New antimalarial candidates and combination treatments being studied currently include compounds chemically related to methylene blue.[37]

Monotherapy for malaria is now ineffective in much of the world.[38] Treatment of highly prevalent *falciparum* malaria is complicated by geopolitical and economic circumstances. Most deaths occur in sub-Saharan Africa in children under age 5, in association with extremely limited access to health services and ability to purchase antimalarial treatments. In children, *falciparum* malaria is associated with persistent neuropsychiatric impairments.[39]

WHERE ARE WE NOW IN THE TREATMENT OF PSYCHOSIS?

Chlorpromazine and other first-generation neuroleptic-antipsychotic drugs, though effective, have many adverse effects, including neurological disorders (acute dystonia; restlessness or akathisia; acute and late-chronic [tardive] dyskinesias; parkinsonian bradykinesia and tremor). Important recent advances in psychopharmacology include the development of modern or "second-generation" antipsychotic agents, with lower risks of most adverse neurological effects typical of phenothiazines and other early neuroleptic agents.[25,40] The first of these agents was clozapine, a relatively old tricyclic compound (patented in 1960) that is more effective than most other antipsychotic agents but has major and potentially life-threatening adverse medical effects, including weight gain, type 2 diabetes mellitus, epileptic seizures, risk of aspiration pneumonia, severe bowel dysfunction, and an idiosyncratic form of agranulocytosis.[41] Despite the development of a growing number of modern antipsychotic agents—most of which are related chemically (olanzapine, quetiapine) or pharmacodynamically (risperidone, ziprasidone) to clozapine—phenothiazines remain useful for the treatment of psychosis or mania, and are cheaper than newer agents. In recent comparison studies, schizophrenia patients treated with modern antipsychotic agents did no better than those treated with older neuroleptic drugs, including phenothiazines such as perphenazine.[42,43] As in the treatment of malaria, evidence of the limitations of monotherapies for psychotic and manic-depressive illness has resulted in growing reliance on combinations of dissimilar agents.[44–48] More generally, the discovery of chlorpromazine (and later, haloperidol) led to striking progress in molecular theories of antipsychotic and antimanic drug action. These theories led, in turn, to the development of many chemically or pharmacodynamically

similar agents but may have constrained the search for innovative treatments based on alternative mechanisms.[25,40,49]

CONCLUSIONS

Discoveries in therapeutic innovation are often circuitous, indirect, and seemingly serendipitous, as well as being marked by error and frustration. The rewards are not always consonant with the importance of the discovery. Neither Mamani nor Ledger benefited personally from their discovery of the *Cinchona* species that was most important in treating malaria for many years. Decades of efforts by organic chemists to synthesize quinine failed, as did the efforts of many scientists to develop antimalarial phenothiazines. Nevertheless, these efforts led to the development of many important medicines, including the first effective antipsychotic-antimanic agents—and to chlorpromazine, in particular. Ironically, Wagner-Jauregg's use of malaria to treat neurosyphilis led to one of only two Nobel Prizes ever awarded to a psychiatrist, but the discovery of chlorpromazine—the first effective antipsychotic drug, with far more important clinical and scientific implications—received no such accolades. Meanwhile, the search continues for simple, inexpensive, and tolerable treatments for drug-resistant forms of malaria, as well as for psychotic and manic-depressive disorders.

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