Malariotherapy

Ambika Natarajan

Before the use of antibiotics in the 1940s, syphilis was a dreaded disease with little chance of a survival of those affected by it. In the pre-antibiotic era, the Viennese physician Julius Wagner-Jauregg introduced a controversial treatment for syphilitic paresis called malariotherapy. This involved infecting the patient with tertian malaria and allowing the fever to develop. Wagner-Jauregg won the Nobel Prize in Physiology or Medicine in 1927 for this therapy, becoming one of the only two psychiatrists to have won the Nobel Prize this far. In this note, I recreate the case of Wagner-Jauregg's fever therapy.

In his 1927 Nobel lecture, Julius Wagner-Jauregg, one of the only two psychiatrists to have won the Nobel Prize this far, posed a question and offered an answer: 'How would it have been possible to release so many paralytics and advanced syphilitics from the hospitals when outside they first of all ran the continual risk of a relapse and secondly, particularly where there were anopheles, were a danger to their environment? This danger…can be excluded with a fair degree of safety, if patients are kept under mosquito-proof netting during the whole duration of the treatment'[1]. The above statements pertain to the discovery of a controversial treatment – the artificial and purposeful inoculation of syphilitic patients with another potentially dangerous disease called malariotherapy or malarial fever therapy. The treatment involved inducing tertian malaria in syphilitic patients. Wagner-Jauregg was an Austrian physician who specialized in experimental pathology and psychiatry. An interest in the brain led him to study psychiatric and neurological diseases. Although cases of malaria were not seen in Vienna for a long time, the idea to artificially generate fever to cure paresis occurred to Wagner-Jauregg well before he encountered it.

The concept of treating one disease with another was not new at that time. A well-known example is that of Edward Jenner's use of cowpox to prevent smallpox in 1798. Furthermore, the notion of like-cures-like was embraced by the father of homeopathy, Samuel Hahnemann. The beneficial effects of fever on certain mental diseases like epilepsy was known since the time of Hippocrates. Further, the ameliorative effect of certain tropical fevers on psychoses has been noted in the modern scientific literature. However, the idea remained controversial, especially for the treatment of mental illnesses. Moreover, general paresis was for a long time considered to be hereditary rather than associated with syphilis[2].

Syphilis in the 19th century bore the same stigma as AIDS in the 1980s. Associated with sexual behaviour, the disease exploded social barriers through its ability to move across social hierarchies. The contraction of syphilis implied sexual contact with populations who allegedly served as contagions of the disease, viz. women prostitutes. Despite its treatability today, syphilis continues to be a major cause of mortality around the world and the rates of infection continue to increase[3]. Following Noguchi and Moore's famous demonstration of the presence of spirochete organisms in the brains of paretic patients in 1913, the European medical community widely accepted the relationship between syphilis and general paresis. The pressure to cure GPI (general paresis of the insane) existed long before its connection to syphilis. Psychiatrists were embarrassed that they had no ready solutions to such a widespread form of insanity. However, syphilis undoubtedly enhanced the pressure experienced by the psychiatrists.

In the mid-1880s, Wagner-Jauregg discovered the association between fevers and improved symptoms of paresis. A small percentage of his psychiatric patients had reported improvement after bouts of fever. He meticulously studied 30 different patients with typhoid, malaria, smallpox, scarlet fever and erysipelas before arriving at the conclusion that organic causes of mental disorders required organic remedies[4]. In 1890/91, Wagner-Jauregg began injecting tuberculin to induce febrile reaction. In 1895, he noticed that paretic patients did better with fever therapy than other psychotics. In 1913, his assistants published a significant study comprising 4134 cases of syphilis, reporting that those who contracted a febrile disease early on never developed neurosyphilis.

Wagner-Jauregg had suggested the use of malaria to produce fevers as early as 1887. However, he only began to use this treatment in 1917. It was the presence of a soldier with malaria in his neuro-psychiatric hospital that gave him a chance to try out the therapy. He took blood from the malaria patient and introduced it into paretic patients. Six of the first nine patients showed improvement, but four suffered relapses. In 1921, Wagner-Jauregg reported that 25% of about 200 patients could return to work. In 1922, his assistant reported that over 60% of 400 cases observed over two years had achieved remissions to varying degrees[2].

The selection of malaria as the febrile agent seemed ideal as it was a disease with a readily available cure – quinine. The standardized fever therapy procedure involved inoculation of syphilitic paretic patients with blood contaminated with tertian malaria. Once the patients developed malarial fever, the physician treated them with quinine. The results were promising considering that the prognosis of GPI patients was in any case poor. The precise treatment mechanism was – and still is – unclear. Equally unclear is the fact that the procedure worked only with tertian malaria as a febrile agent and not malaria tropica.

Vienna was a particularly apt location for the discovery of malarial fever therapy. The intellectual scene in fin de siècle Vienna was influenced by two main streams of thought: first, the acceptance of modern science and second, the reception of chance-based thinking by intellectuals[5]. The perception of Nature among Viennese intellectuals differed from the rest of Europe. While British and German intellectuals conceptualized scientists as heroes who triumphed over Nature and allowed the colonization of untamed lands, Viennese intellectuals evoked Nature as a teacher. Such a perspective on Nature was typical of the scientific community in Vienna. A scientist's interaction with Nature included its co-option for scientific discoveries and the rational management of natural resources. The naturalist view of science arose from the high regard for medicine in Vienna accompanied

by the relatively low level of industrialization compared to Germany. The poet and scientist Johann Wolfgang von Goethe is a famous counter-example of a German with a naturalist view of science. This vision simultaneously implied a greater tolerance towards and acceptance of the uncertainty that Nature presented.

So, contrary to the rest of Europe, scientists in *fin-de-siècle* Vienna worked well with uncertainty. The rise of probability-based statistics and physics in Austria bolstered increasing reliance on chance rather than educational dogmatism. Important scientists and educationists of the period such as Boltzman, the Exners, Jodl and Menger promoted uncertainty-based teaching and reforms in the educational institutions. Probability and chance represented freedom of scientific thought and expression, while certainty embodied destiny or a pre-programmed route suggested by faith mostly of a religious kind. Operating under uncertainty was viewed as important in constructing ethical and moral frameworks as well: 'Ethics could indeed be taught, but not as a set of "absolute rules", because the multiplicity of life's situations leads each absolutely rigid rule or habit of action inevitably as absurdum'[6]. Discovering suitable treatments to incurable diseases relied on chance and uncertainty, and not on rigid moral standards. Such an ethical ambiguity provided the openness to observe and pursue treatment methodologies that would otherwise be ignored had the rules of medical intervention been rigid.

Wagner-Jauregg's pursuit of research on malariotherapy represented the chance-based moral standard prevalent among the Austrian scientific community at the time. The combination of naturalism and scientific uncertainty prevailing in the medical community was apparent in the field of psychiatry. His contemporary Sigmund Freud's psychoanalysis, for example, rested on the irrational impulses in human life. Freud, however, located psychiatric problems in the unconscious rather than attributing organic causes to them. The Judicial Inquiry of 1920 that brought Freud and Wagner-Jauregg face to face represented the tension between two perspectives in the field of psychiatry at the time. The hearing centred on Wagner-Jauregg's use of electrical shock therapy for soldiers suffering from shell-shock to enable them to return to the battlefield during World War I. Freud asserted that Wagner-Jauregg did not take into account the unconscious aspects of war neuroses. While Wagner-Jauregg consciously wished to help his patients, his belief in the curative property of harsh treatment methods aided him in devising a strategy such as malariotherapy[7]. On commenting about the therapeutic uses of bacterial fevers, Wagner-Jauregg argued, 'we cannot be reproached for using a procedure that is irrational. We have listened to nature; we have attempted a method by which nature itself produces cures'[8]. The use of malariotherapy, thus, rested on viewing Nature as a teacher. By extension, the therapy which was a mere imitation of Nature was acceptable as well.

The chance-based ethical framework did not imply that Wagner-Jauregg pursued his research recklessly. In fact, he abandoned experiments with the febrile agent tuberculin early on because of the general belief that it was a dangerous preparation. He did, however, return to using tuberculin in 1895. Furthermore, he was also careful with his studies on malaria as a febrile agent. In 1917, when one patient died after being inoculated with malaria tropica instead of tertian malaria, Wagner-Jauregg gave up his experiments for a year.

Malariotherapy was the most effective solution to neurosyphilis in the earlier part of the 20th century. Contemporary physicians viewed the therapy with a sense of relief and the demand for the proof of its efficacy was not high. As a result, it received widespread and rapid acceptance despite the controversial nature of the procedure. The scientific community accepted the therapy as the treatment for syphilis and even conferred the Nobel Prize on Wagner-Jauregg, providing the prestige required for the social approval of the treatment[9]. The only opponent to the treatment was a Swedish professor of psychiatry, B. Gadelius, who could not be persuaded, as a referee, to recommend the award for Wagner-Jauregg. Historian Magda Whitrow observes, 'No one aside from Gadelius seemed to have raised the ethical issue until 1930s, when some American writers did so'. She argues that it was the best possible solution to GPI at that time, but admits that the treatment was only 50% effective[8]. It is impossible to determine whether malariatherapy was truly as effective as was claimed, since the data that were produced during Wagner-Jauregg's time did not comply to standards of human experiments as we know it today. To name a few shortcomings, follow-up studies on patients were few and far between, test subjects were not compared with control subjects and randomized trials on patients were never carried out.

Malariotherapy was used as late as 1960s even after the introduction of penicillin in the 1940s. In its heyday, many nations, including Denmark, the Netherlands, USA and Germany adopted malariotherapy as the standard treatment for syphilis. The ethical issues regarding the deliberate introduction of a pathogenic organism into mental patients led to the establishment of informed consent in psychiatric wards in Denmark[10]. Informed consent was not prevalent in Denmark alone. Historian Joel T. Barslow examines the effects malariotherapy had on physician–patient interactions in the US, arguing that: 'In contrast to the virtual silence of families in the premalaria era about the origins of the disease, families after 1928 became increasingly candid about syphilitic infection and family questionnaires returned in the malaria era often cite syphilis as the cause of their loved ones' difficulties'[11].

More recently, malariotherapy has been suggested as a treatment to incurable autoimmune diseases. In 1969, the physician B. M. Greenwood observed that there was lower incidence of rheumatoid arthritis in western Nigeria, where malaria is frequent. Similar results have been reported in populations in which malaria is endemic as well as from studies using animal models[12]. This mostly forgotten therapy from the annals of recent medicine has thus made a comeback. Even though the widespread acceptance of treatments lacking the necessary proof of efficacy is an ever-present possibility, the context of the discovery is also important to consider. Malariotherapy was a widely accepted treatment in an era when syphilis debilitated a vast number of people. It may be a solution to autoimmune diseases. However, multiple social and contextual parameters such as efficacy of treatment, possible side effects, patient confidentiality and informed consent must be carefully considered for the implementation of such a controversial treatment.

1. Wagner-Jauregg, J., Nobel Lecture. The Nobel Foundation, Stockholm, Sweden, 10 December 1927.
2. Brown, E. M., *Hist. Psychiatry,* 2000, **11**, 371–382; Whitrow, M., *Med. Hist.*, 1990, **34**, 294–310.
3. Kojima, N. and Klausner, J. D., *Curr. Epidemiol. Rep.*, 2018, **5**, 24–38.
4. Raju, T. N. K., *Pediatrics*, 2006, **117**, e320–e321.
5. Luft, D., *Mod. Austrian Lit.*, 1990, **23**, 89–97.
6. Coen, D. R., *Vienna in the Age of Uncertainty: Science, Liberalism, and Private*

Life, The University of Chicago Press, Chicago and London, 2007, p. 242.
7. Eissler, K. R., *Freud as Expert Witness: The Discussion of War Neuroses between Freud and Wagner-Jauregg* (translated by Christine Trollope), International Universities Press, Madison, Connecticut, USA, 1986, p. 348.
8. Whitrow, M., *Med. His.*, 1990, **34**, 301.
9. Austin, S. C., Stolley, P. D. and Lasky, T., *J. Am. Med. Assoc.*, 1992, **268**, 516–519.
10. Vaczy Kragh Jesper, *Hist. Psychiatry,* 2010, **21**, 471–480.
11. Barslow, J. T., *Bull. Hist. Med*., 1996, **70**, 577–608.
12. Abdel-Maksoud, M. A. and Al-Quraishy, S., *Lupus Open Access*, 2019, **4**, 1–4.

ACKNOWLEDGEMENT. I thank the referee for useful comments.

Ambika Natarajan is in the UM-DAE Centre for Excellence in Basic Sciences, University of Mumbai (Kalina Campus), Santa Cruz (E), Mumbai 400 098, India.
e-mail: nasa7ambika@gmail.com

Edited by S. K. Satheesh and printed & published by the Current Science Association, Bengaluru 560 080.
Typeset by WINTECS Typesetters, Bengaluru and Printed at Lotus Printers Pvt Ltd, Bengaluru (Ph: 2320 9909)