

General article Γενικό άρθρο

Julius Wagner-Jauregg (1857–1940): Introducing fever therapy in the treatment of neurosyphilis

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For centuries, heat has been used in various ways for the cure of mental diseases. Hippocrates noted that malarial fever could have a calming effect in epileptics. Centuries later, Galen described a case of melancholy cured as a result of an attack of quartan fever. In 19th century, the eminent French psychiatrist Philippe Pinel, in his treatise on insanity referred to the beneficial effect of fever. An opinion expressed few years later by his pupil Jean-Étienne Dominique Esquirol in his treatise entitled *Des maladies mentales considérées sous les rapports médical, hygiénique et médico-légal*. However, in 1917, the Austrian neuro-psychiatrist Julius Wagner Jauregg pointed out the therapeutic value of malaria inoculation in the treatment of dementia paralytica. In 1927, Wagner Jauregg received for this work the Nobel Prize in Medicine, being actually the first psychiatrist to win the Nobel Prize. He studied medicine at the University of Vienna and received his doctorate in 1880. In 1889, he was appointed Professor of Psychiatry and Director of the Graz's Psychiatric Clinic, a position that he held until 1928. Working in the asylum, Wagner Jauregg noted that insane patients with general paralysis occasionally became sane after some febrile episode. After experimenting with several artificial methods (*streptococci*, tuberculin) to induce fever, he concluded that malaria was the most satisfactory. Actually, malaria infection was an acceptable risk for the patients, as quinine would be administered as soon as syphilis was cured. In 1917, he reported the first favorable results of his study. Patients were inoculated via intravenous injections with malaria. Some physicians were starting the administration of anti-syphilitic treatment (bismuth, salvarsan and later penicillin) after 10–12 febrile paroxysms, while others initiated the regimen the first febrile-free day after 8 malarial paroxysms. The therapeutic regimen was completed with the administration of quinine sulfate to terminate the malaria infection. It is worth mention-

ing that the above treatment was followed in hospital under strict monitoring of patients' vital signs and regular laboratory tests. In the following years of his discovery, artificial fever was induced by any one of the following methods: the introduction into the patient of a parasitic disease; the injection of a foreign protein; injections of chemical substances such as sulphur; electrical means such as the administration of diathermy or radiotherapy, or placing the patient in an electromagnetic field; and simple immersion of the individual in a hot bath, or placing him in a heat cabinet. Wagner Jauregg's therapy was highly admired and was used on neurosyphilis cases well onto the 1950's. However, with the introduction of penicillin in syphilis' treatment, fever therapy effectively ended. Wagner Jauregg's study led to all the methods of stress therapy used in psychiatry, as electric shock, and insulin.

Key words: Julius Wagner Jauregg, neurosyphilis, fever therapy, malaria

Introduction

For centuries, heat has been used in various ways for the cure of mental diseases.

Hippocrates (460–377 BC) noted that malarial fever could have a calming effect in epileptics “febre[m] convulsioni supervenire melius est, quam convulsionem febris”, in other words “fever resolves spasm”.¹ Centuries later, Galen (130–c. 201) described a case of melancholy cured as a result of an attack of quartan fever.²

In 19th century, the eminent French psychiatrist Philippe Pinel (1745–1826) in his treatise on insanity entitled *Traité médico-philosophique sur l'aliénation mentale*, referred to malarial fever as a disorder operating to produce a “permanency of recovery”.³ An idea that was also mentioned in Jean-Étienne Dominique Esquirol's (1772–1840), Pinel's pupil, book on mental diseases.⁴

In his turn, Dr Selode of Brussels, in his article published on January 16, 1845, cited that the appearance of an intermittent fever in an epileptic had sometimes the effect of modifying the convulsion affection. He mentions two cases in which fever put end to the epileptic attacks.⁵

In 1917, the Austrian neuro-psychiatrist Julius Wagner Jauregg pointed out the therapeutic value of malaria inoculation in the treatment of dementia paralytica.

For this innovation he was awarded, in 1927, with the Nobel Prize in Medicine, being actually the first psychiatrist to win the Nobel Prize.

Julius Wagner Jauregg: Treating neurosyphilis with malaria

Julius Wagner Ritter von Jauregg was born in Wels, Austria, on March 7, 1857. His father, a career bureaucrat, preferred him to choose philosophy but Julius decided to study medicine and obtained his medical degree at the University of Vienna on 1880.⁶

As a student, he worked at the Institute of General and Experimental Pathology, where in 1881 he became an assistant to its head, Professor Solomon Stricker (1834–1898).

From experimental pathology Wagner-Jauregg turned to internal medicine, hoping to be appointed to an assistantship at the Vienna General Hospital. However, his hopes were not realized and he accepted the offer of an assistantship at the First Psychiatric Clinic and at the Asylum of Lower Austria, whose Director was Max Leidesdorf (1816–1889).⁷

Von Jauregg was a member of the psychiatric staff at the University from 1883 to 1889 and Professor of Psychiatry and later Director of the Hospital at the University of Graz from 1889 to 1928.⁸

In the asylum, he noted that insane patients with general paralysis occasionally became sane after some febrile episode.

Actually at the beginning of the 20th century, syphilitic patients comprised as much as 20% of the asylums population.⁹ Despite the advances in the treatment of syphilis made during that period and the introduction of bismuth (Trepol) and arsenobenzol (Salvarsan) in therapeutics, the treatment of general paresis remained uncertain. So,

the prospect of slowing or arresting the progression of the infection was encouraging.

After experimenting with several artificial methods (streptococcus, tuberculin) to induce fever, von Jauregg concluded that malaria was the most satisfactory.¹⁰ Actually, malaria infection was an acceptable risk for the patients, as quinine would be administered as soon as syphilis was cured.

In 1917, von Jauregg reported the first results of his study: among 9 treated patients, 6 responded favorably.¹¹

It was said that the beneficial effects of artificial-fever therapy may result either from injury or destruction of the infecting parasite, or from increased resistance of the host against the parasite.¹⁰

Von Jauregg's therapy was highly admired and was used on neurosyphilis cases well onto the 1950's.

In the following years of his discovery, artificial fever was induced by any one of the following methods: the introduction into the patient of a parasitic disease which is usually accompanied by fever, such as malaria; the injection of a foreign protein; injections of chemical substances such as sulphur; electrical means such as the administration of diathermy or radiotherapy, or placing the patient in an electromagnetic field; and simple immersion of the individual in a hot bath, placing him in a heat cabinet, or wrapping him. However Laveran's plasmodium infection was of choice.¹⁰

Patients were inoculated via intravenous injections with malaria. After an incubation period of about a week, the patients would experience chills and nausea, followed by ranging fever of more than 41 Celsius degrees that lasted several hours. Over the next several days fever would alternate with chills.⁹

Some physicians were starting the administration of anti-syphilitic treatment (bismuth and salvarsan) after 10–12 febrile paroxysms, while others initiated the regimen the first febrile-free day after 8 malarial paroxysms. The therapeutic regimen was completed with the administration of quinine sulfate to terminate the malaria infection. It is noteworthy that this was strictly an in-hospital therapy under vital signs monitoring and regular laboratory evaluation.¹⁰

Fever therapy showed variable results. The distinguished German psychiatrist Oswald Bumke

(1877–1950) applied artificial fever with malaria in 247 males and 60 females with neurosyphilis: "Out of the total, syphilis was acceptably recessed in 33.00% of the patients, while the recession was not acceptable in 14.25%. Repetition of the treatment resulted in acceptable recession in 23.48% of males and 28.33% of females. Mild recessions were observed in 22.26% of males and 23.33% of females. Stable condition was observed in 27.13% of males and 23.33% of females. Morbidity, during or within two months after treatment, was 27.13% for males and 25.00% for females".¹²

In 1943, John Mahoney (1889–1957), of the US Public Health Service, discovered that the spirochete bacterium *Treponema pallidum*, the causal agent of syphilis, was susceptible to penicillin.¹³ The next years, till the prevalence of penicillin as a monotherapy, a transitional period occurred and the physicians were using for the treatment of neurosyphilis all the available methods (mercury, bismuth, salvarsan, penicillin and fever therapy).

It worth's mentioning that even in Greece, combined fever-therapy had been conducted with relatively positive results. In 1954, in Eginition Hospital, the Psychiatry and Neurology Department of the National and Kapodistrian University of Athens carried a study regarding fever-therapy in patients with neurosyphilis.

Professor George Pampoukis (1885–1959) and his collaborators published the results from 92 patients with syphilis induced paralysis who were treated with fever-therapy and anti-syphilis medication.

Patients were divided in two groups. In the first group (A), fever-therapy was combined with a triple antisiphilitic regimen (mercury, bismuth, salvarsan) while in the second group (B) penicillin was added in the regimen. The results were the following:

Group A

Therapy had positive effect in 43.5% of the patients (17.3% showed complete recession of the psychopathologic symptoms; 15.2% significant recession; and 11.0% mild recession).

Condition was stable in 35.0%, while in 21.5% of the patients the outcome was negative (6.5% deterioration; 15.0% death).

Group B (with the addition of penicillin)

Therapy had positive effect in 55.0% of the patients (22.0% showed complete recession of the psychopathologic symptoms; 11.0% significant recession). Condition was stable in 28% of the patients, while negative prognosis was observed in 17% of the patients. Finally, it is of interest that no deaths were recorded in this group.

However, in the following years, fever cure effectively ended as penicillin became the treatment of choice.¹⁴

Conclusion

Julius Wagner-Jauregg's battle with neurosyphilis brought about one of the most stimulating discoveries in modern medicine. His study led to all the methods of stress therapy, as electric shock, and insulin which were used in psychiatry.

Nowadays, interest in fever therapy still arises occasionally. In 2007, Curran LK et al reported that behavior of autistic children improve during episodes of fever. However all improvements were transient.¹⁵

Julius Wagner-Jauregg (1857–1940): Η εισαγωγή της πυρετοθεραπείας στη θεραπεία της νευροσύφιλης

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Η ιδέα της αύξησης της θερμοκρασίας του σώματος για τη θεραπεία των ψυχιατρικών και νευρολογικών νόσων ανάγεται στην αρχαιότητα. Ο Ιπποκράτης (460–377 π.Χ.) αναφέρει τη θετική επίδραση του εμπύρετου στην επιληψία. Αιώνες αργότερα, ο Γαληνός (130–π.201) περιγράφει ένα περιστατικό μελαγχολίας που θεραπεύτηκε μετά από επεισόδιο τεταρταίου πυρετού. Τον 19ο αιώνα, ο διακεκριμένος Γάλλος ψυχίατρος Philippe Pinel (1745–1826) στην πραγματεία του περί παραφροσύνης ή μανίας, θεωρεί πως το εμπύρετο της ελονοσίας έχει ευεργετική επίδραση στη θεραπεία των ψυχικών νοσημάτων. Άποψη που διατύπωσε λίγα χρόνια αργότερα και ο μαθητής του, Jean-Étienne Dominique Esquirol (1772–1840) στο σύγγραμμά του *Des maladies mentales considérées sous les rapports médical, hygiénique et médico-légal*. Ωστόσο, εκείνος που χρησιμοποίησε το εμπύρετο της ελονοσίας στη θεραπεία της νευροσύφιλης ήταν ο Αυστριακός ψυχίατρος Julius Wagner Jauregg (1857–1940), που το 1927 έλαβε το βραβείο Νόμπελ Ιατρικής για αυτήν του την ανακάλυψη. Ο Wagner Jauregg σπούδασε ιατρική στο Πανεπιστήμιο της Βιέννης απ' όπου πήρε το διδακτορικό του δίπλωμα το 1880. Το 1889 εξελέγη καθηγητής ψυχιατρικής και διευθυντής της Ψυχιατρικής κλινικής του Graz, θέση που διατήρησε μέχρι το 1928. Στο ψυχιατρικό άσυλο παρατήρησε πως οι ασθενείς με προϊούσα γενική παράλυση παρουσίαζαν βελτίωση μετά από κάποιο πυρετικό επεισόδιο και έτσι αποφάσισε να στρέψει την έρευνά του στην πυρετοθεραπεία. Αρχικά πειραματίστηκε με διάφορες πυρετογόνες ουσίες όπως το ερυσίπελας και η φυματίνη χωρίς ωστόσο ενθαρρυντικά αποτελέσματα. Το 1917, ενοφθάλμισε ελονοσία σε 9 ασθενείς που έπασχαν από προϊούσα γενική παράλυση και παρατήρησε πως οι 6 παρουσίασαν σαφή βελτίωση της κλινικής τους εικόνας. Άλλωστε το να νοσήσει ένας συφιλιδικός με ελονο-

σία αποτελούσε ελεγχόμενο ρίσκο μιας και μετά το πέρας της θεραπείας ο ασθενής θα λάμβανε αγωγή με κινίνη. Η μέθοδος αυτή έχαιρε ιδιαίτερης εκτίμησης και χρησιμοποιήθηκε ευρέως στη θεραπευτική της νευροσύφιλης έως τη δεκαετία του 1950. Η αγωγή ξεκινούσε με την πρόκληση εμπύρετου και συνεχιζόταν με τη χορήγηση συνδυασμένης αντισυφιλιδικής θεραπείας (βισμούθιο και αρσενοβενζόλη, αργότερα προστέθηκε και η πενικιλίνη). Ως προς την πρόκληση του εμπύρετου, προτιμότερη ήταν η διά του πλασμώδιου του Laveran μόλυνση ενώ εναλλακτικά χρησιμοποιούνταν άλλα τεχνητά μέσα όπως το αντιτυφικό εμβόλιο, πρωτεϊνικά διαλύματα, θειούχα σκευάσματα αλλά και ειδικοί θερμαινόμενοι θάλαμοι. Κάποιοι ιατροί προτιμούσαν 10–12 εξάρσεις πυρετού πριν την έναρξη της αγωγής ενώ άλλοι αρκούσαν σε 8 πυρετικές εξάρσεις και έναρξη της αντισυφιλιδικής θεραπείας την ημέρα της απυρεξίας. Αξίζει να σημειωθεί πως η παραπάνω θεραπεία ακολουθείτο πάντα σε νοσοκομείο, όπου παρακολουθούνταν τα ζωτικά σημεία του ασθενούς και γίνονταν τακτικός εργαστηριακός έλεγχος. Τα αποτελέσματα της αγωγής ήταν ποικίλα ενώ η προσθήκη της πενικιλίνης συνοδεύτηκε με υψηλά ποσοστά βελτίωσης και ίασης, καταδεικνύοντας την τρεπονημοκτόνο δράση της. Από τα μέσα της δεκαετίας του 1950 η πυρετοθεραπεία σταδιακά εγκαταλείφθηκε.

Λέξεις ευρετηρίου: Julius Wagner Jauregg, νευροσύφιλη, πυρετοθεραπεία, ελονοσία

References

- Hippocrates Epidemic Book 1 (trans) In: Chadwick J, Mann WN (eds) *The medical works of Hippocrates: Coan prognosis*. Blackwell Scientific Publications, Oxford, 1950
- Neuburger M. *The doctrine of the healing power of nature throughout the course of time*. New York Homeopathic College, New York, 1932
- Pinel P. *Traité médico-philosophique sur l'aliénation mentale ou la manie*. Caille et Ravier, Paris, 1801
- Esquirol JED. *Des maladies mentales considérées sous les rapports médical, hygiénique et médico-légal*. Bailliere, Paris, 1838
- Selode B. (Unknown). *Gazette des hôpitaux de Paris* 1845, 1:12
- Dupont M. *Dictionnaire Historique des médecins dans et hors de la médecine*. Larousse/Bordas, Paris, 1999:571
- Whitrow M. Wagner-Jauregg and fever therapy. *Med Histor* 1990, 34:294–310
- Rifkind D, Freeman GL. *The Nobel Prize winning discoveries in infectious diseases*. Elsevier, Edinburgh, 2005:71–73
- De Young M. *Madness: an American history of mental illness and its treatment*. Mc Farland, North Carolina, 2010
- Epstein NN. The present status of artificial fever in the treatment of syphilis. *Cal West Med* 1939, 51:94–97
- Wagner von Jauregg J. Ueber die Einwirkung der Malaria auf die progressive Pralaye. *Psychiatr Neurol Wochenschr* 1917, 20:132
- Bumke O. *Lehrbuch der Geisteskrankheiten*. 2nd ed. Bergmann, Munich, 1924
- Mahoney JF, Arnold RC, Sterner BL, Harris A, Zwally MR. Penicillin Treatment of Early Syphilis. *J Am Med Assoc* 1944, 126: 63–67
- Foteinos PB. *Textbook of Venereal diseases*. Aleuropolos, Athens, 1954:362–363 (In Greek)
- Curran LK, Newschaffer CJ, Lee LC, Crawford SO, Johnston MV, Zimmerman AW. Behaviors associated with fever in children with autism spectrum disorders. *Pediatrics* 2007, 120:1386–1392

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