

# Hot Brains: Manipulating Body Heat to Save the Brain

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CONSIDER A DISEASE with high mortality, severe morbidity, unknown pathogenesis, imprecise diagnostic features, and no known cure—in short, a condition with no hope. One can only offer soothing words and symptomatic remedy.

Then, there is hope. Anecdotal observations lead to a new hypothesis. A pilot trial indicates that 6 of 9 treated patients “unexpectedly recover.” Larger studies follow and show 30% to 50% improvement. On the basis of what was looked for, the treatment is considered safe, and compared with the desperate condition of the treated, the risks (if any) are deemed tolerable. People the world over begin to offer this exciting therapy. Could there be a Nobel Prize in the horizon for the discoverer?

What was the disease, and what was the cure? The disease was not stroke, hepatic coma, or neonatal encephalopathy. It was general paresis of the insane (GPI), the dreaded neurosyphilis, and the magical remedy was “fever therapy,” induced by injecting blood from malaria patients. This idea of “fighting one disease with another” evolved as recently as the 1910s, not in the Dark Ages.<sup>1–4</sup>

Enter Julius Wagner-Jauregg (1857–1940), a Viennese doctor who specialized in experimental pathology but chose psychiatry because he could not get into internal medicine. The choice, he noted dryly, “harmed neither [himself] nor psychiatry.”<sup>1</sup>

An interest in the brain led him to study patients with psychiatric and neurologic symptoms. By the mid-1880s, he had discovered a curious association. His psychiatric patients were reporting improved symptoms after recovering from bouts of fever.

Wagner-Jauregg studied 30 different patients with typhoid, malaria, smallpox, scarlet fever, and erysipelas and confirmed that a small percentage indeed felt better after having had a fever. He correctly surmised that

because at least some mental disorders might have organic causes, one must consider organic remedies for those conditions. He thought of inducing fever by inducing infections.

But how does one go about inducing infections, especially choosing donors and recipients? Spirochetes that cause syphilis had been discovered in 1905, and the Wasserman test was developed in 1906. However, diagnosing infectious conditions was difficult, and therapy was empirical. Wagner-Jauregg tried inducing fever by injecting tuberculin, which did not cause fever consistently.<sup>3</sup> He continued to think about this issue and waited.

In June 1917 there was a break. A soldier with symptoms of malaria was admitted to his clinic. In May of that year, another patient with GPI had been admitted to the same clinic. Because “there was nothing to lose,” on June 14, 1917, Wagner-Jauregg obtained the soldier’s blood and injected it into the arm of the patient with GPI. A photograph taken on a later date depicts the treatment procedure (Fig 1).

The patient with GPI promptly developed malaria, and Wagner-Jauregg wrote that “in the course of the following month, there was a gradual improvement” in

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**FIGURE 1**

Injecting blood taken from a malaria patient (left, background) into the arm of a psychiatric patient (center). Julius Wagner-Jauregg (in black tie) is facing the camera. He looks on, standing behind the psychiatric patient. (Photograph from 1934, Institut für Gescjocjte der Medizin, Vienna, Austria.)

symptoms.<sup>3</sup> He repeated the experiment in 3 others. All 3 got malaria; Wagner-Jauregg then obtained their blood samples and injected them into 5 others, who too developed malaria. He did not check for blood groups, nor did he cross-match blood samples. Blood groups had been discovered in the early 1900s, but few were paying any attention to them. Although cross-matching had been described, few were doing it prior to transfusions; it was not the standard of care!

Wagner-Jauregg did not give quinine to any of his patients with GPI until each went through at least 7 to 10 bouts of malaria fever cycles. For some, he gave neosalvarsan, a mercurial remedy for syphilis in those days, but for others he did not even offer this drug.

How did his first 9 patients fare? Three patients left his clinic alive and reportedly were well at 1 year; 3 patients improved initially but later worsened; for 2 patients, the psychotic symptoms were unaltered; and 1 patient developed a severe “paralytic melancholy.” Another patient died as a result of fever. Wagner-Jauregg concluded that 6 of 9 had recovered. They were “better than expected.” The next year, he published his results.<sup>5</sup>

The rest, as they say, is history. Within 5 years, Wagner-Jauregg’s “malaria fever cure” was the rage. It was the new hope for a desperate condition. Doctors induced fevers by using all sorts of techniques on all sorts of psychiatric disorders. Some patients recovered, and others did not. Death, too, was not uncommon from ther-

apies. Yet, by the mid-1920s, Wagner-Jauregg had become world-famous. In 1927, he was awarded the Nobel Prize in Medicine or Physiology—the first of only 2 psychiatrists to win this prize. *Scientific Monthly* said that “the whole... world should join his patients and students in their congratulations.” Even Sigmund Freud congratulated him.

At the height of its popularity, the proponents of fever therapy experimented with safer methods of causing fever. Colloid sulfur injections, hot-water baths, and “fever cabinets” evolved.<sup>1,3,4</sup> With the dramatic introduction of penicillin in the mid-1940s, however, fever therapy for GPI suddenly came to an end. On the other hand, popular “stress therapies” such as electroshock and severe hypoglycemia for psychotic conditions were the offshoots of Wagner-Jauregg’s fever therapy.

Considering today’s standards of research and clinical practice, the story of malaria cure for neurosyphilis may seem gruesome, unethical, and unscientific. However, in the annals of medical history, there are many examples of desperate remedies for desperate conditions.

During Wagner-Jauregg’s time, fever therapy was the best thing that one could do. A diagnosis of neurosyphilis spelled a death sentence. There were no drugs for psychiatric conditions until after the 1960s. Historians rightly credit Wagner-Jauregg as a pioneer who correctly considered “physical (somatic)” cures for psychological conditions, an idea that took nearly a century to develop into practical realities.<sup>1-3</sup>

The story of malaria fever cure is an interesting cautionary tale, reminding us that new therapies, especially for conditions with poor prognoses, need to be implemented with caution, because the ultimate proof of safety and efficacy takes a long time to evolve.

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