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The mechanisms of action of malaria therapy: experimental studies and a review of action in general paresis

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THE MECHANISMS OF ACTION OF MALARIA THERAPY

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THE MECHANISMS OF ACTION

OF MALARIA THERAPY

Experimental Studies and a Review of Action in General Paresis

by

John Howland Gardner, III
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DEDICATION

To David Weinman, M. D.
with affectionate respect
and with deep appreciation
for the quiet wisdom
patient guidance, and
excellent judgment which
have made working with
him one of my most enjoyable
and rewarding experiences.

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PART I

Background

1. The History of Fever Therapy

Observations of the effect of febrile illnesses on diseases of the central nervous system date back at least to Hippocrates, who, according to Becker (A)* stated that "Fever supervening on a patient suffering from convulsions or tetanus removes the disease." This may well have been in observation of crisis, and if so, factors other than fever itself were almost certainly involved. The complexity of these factors explaining so simple an aphorism has continuously puzzled those concerned with the mechanism of action of malaria therapy of general paresis. His remark "Give me the power to produce fever, and I will cure all diseases" (1) prophesied fever therapy, but its optimism is shared by only a few of the most enthusiastic fever therapists. The therapeutic effect of malaria was noted early in the observations of febrile diseases when Galen recorded the cure of a patient with "melancholia" by spontaneous "intermittens quartana". (8). The Romans used hot air caverns near volcanos and alternated blankets with cold water to produce sweat for the treatment of dropsy. Primrose (1) quotes the belief that English malaria was beneficial for disease.

"In the latter half of the sixteenth century Ambroïse Paré remarked upon the frequent occurrance of aortic disease (aueurysm) in 'those who have often had the unction and sweat for the cure of the French dis-

* Literal references in parentheses after the name of an author or work refer to the Primary Bibliography; numerical references indicate the Supplementary Bibliography.

ease' ". (2, page 357)

In 1659 Jacques Lainet of Paris prescribed mercurial inunction and sweating in a hot oven for the treatment of syphilis. Over the oven was the significant inscription: "For one pleasure a thousand pains." (1). Stove-heated rooms at Montpellier and hot baths at St. Petersburg were in use as late as 1872. (C). Herman Boerhaave (1668-1738) wrote, "I would be the greatest physician if I could produce intermittent fever (i.e., malaria) as easily as suppress it." (1) Christopher Friederick Reus wrote in his Dispensatorium Universale in 1789 of the cure of mental disease by the inoculation of variola (3). In 1790 Metzlu (1) prophesied the use of therapeutic malaria, but the illness he proposed to cure was "congested bowles." In 1816 Dubuisson (4) cited a case of suppuration produced with the conscious intent of curing a mental disorder. Bouillaud (5) in 1820 noted some cures of general paresis which were associated with acute febrile illnesses.

A great deal has been written as well, and probably with much truth, about the aggravation of mental illness by acute febrile diseases. John MacCulloch in his book of malaria* describes its ravages upon the human

*Malaria: An essay on the Production and Propagation of this Poison, and on the nature and localities of the places by which it is produced: with an enumeration of the diseases caused by it, and of the means of preventing or diminishing them, both at home and in the naval and military service. by John MacCulloch, M.D., F.R.S., &c,&c. London; Longman, Rees, Orme, Brown, and Greeen, 1827. The empirical association of pestilence with swamps in a very old one. Grendel and his mother, the monsters who in the epic Beowulf (?8th Century) stole from the fens by night and devoured the brave warriors of Beowulf's Mead-hall, probably represented malaria. Similar is Baeta's (5a) quotation of Erasmus Darwin:

> Fierce from his Fens the Giant Ague springs,
> And wrapp'd in Fogs descends on vampire wings.
>
> (Dr. Darwin's B.G. p. 2 cant. 1)

body, and accuses it of producing almost every ill to which flesh is heir, including dementia, neuritis, and paralysis. Not all, however, held malaria in such awe. Five years later Boisseau (6) wrote, "Those afflicted with epilepsy, gout, mania, and the paralytic should go to the Pontine Marshes, where they are certain to contract the fever and be remedied thereafter".

Many cases of mental disease aggravated by fevers and several ameliorated by them are discussed by Rosenblum (E) with references from 1838 to 1876, when his original article was written in an obscure Odessa medical journal. Köster (7) in 1848 reported twenty-four cases of malaria in the mentally ill of whom seven recovered and seven improved. Griesinger in 1865 described two more such improvements. Improvement during typhoid was found to last only during the fever (Mandsley, 1876, reference E). In 1876 Rosenblum (E) described 32 chronic "incurable" cases of psychosis of his own who were benefited by malaria, "spotted typhoid" (?typhus),* and

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* The confusion and identity of several diseases mentioned in the older literature should be pointed out:

(1) Typhoid fever and typhus are confused in the Russian and early German literature. "spotted typhoid" and "typhöser Fieber" may be typhus.

(2) Recurrent fever = relapsing fever = recurrens.

(3) Malaria = intermittens - intermittent fever.

(4) Variola = smallpox.

(5) Paresis = general paresis = general paralysis = progressive paralysis = dementia paralytica = parenchymatous syphilis of the brain = general paralysis of the insane.

relapsing fever. Of these 21 were cured, 3 improved, and 8 continued to suffer from an "advanced melancholia" which sounds like withdrawn schizophrenia. Those patients helped by relapsing fever whose psychoses subsequently reappeared were said to be the most lucid at the height of the fever. There seems to be considerable debate about how many of these patients were probably paretic. Neymann, in 1938 (C) reviewed the clinical histories of Rosenblum and concluded that "many" were and in 1943 (E) that ten were. Wagner von Jauregg, on the other hand, has said that none were (F). Psychiatric diagnosis* was at this time even less precise than it is today, and although paresis had finally been singled out by Bayle (8) in 1814 as a clinical entity Rosenblum never mentions the word. His favorite diagnosis, indeed, seemed to be "melancholia".

Whether Rosenblum was the first to inoculate a paretic with the infectious agent of a febrile disease with the intention of treating the paresis is therefore doubly complex. The translations of the original article of Rosenblum (F) makes no mention of inoculation. The only contemporaneous statement that twelve of Rosenblum's patients were inoculated with the agent of "recurrent fever" appears in a footnote to an article (9)

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* Rosenblum says (E, p. 53,) "Only recently has psychiatry been freed from its enslavement to metaphysics. Now that it has taken its place among the other branches of medicine, on the basis of natural science, every observation made in the field of psychiatry has some significance". The uncertain validity of his conclusion may arise from a weakness in the major premise of his syllogism. His concept of the pathogenesis of psychiatric disorders was still rather medieval in that he believed that "poisons arising from marshes cause mental derangements". (p. 54) It would have been more significant had he attributed the cure rather than the cause to these poisons.

published in 1880 by B. Oks, whom Zakon (E) says was Rosenblum's associate and which Wagner von Jauregg (F) says was Rosenblum's pseudonym. The footnote states, "According to a personal communication of R., recurrent fever was produced in the patients by the inoculation of spirilla in all these cases". (p. 252), referring to twelve patients whom the text describes being cases in the epidemic of 1874-75. The use of the passive voice in this footnote, probably added as the article was about to go to press, and the lack of discussion in the text may either have been an attempt to disguise why and by whom the patients were inoculated, indicated that this did not seem important to the author, or have been an attempt by minimal discussion to avoid notice and censure. Both Zakon and Neymann, and Wagner von Jauregg (F) point out that to have published a description of the inoculation of any patient with relapsing fever in the Russian literature of his day "would have been equivalent to professional, if not personal, annihilation". (E). The former state that "he was the first to inoculate psychiatric patients with a febrile disease" and infer that he did so in order to treat their psychoses; yet, the latter states (F) that the patients were made available to a friend, the bacteriologist Motschutkoffsky, to study the transmissability of relapsing fever to human beings. Wagner von Jauregg was of the opinion that Rosenblum had no idea of treating their mental illness, and never tried this treatment again. In an earlier paper (B) Wagner von Jauregg points out that Rosenblum's twelve patients never occurred in the relapsing fever literature but that Motschutkoffsky published from the same city in the same year an account of the inoculation of humans with relapsing fever. Perhaps,

says Wagner von Jauregg, the patients were the same and Rosenblum lent his patients to Motschutkoffsky for his research. It is true that the latter published in 1876 (10) a report of inoculating human "volunteers" "die sich gutwillig zu ihnen hergaben" in order to verify the successful autoinoculation of a Dr. Münch, but there is no proof that Rosenblum's permitting Motschutkoffsky to use his patients was a "fact", as Wagner von Jauregg says it was (F). "The question of priority of Doctor Rosenblum in the new method of treatment of general paresis" was raised by Ikhtemann in 1925 (11), and probably cannot be proved one way or the other. This author thought that he does have priority, and points out that Rosenblum published "La Doctrine des Psychoses de la Malaria" in 1881.

Rosenblum's work lay unnoticed for a long time, and meanwhile many others continued to speculate and a few to experiment. In 1876, Raggi (12) suggested that malaria might be used for the treatment of mental disease, but did not try it. Doutrebente (13) in 1878 published a collection of acute febrile illnesses which had benefitted mental disease. In 1880, Nasse (3) reported the improvement of paresis by spontaneous malaria, and later by spontaneous variola. Wagner von Jauregg (D) relates that Mahille in 1882 and Trélat in 1895 both produced suppurative diseases in patients with paresis in the hope of helping their primary disorder. It was during this period that Galloni (F), the director of an Italian mental institution, withheld quinine from his spontaneous malaria patients and observed an improvement in their mental diseases. Weygandt (3) lists ten authors who noticed once or several times the healing of "psychoses" after spontaneous malaria. Several

noticed improvement with typhus and many after such diseases as measles, erysipelas, pneumonia, diphtheria, cholera, abcess, and phlegmatous cellulitis. Only one of them, Ernst Schultz (14) suggested that malaria might be inoculated as a form of treatment. Targowla (G) mentions Mickle with Rosenblum and Wagner von Jauregg as one who inoculated a febrile disease for the treatment of paresis, but gives neither date nor reference. In 1905, Schupfer (95) made one of the first intentional inoculations with malaria for the treatment of disease. During the resulting parasitemia, the white blood count of a patient with myelogenous leukemis fell from 92,000 to high normal, but with no qualitative change in pathological cells. After quinine therapy, however, the count rose rapidly. Wagner von Jauregg discovered that in 1913 Émil Legrain (15) spent the last twelve pages of his book on tropical fevers discussing his experiments with inoculation malaria for the treatment of various conditions.

> "Twelve patients were inoculated, two with malignant syphilis, one case with luetic ulcers, four patients with pulmonary tuberculosis, one with an abcess of the testicle, a case with a slow healing wound, an obstinate eczema, an arthropathy of the knee, and two cases of syphilis of the liver. He also recommended inoculation with quartan malaria in the following instances: inoperable carcinoma, tuberculosis of the larynx, tuberculous meningitis, sleeping sickness, epilepsy, certain forms of melancholia, incipient general paresis, and tabes." (reference F, p. 581)

Perhaps the fact that his work was not taken too seriously was due to the multiplicity of ills, for which his treatment was prescribed, and also to his disbelief in Plasmodia, transmission by mosquitoes, and the use of quinine

in malaria.

Several observations on patients having both syphilis and natural malaria have been made since 1900. Mattauschek and Pilcz (16) in 1912 "followed 241 cases of syphilis infected with malaria and other febrile diseases during the first year of spirochaetal infection on the basis of the normal expectancy of general paralysis. Nine to twelve of these patients should have developed syphilis of the central nervous system, but not a single case was noted". (H, p. 33). Bercovitz (17) in 1924 found that in Hainan, China, 100% of the 3,000,000 inhabitants have malaria and 50 - 60% have syphilis, of which he saw the primary, secondary, and tertiary forms in his clinic daily. Yet in eight years he saw no cases of paresis and only two or three cases of early tabes doralis. He wondered whether this "remarkable absence" might be accounted for by a natural resistance of the Chinese or to the hot climate, but the news of the use of malaria in paresis made him conclude that the high incidence of malaria was the cause. He makes no statement about the incidence of paresis in non-malarious areas of China. Lutraio (18) in 1928 reviewed three years' mortality records in Italy and found an inverse relationship of malaria and paresis. He made no statement as to the natural incidence of syphilis. Mandl and Puntigam, (19) however, studied twenty-two cases which became infected with malaria at various stages of syphilitic disease and found that spontaneous malaria did not have much effect on the syphilis. They concluded that malaria acquired before or after syphilis does not have any effect on the organism or course of the disease. Vonderlehr's

review (H) cites eight articles which reported neurosyphilis in naturally malarious populations and seventeen articles which remarked upon its absence. Of these, one noted a higher incidence of neurosyphilis in Europeans in the tropics than in the native populations of the same regions. McCartney (20) in 1946 dealt with the problem of why neurosyphilis is uncommon in the tropics. He observed that while this fact is usually attributed to malaria, there is no malaria in the Marshall Islands where there is a great deal of syphilis but no neurosyphilis. He concluded that the central nervous system was spared by cross-immunity produced by the high incidence of yaws, which, although it produces a positive serological test for syphilis in the serum, does not do so in the cerebrospinal fluid. While his observations are interesting, his conclusions seem highly speculative. Thus a high incidence of malaria seems, in the more reliable statistics, to be associated with a very low incidence of paresis, although other factors in the regions where these observations were made cannot be excluded with certainty. Malaria appears to have no effect on the incidence of early syphilis.

Bierman (1) mentions without reference that Maisani reviewed publications made prior to Wagner von Jauregg's work and found 160 cases of paresis or insanity which had been benefited by spontaneous malaria. Thus observations of spontaneous malaria made both before and after this time indicate that this disease exerts a favorable influence upon diseases of the central nervous system, especially upon syphilis. It remained for Wagner von Jauregg to make practical application of this fact.

Few will deny that to Prof. Julius Wagner von Jauregg should go most of the credit for the development and continued applications of the therapy of syphilis of the central nervous system by the inoculation of malaria. "Fortune favors the prepared mind" (Pasteur), and a high native intelligence, reviews of cases of cures with spontaneous febrile diseases, and years of experimentation with the production of fever with foreign protein prepared Wagner von Jauregg to take advantage of the Plasmodium vivax provided by a soldier who in 1917 entered his mental hospital with malaria. His first publication suggesting this treatment, however, appeared in 1887 (B). Here he reviewed cases of febrile diseases benefiting mental disorders. His tables show eleven cases of progressive paralysis from the literature who had "febrile diseases." Four were cured, one had a temporary remission, and six were not benefited. He concludes that malaria and erysipelas, of which he gives vivid description, provide the best possibilities of diseases which might be inoculated for the treatment of mental diseases. He reviews the evidence that malaria can easily be transmitted by the injection of the blood of one patient into another. He rejects relapsing fever because it is less common an cannot be cultivated. In reviewing his work with paresis in a later paper (F) he describes combining the injection of 0.3 to 1.0 cc of old tuberculin with mercury therapy. He also produced fever with the intravenous administration of typhoid vaccine. An attempt to infect non-paretic mental patients with erysipelas failed because the inoculum of culture did not take. The remissions produced by his protein treatments were, however, so short that he felt the necessity to look elsewhere for better treatment. He noticed

that his patients who contracted febrile diseases had better remissions than those who were treated with O. T. or typhoid vaccine.

On june 14, 1917, Wagner von Jauregg scarified the skins of three paretics and rubbed in blood containing tertian malaria provided by the above soldier. He got two takes, and passed the strain to seven other paretics by subcutaneous injection. These patients had remarkable remissions during the next year. A second series in 1918 was complicated by the unfortunate inclusion of Plasmodium falciparum in the inoculum of P. vivax causing the death of three of the four paretics. His scepticism of the ultimate results of the remissions of these patients, as well as the post-war chaos, postponed publication of the results until 1919 (21). After this he continued to treat paretics with malaria, interested many others in doing so, and caused the rapid spread of his method throughout Europe and the world. Recognition of the importance of his contributions to the therapy of an otherwise hopeless disease culminated in his receipt of the Nobel Prize in Medicine for 1927. He has been the only psychiatrist to win this honor. His scientific greatness lay not only in his intelligence, but in what he could do with it. Furthermore, he was always willing to accept new ideas and modify his previous ones accordingly. Although he always considered that malarial fever was superior for the therapy of paresis to fever produced by other means, he was willing to admit that artificial fever was of great benefit in paresis, and might well have several mechanisms of action in common with malaria.

2. Malaria versus Artificial Fever

From the preceding history of fever therapy it is apparent that malaria was the most frequent of all the febrile diseases to be associated with the spontaneous remission of paresis. It was dissatisfaction with all previous methods of producing fever which caused Wagner von Jauregg to continue his investigations until his great success with malaria in 1917. Joseph Earle Moore's 1941 text (I) states that "It is certainly true that malaria is more effective than relapsing or rat-bite fever or foreign protein shock". (p. 449). Cecil (22) wrote in 1935, "Wagner-Jauregg was convinced that malaria therapy was much superior to other agents for the production of thermal reactions, and this view is now quite widely held by neurologists." After this, however, he states that some believe intravenous typhoid vaccine to be just as effective and point out that it is easier to administer.

Induced malaria appears to have a moderate superiority over induced relapsing fever in the treatment of general paresis, judging from the text and tone of those few discussions which have been read. The series of twelve cases of Rosenblum have been mentioned. (E & 9). Plaut and Steiner (23) reported six cases of paresis treated with relapsing fever of which one was cured and two were improved. They mentioned the theory that treatment with Borrelia recurrentis may have some antigenic superiority because of its close relationship to Treponema pallidum. Cecil, however, (op. cit.) concludes, "The results with relapsing fever...seem to be about as good as those obtained by others with malaria; this is still further evidence that it is

the febrile reaction and not the agent which produced the fever which is the essential part of the treatment".

The differences of opinion reflected by this discussion of the relative merits of malaria and other febrile diseases in the treatment of paresis was intensified but made more clear-cut by the introduction by Neymann and Osborne (27) in 1929 of a less complex means of producing fever by diathermy. These authors, after experimentation with dogs, produced a fever of 106.1° F. in a paretic after 2 hours and 45 minutes of subjecting him to high frequency currents. After treatment his temperature rose to 106.6° F. and his pulse pressure increased. They warned of the danger of sudden inductions and local reactions to the heat. As mentioned previously, the treatment of syphilis with artificial fever was by no means new. Its practical application, however, had to await the development of renewed interest and special machines in the 1930's. The method gradually became popular; the contorversy over its value relative to malaria grew.

The most obvious property of malarial infection to which its action on paresis might be attributed is the increase in bodily temperature which it produces. Many believed that the fever was the only mechanism of action, favored the use of artificial fever over that of a pathogenic organism, and sought experimental evidence to substantiate their opinion. Their assumptions may have been based on the fact that Treponema pallidum has an unusually low in vitro thermal death point, variously recorded as 105.8° F. (25) to 112-114° F. (A). An intermediate figure is more generally accepted, usually

approximately 107.6° F. (I). One of the first such experiments was that of Weichbrodt and Jahnel (26) who in 1919 cursed scrotal chancres in rabbits by exposing them to 105° F. in an air incubator and thereby producing a rectal temperature of 107.6 - 113° F. They did not transfer any tissue from the lesions or nodes, but planned to do this in later experiments. Some subsequent investigators succeeded in repeating this experiment, but the question was raised of whether the effect of the heat was local or systemic. Frazier (27) found curative effects in hot water baths producing rectal temperatures of 106.2 - 110.6° F., but could not cure scrotal syphilis at 103.5 - 106.7° F. Perhaps his failure may be related to the fact that the exposure of his rabbits was only twenty minutes per bath, repeated ten times. This is somewhat less than that used by other investigators. Levaditi (25) exposed animals to short wave radiation producing scrotal temperatures of less than 105.8° F. Node transfer was negative in 50 - 60% of cases, indicating a cure in some cases at temperatures below the thermal death point of the spirochaete. Yet "unfortunately, these therapeutic and prophylactic effects are far from being constant". He concludes that diathermy acts upon the host and its antibody mechanisms rather than directly upon the spirochaete.

> "In a series of analogous but not exactly parallel experiments, Bessemans confirmed Levaditi's findings. Bessemans found also that temperatures which killed treponemes in more superficial structures did not immediately destroy them in the popliteal lymph nodes of rabbits. Later, however, the nodes became sterile without further treatment. These experimental observations by Levaditi and Bessemans, and the important clinical observations by Neymann and his co-workers that during hyperpyrexia all tissues in the body do not share to the same extent in the

> elevation of temperature, support the assumption of most fever therapists that the beneficial effect of fever, particularly in the treatment of neurosyphilis, depends upon some factor or factors other than the rise in temperature. What in addition to the fever is responsible is not evident at present from either clinical or experimental studies. Moore." (I. p. 372)

I suspect that Neymann would not agree with the conclusions which Moore draws from his observations. On the other hand, Carpenter, Boak, and Warren (25a) found that six hours at 106.7 - 107.6° F. or multiple unsustained fevers of 105.8 - 107.6° F. sterilized testicular and popliteal lymph nodes, as judged by their inability to infect other animals when transferred. They found fever effective at any stage. Schamberg and Rule (25b) concluded from their experiments on heating Treponema pallidum in vitro that its thermal death point was about 105.8° F. for 6 hours. They prevented syphilis by causing rabbits to have fevers of 105 - 110° F. by hot baths. They state that the clinical applications of their work are not certain. In discussing these applications, Paul O'Leary was impressed with their possibilities, but pointed out that malaria therapy should still be continued because there is a certain group of patients who are more benefited by it. Wagner von Jauregg (J) objects to several of the preceding experiments for the following reasons: (a) temperatures attained are higher than ordinarily found in therapeutic malaria, and (b) the spirochaetes of primary syphilis seem in some way to be more sensitive to temperature than those of neurosyphilis. He quotes the experiments of Tuffi (31) who injected spirochaets intravenously into birds and found that they persisted more than five hours at more than 107.6° F. He

does not state whether they were Treponema pallidum or Spirochaeta gallinarum. Breutsch (30) concluded in 1946 from the experimental work in rabbits that hyperpyrexia which was safe in man (generally accepted at about 106.5°F.) does not harm Treponema pallidum directly. The converse relationship of temperature of environment to rabbit syphilis has recently (1954) been demonstrated by the excellent experiments of Hollander and Turner (28) who showed that rabbits and hamsters kept in a cold room developed more severe infections than those kept in a room at summer temperature, and that syphilitic infection has a predilection for the cooler areas of the body. Thus the experimental work on the effect of temperature on Treponema pallidum does not appear adequately to support the contention that its role in the malaria therapy of general paresis is a primary one.

Many clinical observations add valuable evidence to the probable superiority of malarial fever over that produced artificially. Wagner von Jauregg did not believe that temperature per se was the chief cause of benefit, but one of the reasons he gives (F) -- the fact that the benefit occurs after the fever has stopped -- does not seem very conclusive. He provides, however, much more convincing evidence in a later paper. (J). Beginning with Herrmann in 1925, many observers noticed that although patients when inoculated with malaria may develop no fever they do have remissions in their paresis. Nine additional such observers are mentioned. Furthermore, Wagner von Jauregg

points out, complete remissions have been obtained in many more patients whose malarial fevers did not approach temperatures required to kill spirochaetes when rabbits are subjected to diathermy. Targowla (G) describes two such patients. One had all the signs, symptoms, and positive findings of malaria except prostration and fever, which was never over 100.4° F. She had "considerable improvement" in her paretic symptoms. The other had one attack of fever which rose to 100.75° F. but had no more fever in spite of three subsequent inoculations with malaria. Her spleen was enlarged to percussion, so she may well have had malaria previously. She went into clinical and serological remission. Targowla concludes: "C'est, semble-t-il, le processus toxi-infectieux même, dans sa complexité, qui joue un role thérapeutique".* Weygandt (3) reports such afebrile cures, and Nonne (32) states that improvement does not always run parallel to the height of the malarial fever. Breutsch (33) sums up the problem similarly:

> "Furthermore, the observation that clinical and serological improvement occurs in paretic patients, who have had little or no temperature during malaria treatment, supports the thought that elevated temperature is only a minor factor of a number of highly complicated phases which make up the modus operandi of therapeutic malaria." p. 165

There were, however, several prominent investigators who felt that fever was the only important mechanism of action accounting for the success of the malarial treatment of paresis. Chief among them, perhaps, was C. A. Neymann, the developer of diathermy therapy, who in 1938 wrote a paper (C)

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* All foreign quotations are translated unless so to do would alter the meaning or destroy the feeling. All Centrigrade temperatures are written as Fahrenheit equivalents.

describing the treatment of 975 paretics with electropyrexia of which 27% went into remission, 36% improved, and 2% died as a result of treatment. In discussing the history of fever therapy he states,

> "The practice of subjecting the patient to the ravages of one disease or to the action of an organic or inorganic compound totally foreign to body function in order to overcome another malady has always inspired a certain justifiable skepticism." (p. 95)

He concludes without reservations:

> "Many fail to recognize the fact that fever alone is the important common factor of all such therapeutic measures. I have heard of the mythical, unproved, and much extolled magical action of the plasmodium of malaria in the treatment of general paresis until I have come to believe we are dealing with a fetish or taboo in the minds of its most ardent associates. It was precisely because I believed in the value of fever per se that I began my experiments with diathermy for the producing of fever in 1927. The treatment of general paresis without inoculation was the intent and outcome of my plan." (p. 96)

Moore counters:

> "The enthusiasm of Neymann and his collaborators for electropyrexia...is apparently based on their desire to propagandize this type of fever therapy and is not shared by observers who can neither confirm their results nor find reason to condemn malaria so heartily." (reference I, p. 448)

Wagner von Jauregg (J) felt that although the cures produced by artificial fever could not be belittled, malaria was preferable and the theory that fever alone was responsible was "not exhaustive". In 1933 Freeman, Fong,

and Rosenberg (35) reviewed the use of diathermy up to that point and found great discrepancy in the results. On the one hand there was part of the series of Neymann mentioned above. On the other there were equally large numbers of cases having 12% remissions and 15% death following treatment. In 50 patients of their own they had no remissions, 20% improvement and 14% death following treatment. Autopsies on the 7 dead patients revealed no signs of a process of improvement in the brain in marked contrast to that which is almost always found even in the brains of patients who die shortly after malaria therapy. In 1936 Epstein, Solomon, and Kopp (36) published their results with diathermy and compared it to other methods of treatment. It is noteworthy that they produced fever "above 104° F." and that Neymann et al. were using fever greater than 105° F.; hence, the two series may not be truly comparable. These authors feel that diathermy "fails to prove to be a valuable substitute for malaria." The following table is included in their report.

Table 10, p. 1532: Comparison of Clinical Results

	Malaria Series 173 cases	Malaria Series 5,000 cases*	Hyperpyrexia** Series 648 cases	Diathermy Series 33 cases	Tryparsamide Series 81 cases
Arrested	48.5%	45.0%	27.1%	24.2%	42.0%
Partially improved	15.2	25.0	40.1	33.3	29.6
Unimproved	13.8	20.0	24.8	12.2	22.2
Dead	22.5	10.0	8.0	30.3	6.2

*J. E. Moore's Review of Literature **Literature

The original figures reported above differ somewhat from the expected for that period in the following respects: (a) unusually high mortality from malaria, for which there must have been some reason in this series; (b) the mortality with diathermy is somewhat above average; and (c) the per-cent arrested with tryparsamide is higher than usual.

Further definite statements concerning the merits of malaria relative to other forms of fever therapy came from Targowla (G) who stated that "the curative action of the well-known various procedures is distinctly inferior to that of therapeutic infection." In 1938 O'Leary's group at the Mayo Clinic (37) found that remissions produced by malaria therapy lasted longer than those produced by artificial fever, although their number was about equal. In the same year Solomon (38) reported two times as many cures with malaria as with artificial fever. In 1940, however, the Committee on Non-Specific Therapy of Syphilis of the Cooperative Clinic Group, headed by O'Leary* published a report (39) stating that while the results of malaria and artificial fever therapy were equal in mild and intermediate paresis, ten times as many remissions were obtained in severe paresis with artificial fever than with malaria. They state that the differences in mortality of 13% with malaria and 8% with artificial fever are not statistically significant, and that malaria produced more serological conversions in cerebro-spinal fluids, but point out that the malaria group received 17% more chemotherapy. Perhaps the reason why

* Committee on Non-Specific Therapy of Syphilis: Paul A. O'Leary, Walter L. Breutsch, Franklin G. Ebaug, Harry C. Solomon, Stafford L. Warren, and Walter M. Simpson. This was a sub-committee of the Cooperative Clinic Group, which included the above men, Assistant Surgeon General R. A. Vonderlehr (Chief of Divisions of V.D. U.S.P.H.S.) and five other clinic heads.

the malaria group received more chemotherapy was that they were in worse condition and that their paresis had been of longer duration. These results and those of other members of the Cooperative Group Clinic were summarized and commented upon by Simpson, Kendell, and Rose in a pamphlet entitled "Treatment of Syphilis: Artificial Fever Combined with Chemotherapy" (K), 1,420 patients were treated for paresis in several clinics throughout the country. 1,100 received malaria and 320 were treated with artificial fever. Most of these patients were the same as those previously reported by O'Leary et al. (38), and so the superior results with artificial fever were again noted. No difference was found in the rate of relapse and concomitant chemotherapy was found distinctly beneficial. The results from the individual contributing groups are reviewed and have no great variation from the composite picture presented above. The authors feel that the malaria versus artificial fever controversy should be ended, and conclude: "The persistent claim that the malarial plasmodium exerts a specific beneficial influence in cases of neurosyphilis, apart from the production of fever, has little justification in the light of the developments of the past decade".

Despite the laudable efforts of the authors to collect and compare a large number of cases treated by either method, there are several aspects of the report which are open to question: (a) Little attention is paid to the past history of the patients, who are merely classified according to the severity of paresis at the time of treatment. It is of primary importance to know for how long a patient has had his paretic symptoms; for it is well known

that a patient with recently developed paresis has a better prognosis than one who has had his paresis for years, regardless of the form of treatment contemplated. Furthermore, a knowledge of previous attempts at treatment is necessary; a refractory patient is harder to improve with anything. It may well be significant that patients not benefitted by artificial fever have had remissions after subsequent malaria therapy; yet, some patients who have not responded to the first course of artificial fever therapy have done so to the second, and a few not helped by malaria have been by artificial fever. Because artificial fever was a newer form of therapy, it would naturally tend to have been used on a patient when he entered the hospital. The malaria group would thus tend to be made up more of those already afflicted. Moreover, there was a distinct tendency to use malaria when everything else had failed. (b) In the introduction to their report the authors reproduce a quotation from a paper by Wagner von Jauregg which points out the effectiveness of artificial fever and discusses certain practical advantages. Yet the latter also states that one of the advantages of artificial fever, with its simplicity, is that if it does not work, one can always use malaria. He recommended the alternation of the two methods in the same patient. Wagner von Jauregg's observations do not seem to support so thoroughly as the authors of the report infer his contention that he prefers artificial fever. (c) To support the conclusion that fever is the only beneficial effect of malaria, and hence that artificial fever is superior, the authors of the report quote an article by Doan*. While the portion quoted appears to do so, the quotation

* This paper will be discussed later when dealing with the stimulation by malaria of the reticulo-endothelial system and other body defenses.

is taken out of the context of the original paper. Doan's conclusions either do not support these contentions, or are the reverse of those which may be drawn from his data. He merely wishes to show that artificial fever stimulates the haematopoetic system, and may thereby be beneficial in addition to any treponemicidal effect of temperature. (d) Conspicuous by absence of mention in the Cooperative Clinic Group (C.C.G.) report are the patient series and opinions of Joseph Earle Moore. In a discussion of the treatment of primary optic atrophy, they state that he favored "fever therapy", but fail to mention that in the reference they quote (I) the fever therapy advocated was malaria. Moore states that the C.C.G. survey still leaves the question of artificial fever versus malaria far from settled. He points out their lack of subdivision of patients as to duration of symptoms and type of artificial fever. Artificial clearly has "some merit", but he prefers malaria. He concludes that the physician should use the form of fever therapy with which the individual has had the most experience, and which is most convenient to him.

More recently, in 1946, the question of artificial fever alone versus malaria alone came up again. Lascara (39) published a report of the treatment of 190 paretics, 88 with malaria (Plasmodium malariae) and 102 with electropyrexia. Malaria produced 33% remissions, 15% improvement, and 22% deaths occurring within three months; electropyrexia produced 64% remissions, 20% improvement, and 3% death occurring within three months. He concludes that artificial fever is superior because it is better tolerated, can be given without prolonged constant hospitalization, and does not combine two diseases.

His conclusions are in agreement with those of the C.C.G., especially since their phraseology bears a remarkable identity to those of this report. (K, pp. 43 & 45). In their review article (41) for 1946, Reynolds and Moore state that Lascara's report of 22% mortality with malaria is at variance with most previous reports. In this article their examination of artificial fever therapy indicates strong disapproval of the papers published claiming its superiority. They state that the clinical experiments were not well controlled and that discussion of them lacked clarity. They feel that many authors minimize the dangers associated with artificial fever. Lascara's report was one of the last such studies to appear which did not concern itself at least in part with the penicillin treatment of general paresis. Yet in his 1947 book Penicillin in Syphilis (42), Joseph Earle Moore's conclusion reflects the opinion of many others:

> "In spite of the absence of definite proof, I still feel that malaria is superior to mechanical fever, on the grounds of less discomfort and (except in the most expert hands) lower risk of death, and higher incidence and permanence of satisfactory results."

* * * * * * * * * * * *

3. The Combination of Malaria with Other Methods of Treatment of Central Nervous System Syphilis.

The advent of penicillin has obviously caused a great change in the treatment of all forms of syphilis. This antibiotic appeared to be an almost perfect therapeutic agent in that it is non-toxic to the recipient even in

very large doses (unless he is allergic to it), and that Treponema pallidum is remarkably sensitive to it and does not develop resistance. The question of the advisability of retaining older forms of therapy naturally arose. Many studies were conducted to decide whether or not malaria therapy augmented the effect of penicillin treatment of syphilis. In addition to the obvious clinical application, an evaluation of the results of some of these studies may suggest a few of the mechanisms of action of malaria on paresis.

The combination of malaria with arsenicals has produced results superior to those obtained with either form of treatment alone. A few experimental and many clinical observations provided the basis for this conclusion. Most experimental studies were confined to the combination of arsenicals with fever produced by artificial means. In 1937 Simpson and Kendell (43) found decidedly better results in rabbits with both forms of treatment. Many clinical results are summarized by Moore (I, 1941)* and the Cooperative Clinics Group (K, 1942) with the distinct impression that the combination is superior. Such observations hint that while the mechanism of action of malaria may overlap that of so obviously treponemicidial a compound as an organic arsenical, some difference exists further than degree of spirochaeticidal activity.

The demonstration of the safety and degree of anti-syphilitic activity of penicillin was soon followed by its use in the treatment of neurosyphilis. In an early report (44, 1945) Rose et al. observed that penicillin looked promising for such treatment, but warned against casting aside older

* Reference I, published in 1941.

forms of therapy before a thorough evaluation. No mention was made of malaria. The next year, however, Stokes et al. (45, 1946) stated that penicillin alone "compared favorably with other forms of therapy" for neurosyphilis. Yet al. et Moore (46, 1946) found penicillin plus malaria superior to penicillin alone. Breutsch (47, 1947) condemned surgery for syphilitic optochiasmatic arachnoiditis and concluded that the combination was superior to penicillin alone in the treatment of this disease. These conclusions, however, were based on the use of only 5,000,000 units of penicillin, and further experience caused him to modify them as will be shown. Observations of his own (30, 1946) and those of others he mentions caused him to prefer malaria to artificial fever. O'Leary and Kierland (47, 1946) failed to achieve remission with penicillin, but told of others who had.

In 1947, Koteen et al. (48) found that "The penicillin therapy of neurosyphilis (exclusive of primary optic atrophy) approaches and may equal fever therapy in effectiveness". Others generally found penicillin and malaria more effective. Reynolds (49) found this to be true in cerebrospinal fluid determination. Curtis, Burns, and Norton (50) found this superiority after one year's observation of 118 patients even though, as was frequently the case in other studies, the more severely ill paretics were given both penicillin and malaria. They found no difference between single or combined treatment in tabes dorsalis. Rose and Solomon (51) made the highly significant observation that in their series penicillin plus malaria had proved superior to penicillin plus artificial fever, and that the latter combination was no better than

penicillin alone. Although this fact appears only in the form of a chart in this article, it was commented upon in another article by them (52) published the same month. As discussants to the first article, O'Leary and Epstein both agreed that penicillin plus malaria was better than penicillin alone, but did not comment on artificial fever. Here, it seems, is further evidence for the superior results obtained with malaria as compared with those with artificial fever, even though the picture is complicated (but made more practical) by the inclusion of penicillin in both series. In summarizing the year's findings, Moore (53) concluded with appropriate caution:

> "In the more serious parenchymatous forms (paresis, tabes dorsalis, primary optic atrophy, and nerve deafness) the combination of penicillin and fever from induced tertian malaria simultaneously administered may be superior, both from clinical and laboratory standpoints, to penicillin alone."

By 1948 penicillin had been included in the treatment of enough paretics for long enough a time so that more valid conclusions could be drawn from studying the results. At least five authors concluded that malaria plus penicillin was better treatment than penicillin alone. Breutsch (54) added subsequent penicillin to the 5,000,000 units which he gave with malaria for the treatment of primary optic atrophy. Byliner and Winkel (55) favored malaria with penicillin, and Kaplan and Read (56) concluded that malaria was still useful in spite of the efficaciousness of penicillin. The yearly review of Reynolds and Moore (57) made no direct statements but implied a preference of the reviewers for combination therapy. Kopp, Rose, and Solomon (58) concluded from their work at the Boston Psychopathic Hospital that

malaria and penicillin together were more effective. They had to re-treat 52% of all patients treated with penicillin alone, but had to do so to only 21% when malaria was used with the penicillin. Wong and Packer (59) treated a mixed group of neurosyphilitics and preferred penicillin alone. The fact, however, that 64% of their penicillin plus malaria group were paretic while only 52% of their penicillin alone group were may explain why in nine-teen months they obtained 33.9% C.S.F. (cerebrospinal fluid) Kolmer reversals with the second group, but only 26.6% with the first. Chesney and Reynolds (60) preferred penicillin plus malaria in the treatment of tabes dorsalis, causing improvement in 57% of those so treated as opposed to only 27% of those treated with penicillin alone. This series is interesting in view of the fact that the treatment of tabes with malaria has usually been a rather controversial subject. It has been definitely indicated for tabo-paresis and tabes with primary optic atrophy, and has been of considerable help in some cases of ataxia and lighting pains. It has rather often aggravated "burnt out" tabes and tabetic bladders. Hence the chief symptom of the tabes seems to be the most important factor in the consideration of malaria therapy. Solomon (61) also reports the beneficial effects of combined therapy on tabes and urges it use in optic atrophy. His review of penicillin in paresis cites three authors who prefer to add malaria and two who do not. He favors the addition himself, but uses a reduced course of only 5 to 7 paroxysms with six to nine million units of penicillin. Debilitated patients were subjected to twenty hours of 104-105° F. fever produced by a fever box, indicating the author's preference for malaria when possible. He states that Moore uses a

full course of malaria and six to twelve million units of penicillin. Solomon makes the additional valuable suggestions, later used by others as well, that electroconvulsive therapy is useful for the management of severely disturbed patients with "galloping paresis" during penicillin therapy. In the past all forms of therapy had given poor results with this fulminating type of paresis. Stokes et al. (62) compare their cases treated with penicillin alone with cases from the older literature treated with malaria alone and conclude on clinical and serological grounds that while results are better with malaria during the first year, cases treated with penicillin alone are equal clinically by the end of the third year and have superior C.S.F. serology results. They make the suggestion that penicillin be combined with malaria. They also arrive at the extremely important conclusion that penicillin therapy should be started with 500 units on the first day with gradually increasing doses thereafter in order to avoid the disastrous Herxheimer reaction or afebrile therapeutic shock with rapid deterioration.

After a discussion of the lack of effect of malaria outside the central nervous system and of the gummata which may appear a few weeks after the malarial treatment of paresis, Rose and Solomon (81) summerize the feeling at this time as follows:

> "Neither the malarial parasite nor the elevation per se appear, therefore, to destroy spirochaetes. No one seems to know the modus operandi of malaria therapy, yet no one seems to want to cast it aside because of this inadequate understanding or because of its dangers."

In 1949 larger doses of penicillin came into use and, despite lack of comment about the relative merits of penicillin plus malaria as opposed to penicillin alone, it appears that less malaria was utilized. One paper from France is significant mainly in that it differs so markedly from all others. Nicholas Blatt (63) discussed the ocular complications of spontaneous malaria and stated that malaria aggravates all diseases of the eye, produces retinal haemorrhages at the time of greatest fever, and may produce optic atrophy. He has treated 387 cases of syphilitic primary optic atrophy with malaria, but gives no details about their extent of disease or treatment, stating only that such statistics are available to anyone who is interested. He omits the important consideration of visual acuity at the time therapy was started. He found that in tabetic optic atrophy patients treated with malaria became blind sooner than those who received no treatment. He is in accord with others, however, in advocating malaria therapy for the much less common optic atrophy associated with paresis. For tabetic optic atrophy he prefers iodine therapy and sedation. He feels that the death of the spirochaete produces an endotoxin which results in a sudden loss of sight. Breutsch particularly had always found use for malaria in optic atrophy, and many others agreed with him. Breutsch's statement (30) however, that the process of optic atrophy is really more akin to paresis than tabes has produced considerable disagreement. In paresis, he found (64) that sufficient penicillin alone, in the doses employed in 1949, was equal or somewhat superior to malaria alone. He did not comment on combined therapy. His discovery of a spirochaete in the brain of a paretic dying after treatment with ten million units of penicillin caused him to advocate

fifteen million units. Boyd's text was also published in 1949 (A), and as the author of the chapter on malaria therapy, Becker strongly advocated the use of malaria for paresis, taboparesis, and optic atrophy. He also found it very useful for the treatment of other complications of tabetic or ocular neurosyphilis and for prophylaxis in asymptomatic neruosyphilis. He also felt that it has produced good results in many cases of syphilis of all types refractory to other forms of therapy. In all cases he advocated the judicious use of concomitant penicillin, but strongly warned against the use of trypars-amide in primary optic atrophy because it seems to have a toxicity all its own for the optic nerve. This latter finding did not concern Moore (I) in 1941. Despite such firm support, however, the use of malaria in neurosyphilis became more restricted. Solomon's group (65) in their study of retreatment used malaria in only 6 of 73 cases. They made no comment on why this was so or on the comparative results. They did show, however, that retreatment produced some improvement in 49% if it was performed for clinical reasons, but did so in 75% if it was done because of C.S.F. serology. They reinterated the value of combining electroconvulsive therapy with the other forms of treatment in patients the manifestation of whose paresis included an affective syndrome.

In 1950 at least two studies sought to compare combined therapy with penicillin alone. That of Curtis, Kreuse and Norton (66) compared on this basis two numerically equal groups of many types of neurosyphilis. Fever consisted of fifty or more hours of malaria at more than 103.5° F. and penicillin of a total of 4,000,000 units. Thus both forms of therapy were of questionable adequacy, although some feel that this amount of malaria is sufficient. The group

which received combined therapy were, especially in the first two years of the study, admittedly in worse condition, and included more cases with severe initial C.S.F. abnormalities and more cases of paresis and taboparesis. Despite this fact, however, the final results of comparing these two groups with different disease patterns were approximately equal. Combined therapy produced earlier C.S.F. conversion in paretics and taboparetics, but not in other groups. The authors warn, however, that C.S.F. studies often bear no relation to clinical outcome, as judged by working ability, which was somewhat worse in the combined treatment group. Their discussion of malaria therapy seems to overemphasize its dangers. They conclude, "We believe that penicillin alone is adequate in all types of neurosyphilis except severe paresis and possibly primary optic atrophy." The other study, that of Spiller et al. (67), obtained similar results to those described above in two groups of neurosyphilitics similar indicating the equal effectiveness of penicillin plus malaria (20-40 hours over 104° F.) and penicillin alone. Patients had been followed from one to four years. The two groups in this study were, however, much more comparable than in the other one. A somewhat greater improvement was found clinically and serologically with combined therapy in the paresis-taboparesis groups, but in view of small numbers may not be statistically significant. The authors make the important suggestion that 6 to 8 Bismuth injections be given prior to penicillin treatment in order to avoid Herxheimer reactions. Three discussants agreed with their evaluation of combined penicillin and malaria therapy.

Since 1950 little definite work has been done on evaluating malaria

therapy. One important study, however, was that of Perlo, Rose, Carmen, and H. C. Solomon (68) at the Boston Psychopathic Hospital in 1951. They found penicillin alone was equal or superior to penicillin plus fever (74% was malaria) for the treatment of neurosyphilis (72% paresis or taboparesis, of 469 patients altogether). Malaria was administered on the reduced schedule used by this hospital, and 5 to 7 paroxysms over 104° F. were given. Artificial fever consisted of 20 hours over 105° F. The paretics so studied were admittedly and of necessity a heterogeneous group, as in similar previous evaluations. The paresis of the ones receiving combination therapy was initially more severe than that of those receiving penicillin alone. Despite this face, less retreatment was required in the combined group. A comparison of cases of simple dementing paresis of relatively severe degree, however, indicated the slight superiority of penicillin alone. The authors feel that this comparison is fairly valid, and conclude that penicillin is somewhat better in all forms of neurosyphilis. They caution, however, that the long-term comparison for final evaluation is not yet possible.

In 1953 Kenney and Curtis (69) studied the results of treatment of optic atrophy and concluded that malaria did not add enough to penicillin therapy to warrent its use. In 1954 Klander and Gross (70) studied the fever therapy of the same conditions but produced fever with intravenous typhoid vaccine. Fever produced in this manner failed to stop progression of the disease. They obtained better results with malaria. Despite some excellent results, a greater percentage were benefited by penicillin. They prefer penicillin, but quote Moore as obtaining better results with the addition of malaria. This problem of

the treatment of primary optic atrophy was reviewed extensively by Hahn and Zellerman (71) in 1955 who found a very confused and undecided literature on the subject. They reviewed 233 cases seen at Johns Hopkins and concluded that an excessive number of variables caused their results to have no statistical significance. It may be worthy of note, however, that a 10% loss in vision was sustained by 70% of their penicillin patients, while those groups treated by one of the other methods all suffered such a loss in approximately 50% of cases. An 80% loss of vision over three or four years occurred in 23.5% of patients treated with penicillin alone, 17.1% of those with metals alone, 5.5% of those malaria alone, and 11.8% of those with penicillin plus malaria.

Reviewers of the recent period sum up the results of the treatment of Neurosyphilis as follows. Harry C. Solomon, writing the chapter on this subject in Cecil and Loeb's text (2), concludes that twelve to fifteen million units of penicillin is the treatment of choice in paresis. He advises the addition of fever therapy if the response to penicillin is inadequate, and advises combined penicillin plus fever for primary optic atrophy. He does not specify the type of fever. Joseph Earle Moore in his articles on "The Changing Pattern of Syphilis, 1941-1953" (L) summarizes:

> "Some therapists still employ fever therapy (induced tertian malaria) in selected cases, especially primary optic atrophy, where the effectiveness of penicillin is not yet completely demonstrated; and in general paralysis, where initiation of treatment with penicillin may cause serious, even diastrous, Herxheimer reactions." (p. 646)

To summarize this section, it seems that the results obtained with

the malaria therapy of general paresis since the introduction of penicillin indicate that malaria is still of additional value in selected cases. While enthusiasm for its use was high at the end of the last decade, the number of studies attempting its evaluation have decreased. Some studies which were carried out indicated a decrease in the number of subdivisions of neurosyphilis in the treatment of which malaria was definitely indicated as providing results additional to that which could be obtained with penicillin. The selection of cases seems to be of primary importance. The use of malaria appears contraindicated in severe debility, all but the mildest aortic aneurysms and pulmonary tuberculosis, and in arteriosclerotic heart disease. The frequency of these conditions in the group of patients who most frequently develop paresis at once limits its usefulness. Yet in those patients who are candidates for malaria therapy, its employment in addition to penicillin appears in severe paresis and primary optic atrophy. Some of the older studies (1947-1949) demonstrating the value of combined therapy have not been convincingly disproved by recent data. The recent apparent neglect of malaria therapy of syphilis of the central system, therefore, may be on the basis of the comparatively cumbersome nature of the treatment than of lack of effectiveness.

Malaria, then, is an effective means of therapy of central nervous system syphilis, though the indications for its use are now somewhat less than they used to be. It seems to augment the action of penicillin, though probably by a more complex means than by its treponemicidal powers. Because it is of clinical value, the mechanism of action of malaria therapy needs to be better understood. A yet more important incentive, however, for trying to elucidate as

many components as possible of this undoubtedly complex mechanism is that to do so might solve a fascinating problem and possibly lead to further information of even greater significance and application.

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4. The Mechanism of Action of Malaria Therapy

From the preceding chapters one thing is clear: the mechanism of action of malaria in the treatment of central nervous system syphilis is by no means well understood. The probable superiority of malaria therapy over that of fever induced by artificial means suggests that there is more to the action of malaria than can be accounted for by an increase in bodily temperature, even with all the complex changes which fever entails. The experiments previously discussed which were designed to demonstrate the effect of temperature on Treponema pallidum in vitro and in vivo have succeeded in doing so, but their application to clinical tertiary syphilis of the central nervous system is highly questionable. The objections to them have already been pointed out. A great many theories have been developed to explain what in addition to fever malarial infection might produce which would be detrimental to the spirochaete of syphilis. Most of these deal with reactions of the host to infection with malaria.

The pathological reactions which take place in the brain, as well as in the rest of the body, in response to malarial infection have long been of great concern to those interested in the action of malaria on paresis. The foremost among those who have studied the problem from this aspect is Walter L. Breutsch. In 1932 he described (M) the activation by malaria of the

histiocyte.* This essential cell of the reticulo-endothelial system undergoes rapid proliferation during malaria, especially in the liver and spleen. Breutsch quotes the work of Jungeblut and Berlot (72) who demonstrated the association of the reticulo-endothelial system (R.E.S.) with the formation of antibody. These authors blocked the R.E.S. by the injection of india ink, injected diphtheria toxin-antitoxin and found a considerable delay in the time required to develop a positive Schick test. Their observations and conclusions agree with those who preceded and followed them. Histiocytes have been shown in relatively small numbers in the leptomeninges. Yet under the influence of malaria, an extreme degree of proliferation takes place, and these cells enter the blood stream and subarachroid space and become phagocytic. The cells of the venular capillary endothelium also proliferate, detach, enter the lumena and do likewise. Undifferentiated mesenchymal cells were also activated. The concentration of phagocytic cells in such vessels (as elsewhere where the R.E.S. is active) is far greater than in the peripheral blood. The assumption is, therefore, that these cells are in greatest concentration where the R.E.S. is most activated, and, apparently, where they are most needed for defense. There are, however, few perivascular histocytes in the cortex, but more in other parts of the brain. In later work (33) he describes the associated monocytosis and increase in capillary permeability. Cunningham et al. (73) related the defense against experimental syphilis to the very mononuclear cells which Breutsch said are activated by malaria. Breutsch later pointed out that no such stimulation occurs in patients dying after treatment with only penicillin (64), and Boyd's

*Histiocyte = macrophage = clasmatocyte= resting-wandering cell of Maximow

text (A) denies that any such activity takes place in the brain of an untreated paretic. The work of Freeman, Fong, and Rosenberg (35), mentioned previously, is in accord. Thus malaria causes the proliferation of a system of cells which are associated with the phagocytosis of foreign particles and, according to one group of workers, the production of antibodies.

The question of whether or not such stimulation is also caused by artificial fever is a very petinent one in trying to decide whether malaria has a different mechanism of action. Doan (N) studied the effect of hyperpyrexia and malaria on the bone marrow and peripheral blood of humans and of hyperpyrexia on the lymph nodes, marrow, and R.E.S. of rabbits. In rabbits he found no increase in monocytes and no histiocytes in either peripheral blood or bone marrow, but did find an increase in histiocytes in the lymph nodes, liver, and spleen. In humans an immediate increase in white blood cells, mostly neutrophils, to 10,000 - 60,000 was noted. There was an initial fall in monocytes, but after 9 - 12 hours a monocytosis of younger cells occurred. These cells, however, had no increase in phagocytic activity for dyes. No difference with respect to monocytes after artificial fever was noticed in a patient who had been splenectomized on the one hand nor in a normal patient after 1 cc of 1:1000 adrenalin on the other. The monocytes were found more "stimulated" when typhoid vaccine was used to produce the fever.

Doan found that "the hemogram produced by malaria is distinctive". After an initial leukopenia, the count rises, but only to 14,000 - 15,000 during the chill. The secondary lymphocytosis after the fever involves more lymphoblasts and younger lymphocytes than that following artificial fever. Monocytes

> "return to the circulation to make at times 30-40% of total count and are extremely young and markedly stimulated [to phagocytosis]. The entire age range of this cell type can be seen, from monoblasts to mature monocytes."

The monocytes are larger than normal and greatly vacuolized.

> "During the period of monocytosis there also appears in the peripheral blood an abnormal number of actively phagocytic clasmatocytes. They have been seen in same counts as high as 7 to 8 per cent, and this has been observed in no febrile hemogram induced by agents other than malaria" (p. 388).

Doan biopsied the bone marrow of the same patient three times: once before treatmeht, once just after the third hypertherm treatment, and once just after a subsequent course of eight paroxysms of malaria. The pre-treatment and post-hypertherm biopsies were almost the same, but that after malaria showed a "shift to the left" in myeloid and erythroid elements. "The appearance of plasma cells and a marked increase in highly phagocytic clasmotocytes was outstanding." These clasmotocytes (= histiocytes) and monocytes are the same cells which Breutsch found so stimulated in his autopsy study on malaria in paresis and which have been associated with defense by phagocytosis and antibody production. More recent work, furthermore, has indicated that the plasma cells that were also stimulated may be the most important cells in the production of antibody. It appears significant that they have not been found increased in the peripheral blood or bone marrow of patients or rabbits subjected to diathermy. Although they were found increased in the nodes, liver, and spleen of these rabbits, the whole picture of the stimulation of these cells in malaria is certainly far in excess of that in artificial fever. It is unfortunate that their stimulation in the brain by artificial fever has not been adequately studied.

Doan points out that they are the most significant cells and that the polymorphonuclear leukocyte, the peripheral stimulation of which by mechanical fever is more marked in artificial fever than in malaria, "is by no means necessarily the most important from the standpoint of fundamental body defenses." Yet the relatively small stimulation of histocytes and lymphocytes in the nodes, spleen, and liver of rabbits may be of significance in helping to explain the mechanism of action of fever in paresis. Doan concludes:

> "To that extent, at least, artificial hyperthermia by physical means not only provides the thermal factor of importance for the inactivation of Treponema pallidum and the gonococcus, but also has now been demonstrated to exert a profound effect upon the cellular equilibrium of the body - in the direction which we believe, at the present time, to be the most effective in mobilization of the defense forces of the body against these diseases." (p. 389)

The cooperative Clinic Group report (K) mentioned in the last chapter quotes the above paragraph but omits "To that extent, at least".

It seems apparent from Doan's data that by "The most effective..." he means that the clasmatocytic response is the most effective mobilizer of defense forces and may be inferred that malaria is clearly superior to artificial fever in this respect, since it is shown to be a more effective mobilizer of clasmatocytes. Yet the C.C.G. report interprets this as meaning that artificial fever is the most effective of all means of mobilizing the defense forces, and emphasize the superior polymorphonuclear response of artificial fever. This conclusion does not seem justified in the light of Doan's data; in fact, the opposite conclusion is apparently valid.

One of the effects of malarial infection on the brain which has already been mentioned in connection with the work of Breutsch is an increase in the permeability of the capillary endothelium within and around it. This breakdown of the "blood-brain barriers" was investigated in 1928 by Kral (74) who studied differences in the bromide levels in the serum and C.S.F. before, during, and after malaria therapy and concluded that the increased permeability present in paresis was still further increased during malaria, but fell to normal during the healing process after therapy. He also found determinations of permeability by this method of doubtful significance in the diagnosis of paresis. Paulian and Tanasesch found the same thing using novarseobenzols in 1935 (75). Freeman (76) thought that these changes might be significant in permitting drainage of fluids carrying spirochaetes out of the brain into the subarachnoid space. He made analogy to the enlargement and even infiltration into the subarachnoid of vessels during water intoxications. He opined that a similar process in malaria might help the cerebrospinal fluid forcably to flush out the organisms and exudates liberated when the increase in permeability permitted drugs, the R.E.S., and the body's immune mechanisms to dislodge and affect adversely the spirochaetes in the parenchyma. He favored malaria over artificial fever because it combines most favorably temperature, activation of the R.E.S., and flushing out of the brain and subarachnoid. Targowla (G) was thinking along the same lines when he stated that malaria strikes a direct [?] blow against the spirochaete by injuring the brain just slightly enough to permit antibodies and drugs to get at the spirochaete, but not so badly that the damage is not readily repairable by the host. The evidence for such changes

during malaria therapy, however, is by no means conclusive. Wagner von Jauregg (F) feels that they merely reflect inflammation and questions their importance. Moore (I) feels that the effect of malaria on permeability has not been definitely proved and believes that the results of investigation of this problem and interpretations of their significance are in conflict.

The role of cerebral lymphatics in malariatherapy is a topic allied to that of permeability, and appears to be even less understood, von Sarbo (77) felt that the plasmodia travel in the same lymphatics* as the spirochaetes and pointed out that the endothelium of these channels was full of parasitic pigment. He found emboli of highly parasitized red cells within their lumena and suggested that the parasites might compete with the spirochaetes for nutrition and aid the leukocytes in disposing of them. While others have recently considered the nutritional competition of plasmodia, this theory does not seem very likely. Others disagree with it. Freeman's theory of forced drainage seems opposed, and Bruce (78) felt that malaria caused an unplugging of the cerebral lymphatics.

The action of malarial infection upon the non-specific formation of antibody and upon the stimulation of immunity to Treponema pallidum in particular is an extremely complex problem about which a fair amount has been written and very little understood. It has often been said that the long term, often latent, existence of the spirochaete within the human body is evidence for a delicate balance of power in the host-parasite relationship. If this be so,

* By this we presume that he means the perivascular spaces of Virchow-Robin.

any factor sufficient to upset this balance by increasing the defenses of the host or decreasing the resistance of the spirochaete will either kill the invader if that factor is strong enough or if it is not will alter the pathological reaction in a way which may or may not be recognizable. The Plasmodium is a foreign protein with cyclical changes which produce fever and stimulate profoundly the reticulo-endothelial and haematopoetic systems. The production of antibody and phagocytic cells by these systems has already been discussed. Becker (A) concludes:

> "In some manner yet unknown, there is an alteration in the patients immune reaction as evidenced by the favorable response which occurs in the treatment of the patient with resistant syphilis after a few malarial paroxysms."

The question of the role of fever in the therapy of paresis again appears, this time from the standpoint of the production of antibodies. O'Leary (37) stresses the action of fever:

> "In fever induced by the malarial treatment, as well as in that produced by other non-specific agents, it is my impression that the satisfactory therapeutic effects are the result of some fundamental change in the immunologic process, the nature of which is unfamiliar. The high temperatures which are produced may be a factor in bringing about these changes."

Some of the early investigators supported the idea that fever enhanced the production of antibodies. In 1942, however, Ellingson and Clark (O) demonstrated the inhibitory effect of fever upon the formation of antibody in several antigen-antibody systems. Fever of 106.7° F. in rabbits impaired the formation of antibodies to sheep red blood cells, typhoid vaccine, and egg albumen. In an exper-

iment with rabbits whose rectal temperatures were raised to 106.9° F., they demonstrated a decrease in existing typhoid antibody over that of an afebrile control, but were unable to show any effect on compliment. When the temperature of the rabbits was raised only to 104° F, however, there was no effect on the formation of antibody to sheep red blood cells. Interesting experiments on the phagocytosis of Staphylococci by white blood cells demonstrated a maximum range of activity for the guinea pig 102.2 - 105.8° F. and was 100.4 - 104° F. for man. These experiments indicate that fevers at the upper limit of that produced in fever therapy are detrimental to antibody formation, while those at the lower limit neither enhance nor antagonize it. They seem further to support the supposition that there is more to the action of therapeutic malaria than can be explained by fever alone. These findings correlate well with the superior activation by malaria of the reticulo-endothelial and haematopoetic systems.

The role which anamnesis may play in the action of therapeutic malaria is certainly an intriguing consideration, and perhaps a rather important one. Cannon (P) recalls that when a rabbit previously immunized with typhoid vaccine is injected with E. coli, diphtheria toxin, and several other materials, the anti-typhoid titer rises appreciably. He postulates that the stress of a foreign protein such as malaria or typhoid vaccine, and perhaps that of hyperpyrexia, applied to a patient with chronic syphilis activates the protein "templates" which have been formed in response to the syphilitic infection. These "templates" modify the gamma-globulin to form specific antibodies against Treponema pallidum. While the apparent superiority of malaria argues in favor

of the presence of other mechanisms as well, the sudden increase in antibody which would occur might explain not only the death of the spirochaetes, but also a number of pathological processes which have been seen to occur with malaria therapy of paresis.

It has been requently observed that in some cases following therapy with malaria the histopathology of lesions in the brain ceases to resemble that of paresis and becomes more like the inflammatory lesions of secondary or tertiary lues. A change in pattern favoring the formation of gummata has been found. Wilson (79) noticed these as well as presenting the transport of iron pigment to microglia as further evidence of phagocytosis. While prior to treatment patients with paresis seem to escape apparent syphilitic lesions elsewhere in the body (80), it has been noticed on several occasions that gummata appear outside the central nervous system (as in the skin and liver) within a few weeks after treatment with malaria (81). These observations caused Dujardin (82) to postulate that during paresis the absence of profound host reaction to the invading spirochaete indicates a defect in allergy of the host to the parasite. He uses this state of "anallergy" or anergy to explain the pathogenesis and progression of paresis. During therapy with malaria, however, the allergic state of the host is restored and gummata formation can occur. To support his claim that there is increased antibody formation to Treponema pallidum he quotes studies of immobilization of spirochaetes by the C.S.F. and leukocytes of malarial paretics. These studies were probably those of Hoff and Silberstein (Q) and will be discussed later in more detail. Targowla (G) found Dujardin's theory of anergy "séduisante"*. He describes the

*See footnote page 17.

latter's theory and ascribes to the reappearance of allergy the great meningeal inflammation and return of the C.S.F. serology to normal which occur following malaria. These events are favorable to the host, for such lesions resembling tertiary lues almost always subside. Yet he mentions this "meningeal storm" has occurred either as the first sign of paresis or following malaria treatment and may result in rapid progression rather than the inflammation with subsequent clearing which usually takes place. He points out, however, that some cases improve very gradually after therapy with malaria, and feels that restoration of allergy plays less of a part in reactions outside the central nervous system. Others, however, seem to favor a generalized anergy. The gummata which appear elsewhere would otherwise have to be explained as a spread of treponemata, perhaps caused by forced drainage of the C.S.F. and increase in permeability of the blood-brain barrier. The later explanation is, of course, also possible.

Wagner von Jauregg (J) is also impressed with the return and increase of antigenicity for Treponema pallidum which follows the cure of paresis by malaria. While reinfection has been reported after treatment of early syphilis, he claims, it has never been after treatment of paresis. He also relates the significant fact that in paresis tuberculin and luetin reactions have been negative before treatment with malaria, but positive afterwards.

> "Therefore it may be concluded that the malaria acts principally by increasing the faculty of resistance of the brain and other organs to the spirochaetes and probably also to noxious substances, produced by them."

Theories of how malaria does this must involve consideration of a great many factors, some of which are described in this chapter, the nature and significance of which are not very well understood.

The effectiveness of malaria in the treatment of syphilis and its stimulation of the production of antibodies against the organisms of syphilis suggests the possibility that the antibodies produced by the host in reaction to malarial infection may be similar to those which are effective against syphilis. The marked stimulation of the reticulo-endothelial and haematopoetic systems by the Plasmodium hints that the majority of antibodies so produced will be to that organism, although other pertinent and strong possibilities have previously been considered. Some serological work, indeed, has demonstrated the similarity of at least some of the antibodies produced by malaria to some of those by syphilis. The false-positive serological tests for syphilis which occur in cases of malaria are well known, but the explanation is not. In 1939 Eaton and Coggeshall (83) found that when extracts made from the spleens of malarial monkeys were used for a compliment fixation test for malaria, they gave a positive reaction with luetic sera. The standard antigen prepared from dried, frozen, thawed, and saline-extracted red cells with Plasmodium knowlesi, however, did not react. This appears to indicate a similarity in action between the two antigens, but not an identity. These authors point out that the Wasserman antigen is an alcohol-extractable lipoid whereas the malarial antigen is a saline-extractable protein. Babin and Dulaney (84), however, found in 1945 that when the compliment fixation (C.F.) test for malaria was done with ice-box fixation, the sera of non-malarious syphilitic patients gave a positive reaction. In paretic patients being treated with malaria, the C.F. test for malaria and the serological test for syphilis (S.T.S.) rose together. They felt that either the antibodies were closely related (but not identical because one could be absorbed without absorbing the other) or the

malaria has reactivated latent syphilis to make antibody by an anamnestic reaction. The latter explanation does not seem to apply to the false positive test for malaria obtained on the sera of non-malarious syphilitics. Charpy et al. (R) have discussed the false-positive S.T.S. reaction in cases where the absence of syphilis was assumed from the negative the Treponema immobilization test (T.P.I.). They found that "authors seem unaminous in recognizing that the positive reaction is not in direct relation to the temperature but to the degree of infection". (p. 196.) They felt however, that the explanation lies in several factors: (a) fall in compliment during paroxysm, (b) circulating autoantigens from tissue breakdown rich in lipid substances and capable of promoting the formation in vivo of anti bodies against lipids of the reagin type, and (c) anemia. They assumed that the presence of a positive T.P.I. in some of these cases proves infection with syphilis as well. They made no mention of possible similarity of antibodies.

The T.P.I. test provides some interesting possibilities for studying the antigenic relationship between malaria and syphilis. In this test the patients serum is incubated with Treponema pallidum suspensions in the presence of compliment. Thus if there is cross-antigenicity between malaria and syphilis and it involves the immobilizing antibody, one would expect the serum of a patient with malaria to give a positive T.P.I. reaction even if he did not have syphilis. One difficulty with trying to evaluate this possibility is that this test is the most accurate known for the diagnosis of syphilis; thus a patient who reacts positively is assumed to have latent syphilis. This was the case with the patients who had malaria who were discussed in Charpy's symposium (R).

Yet negative information is plentiful. Dagnet and Fribourg-Blanc (85) reported two cases of malaria with positive S.T.S.'s but negative T.P.I.'s. Chacko (86) reported a series of evaluations of T.P.I.'s in diseases other than syphilis, especially those which gave a false positive S.T.S. He found no positive T.P.I. tests in his malarial patients, but did obtain two in cases of leprosy. He was unable, however, to rule out syphilis absolutely. Benzet et. al. (87) reported the case of a soldier who had had many disease in Indochina but denied syphilis. He had been treated for these with drugs which were also treponemicidal. He had a negative S.T.S. two to three years prior to admission for malaria. He had S.T.S.'s which oscillated with the malarial attacks as expected, were negative at times, but were also positive at times other than during a malarial attack. The T.P.I. was always positive but only weakly so (one as low as 20% immobilization). The authors conclude that the S.T.S.'s were not always positive because of prior treatment, that the T.P.I. was weak for the same reason, and that the patient had syphilis. Dr. Nelson knows of no proven case of false positive T.P.I. in malaria (88). The lack of an inordinately high number of positive T.P.I. tests in patients with malaria indicates that there is not a strong cross-reaction of the antibodies involved in immobilization. It is still possible, however, that either the small number who do cross-react are being recorded as latent syphilitics, or some antigen-antibody system other than that related to immobilization is involved, or both. The answer will probably come only from a series of animals or patients who have negative T.P.I.'s before acquiring malaria and no chance of contracting syphilis from before the first test until late enough after the onset of malaria for the cross-reaction, if any, to appear in a second test.

5. Experimental Evaluations of the Humoral Antagonism of Malaria for Syphilis.

Early workers sought to explain the action of malaria by studying the effect upon Treponema pallidum of serum and C.S.F. from paretics who had been treated with malaria. As has apparently been common with other experiments in this field, the results are contradictory. Wagner von Jauregg (J) reviews three such experiments, the original descriptions of which are unfortunately unavailable. Those of Gallinek (89) and Benvenuti (90) were essentially the same. They incubated the serum of C.S.F. of paretics in remission after malaria therapy with treponemata and found that although there were more treponemicidal substances present after treatment than before, there were no more present than in that of normal patients. Injury to the spirochaete was judged by immobilization and failure to produce infection when transferred to rabbits. Lorant (91) also demonstrated factors producing immobility of spirochaetes to exist in the C.S.F. of paretics after malaria therapy, but found that when these "immobile" spirochaetes were injected into rabbits, they produced infection. Hoff and Silberstein (Q) demonstrated an increase in opsonin index for Staphylococci, Streptococci and E. coli in the serum of a paretic being treated with malaria was incubated with his leukocytes. Substances producing this increase (compared with that obtained from similar experiments with the serum and leukocytes of normal patients) were present from the first paroxysm on into remission. The same authors also incubated at 37° C. pieces of syphilitic rabbit testicle with C.S.F. and leukocytes of paretics before and after malariatherapy. The leukocytes were obtained from abcesses produced in the same patient who contributed the C.S.F. by the injection of turpentine! With the C.S.F. obtained after therapy they found immobili-

zation in 3 hours, and clumping and beginning lysis at 4 hours. No spirochaetes were to be seen at 24 hours. With the pre-treatment C.S.F., however, there was no immobilization at 6 hours. At 24 hours immobilization was complete and lysis had begun. They took samples of both groups at 3 hours and inoculated them into rabbit testicles. Lesions appeared in these rabbits injected with the spirochaetes which were incubating with pre-treatment C.S.F., but none appeared when the C.S.F. had been obtained after treatment. Several objections might be raised to this experiment. Either the pre-treatment C.S.F. was stored until after treatment before the experiment could be performed, or syphilis preparations from two different rabbits were used. In the former instance the active principal might have decayed. In the latter, the two spirochaete suspensions might contain different amounts of nutritional factors carried along from the rabbit with the spirochaetes. The protein in the C.S.F. of a paretic would depend on how long ago he had been treated. This objection applied just as easily, it may be suspected, to the experiments of Gallinek, Benvenuti, and Lorank, although the details of their procedures are not available. Wagner von Jauregg (J) reviews this experiment and concludes that it demonstrates no spirochaeticidal activity in the serum or C.S.F., but claims that "on the other hand, modifications in the reactions of the body against the spirochaetes after this treatment is evident". The leukocytes in this experiment were not stated to have phagocytized the spirochaetes; hence their activity if any was antigenic. The type of leukocyte involved was not stated; yet one would suppose that the injection of turpentine would call forth those cells found in acute inflammatory reactions rather than those cells involved in the

production antibody - i.e., neutrophils rather than plasma cells (or lymphocytes or monocytes). Hence the presence of the leukocytes may not represent such an agent of the modified body response as they were supposed to be the reviewer. It may be that the antibodies in the C.S.F. were still the more important factor. Wagner von Jauregg himself concludes that the action of malaria is a local one upon the pathological process in the brain. As evidence he cites the disproportional increase in albumen, amino acids and cells in the C.S.F., the local inflammation found in the brain after therapy, and the fact that certain latent syphilitics undergoing prophylactic malariatherapy for reactive C.S.F.'s develop tranient psychiotic symptoms resembling those of very mild paresis. Just what is reacting with what in this local reaction is not clear. Wagner von Jauregg's theory and his evidence seem valid, but neither provides anything like a final picture of the most exact mechanisms of action of malaria in the treatment of paresis.

One experiment which Wagner von Jauregg does not cite provides information which hints that malaria may have a more fundamental action against syphilis. In 1930 Horn and Kanders (S) noticed that when they tried to use for the routine passage of Borrelia recurrentis mice which had previously been inoculated with the serum and C.S.F. of paretics who had been treated with malaria, it was difficult if not impossible to infect the animals with the relapsing fever spirochaete. This chance observation prompted a series of experiments in which the serum and C.S.F. of paretics at all stages of malaria therapy was injected into mice and an attempt was made subsequently to infect them with relapsing fever. The original observations were confirmed and a step-like immune reaction

to relapsing fever demonstrated which was greatest in the C.S.F. at the height of the malaria. The reaction of the serum followed suit, but was less marked. No patient who did not have or had not had malaria produced this reaction. It was inferred that because Borrelia recurrentis is so closely related to Treponema pallidum, substances which antagonized Borrelia in the blood and C.S.F. of patients being treated for syphilis with malaria might also antagonize Treponema pallidum. Such antagonism might explain part of the modus operandi of malariatherapy.

It is perhaps noteworthy that all the patients who provided serum of C.S.F. for the above experiments had paresis. On the one hand, if one is trying to elucidate the mechanism of action of one disease on another, one should have both diseases present in one's experimental situations; on the other, a great deal of information can often be obtained by making several simple situations out of the one complex problem and studying one variable at a time. Thus it might have been advantageous to study the above experiments involving incubation with spirochaetes and prophylaxis of mice against Borrelia using the serum and C.S.F. of a patient who did not have syphilis but did have malaria. By this means any antagonism for treponemata of the Plasmodium itself or the products of the host's reaction to it alone would stand out in comparative simplicity. The coexistence of early syphilis and malaria in several recorded human cases indicates that direct antagonism of the two infections on a fundamental level must be mild if present at all, but the question of degree still remain open. If no such reaction occurred, of course, it would be necessary to attempt the isolation and investigation of another variable, such as the production of

anamnesis by malaria. Furthermore, such an investigation might well provide useful information in any case. From the preceding discussion it is abundently clear that there is more than one factor contributing to the mechanism of action of malariatherapy. Ideally, once as many variable as possible are understood, they should be combined.

The introduction of Plasmodium berghei has made research on these and other aspects of malaria much easier and more practical than was possible when most of the experimental work quoted above was performed. This malaria produces an acute or chronic infection in most rodents. Furthermore, the recent popularization of the golden hamster has provided an animal more practical than the ape which is susceptible to the acute or subacute forms of both syphilis and malaria. The need for further study of the biological antagonism of malaria for syphilis has been discussed previously; these newer developments provide the means.

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6. The Biological Antagonism of Malaria for Diseases Other Than Syphilis

The cure by spontaneous malaria of diseases of the central nervous system outside of those caused by syphilis has been mentioned in the chapter on the history of fever therapy. It seems from reviewing such cases that malaria is mentioned somewhat more frequently than other diseases. Boisseau's advice (page 3) that one should contract malaria for epilepsy, mania, and parlaysis might all refer to symptoms of paresis; yet they more frequently occur as

symptoms of other diseases. Likewise, "Melancholia" and "psychosis" were the most frequent diseases in which spontaneous remission was noted. As late as 1929 Marie (92), in addition to recommending malariatherapy for all forms of neurosyphilis, suggested its use in encephalitis lethargica,* especially in the postencephalitic phase which was the only remnant of the disease left at that time. He reported the success of Aguglia and d'Abundo in Italy with this disease and epilepsy, of which they achieved two cures. He found it of disputed value in non-organic psychoses.

In addition, however, to its rather general application to organic disease of the central nervous system, malaria seems to have a rather peculiar specificity for venerial disease. In treating syphilis it was found that the gonorrhea which so often accompanies this disease was remarkably sensitive. Investigation of the antagonism of malaria for Neisseria would therefore seem indicated. Spontaneous amelioration by malaria of other bacterial diseases** have not been frequent enough to cause much notice, unless one includes diseases which result indirectly. Sensitivity to the β haemolytic Streptococcus

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* Encephalitis lethargica = Epidemic encephalitis (ca. 1918-1923) = von Economo's disease

** At least one case, however, of the converse of this antagonism by malaria has been reported. Boyd and Coelo (93) describe the case of a negro who was inoculated with Plasmodium falciparum and did not have a normal parasitemia. He was cured of his mild disease with doses of quinine which would ordinarily have been sub-curative. A gas-bacillus infection of his perineum then became apparent. The authors suggest that the clostridial infection may have antagonized the development of the malaria.

may cause kidney disease finally resulting in nephrosis, the treatment of which by malaria has been tried with moderate success during the past few years.* Antibody of course, is also important in the pathogenesis of this disease, but as hypersensitivity rather than as the anergy of paresis. Yet here as in paresis, damaged capillary permeability is helped by malaria. Many non-specific stimuli are known to throw the nephrotic syndrome into remission. With considerable effort, a condition bearing some resemblance to human nephrosis can be produced in rats; the analogy is only fair. Yet work done with P. berghei in rats in this field might be useful in evaluating this form of treatment of this very serious chronic disease. Another group of diseases possibly benefited by malaria are the neoplastic diseases, the infectious nature of some of which has only recently been discovered. Tumors of chickens have been inhibited by Plasmodium lophurae. Forkner (95) has reviewed the antagonism of malaria for leukemia. Schupfer's intentional inoculation of a patient in 1905 has been mentioned (see p.7). Six subsequent investigators before 1938 confirmed this finding, and one did so with mycosis fungoides. Forkner thought that this might have therapeutic possibilities. Very recent work, however, has shown that abnormal cells from acute or granulocytic leukemias are more easily destroyed by heat than normal cells or those of chronic lymphatic leukemia (99). This would suggest that the fever of malaria may also be a factor in the improvement which it produces. In considering with what representative diseases the spectrum of biological antagonism of malaria should be tested in this series of

* It made the J.A.M.A. on January 7, 1956 (94)

of pilot experiments, leukemia was chosen as one. The suggestion of similar growth requirements of the plasmodium and leukemic process made by the fact that similar antimetabolites inhibit both caused the experiment to look fairly promising. Just before the mice arrived, however, Nadel et al. (T) published a similar article. Their reason for being interested was the same. With a large series of mice they found that when the malaria was given before the leukemia, there was no difference in the date of demise. Yet when the leukemia was inoculated first, the controls died in an average of 10.5 days while those with malaria lasted 12.5 days. Their only proof that some of the mice did not die of malaria was statistical: 18% were expected to die within 14 days of the injection of a very dilute suspension of mouse red cells parasitized by P. berghei. Chloroquinine might have been more certain. No studies were done on the effect of the injection of malarial plasma. Perhaps, therefore, such an experiment might be carried out in the future, using the intraveneous method outlined in Appendix I.

Mention has already been made of the possibility of the biological antagonism of malaria for spirochaetes other than the one causing syphilis. The results of the experiments of Horn and Kanders (S) indicate antagonism for Borrelia recurrentis, although interpretation is not certain because all patients from which malarial sera or C.S.F.'s were obtained also had syphilis, the antibodies to which might have been activated by the malaria. Leptospira icterohaemorrhagiae is also closely related to treponemata, but has the advantage for laboratory purposes that it can be grown on culture media. A hint

of close antigenic alliance to treponemata is provided by the observations of Rein and Elsberg (96) that 43.6% of 87 patients with Weil's disease had false positive serologies. Mohr, Moore, Nelson, and Hill (97) found a negative T.P.I.'s in animals injected with this organism.

Doctor David Weinman (U) first observed that when small inocula of cultures of Leptospira icterohaemorrhagicae actively growing on modified Noguchi's semi-solid agar medium, were placed in tubes with the serum or lysed red blood cells of mice or rats with Plasmodium berghei malaria, the Leptospira were killed and attempts to suboculture them in vain. These observations were confirmed by Marie-Louise Johnson (V) in who found "leptocidal activity" even at 36 hours. Protein fractionation was performed by salting out with $(NH_4)_2SO_4$, the salt was removed by dialysis, and the protein tested for activity against Leptospira by sealed coverslip technique. Greatest activity was found to be associated with the fraction precipitating at 18% $(NH_4)_2SO_4$ which consists largely of gamma-globulin.

The investigations described in this chapter, as well as those few clinical observations of double infection, suggest that malaria may be active not only against Treponema pallidum but against other organisms as well. In addition to the antagonism demonstrated for those organisms closely related to the spirochaete of syphilis, there appears to be a spectrum of action against such widely separated disease processes as bacterial infection, nephrotic syndrome, and leukemia. It is the purpose of this laboratory investigation further to determine the extent of this biological antagonism of malaria for

various representative microorganisms as well as to determine the extent of the role it may play in explaining the mechanism of action of the malaria-therapy of general paresis.

PART II

Experimental Investigations on the Extent of the Biological Antagonism of Malaria for various Representative Organisms

1. Experimental Results

I. Bacteria

A. Method.

"Swiss" mice moribund from Plasmodium berghei infection (Strain KBG 173) were exsanguinated by cardiac puncture. Coagulation was prevented by drawing 0.5 cc of 2.5% Na Citrate into the syringe before puncture. Average yield per mouse was 1.5 cc of citrated blood. The blood was pooled and spun for 30 minutes at 4000 RPM. In experiments, I, II, and III, the supernatent plasma was filtered through s Swinny filter adapter inserted between syringe and needle and 0.5 cc was used per tube. In experiment IV, 0.3 cc of supernate was used per tube after filtration through a Seitz suction filter. 8 cc of appropriate liquid medium were placed in clean Klett tubes and autoclaved. Thioglycollate broth was used for growing Cl. tetani, Dubos' medium for B.C.G., and beef heart infusion broth for the rest. Oleic albumen was added to cooled Dubos' medium. Thus the dilution of pure plasma, including correction for citrate, was about 1:25 for the first three experiments, and about 1:40 in the last. Tubes to which the plasma of normal "Swiss" mice was added were prepared in the same manner. All tubes were inoculated within a few minutes of each other with a loopful of bacteria (or a small particle of B.C.G.) obtained from the Department of Microbiology stock cultures. These were read immediately on a Klett meter with a green filter, the least dense tube (usually the malarial Dubos' medium) being used as zero. Thereafter the standardization knob was not readjusted. Uninoculated tubes of plasma containing beef heart infusion broth were used to control increase in density due to protein decay. The greatest

factor necessitation this control was the fact that normal plasma contains more haemoglobin (from haemolysis during processing) than does malarial plasma. Subsequent readings were made after stirring with a sterile loop.

B. Analysis

Correction of the differences found between the normal and malarial cultures was made for initial differences and for protein decay by calculating the "controlled difference."

If: N_x = Reading of the normal tube at time x

N_i = Initial reading of the normal tube at time x

N_{cx} = Reading of the uninoculated normal tube at time x

N_{ci} = Reading of the uninoculated normal tube initially

with a similar designation for tubes containing malarial plasma (M_x, M_i, M_{cx}, + M_{ci}), then, the "Controlled difference" (C.d.) is

$$C.d. = \left[(N_x - N_i) - (N_{cx} - N_{ci})\right] - \left[(M_x - M_i) - (M_{cx} - M_{ci})\right]$$

$$\text{or } (\Delta N_x - \Delta N_c) - (\Delta M_x - \Delta M_c)$$

Thus a positive C.d. indicates that the density due to bacterial growth in the tube containing the normal plasma is greater than that in the tube containing malarial plasma; that is, there is something in the malrial plasma which is inhibiting the growth of the bacteria. A negative C.d. indicates better growth in the malarial culture.

In dense cultures a given C.d. is less significant in terms of how many times as much growth there is in one tube than in another than it would

be in a more recently inoculated tube. To correct for this misleading situation, the "Significance factor", the quotient of the C.d. by the reading of the malarial tube, is calculated.

$$S.f. = \frac{C.d.}{M_x}$$

The sign is retained to indicate which tube is growing faster. Thus a S.f. with an absolute value of one indicates that one culture contains twice as much growth as the other. A rising S.f. indicates increase in the rate at which one culture is outgrowing the other; a constant S.f. indicates that such a rate is constant; and a falling S.f. indicates a decrease in such a rate, parallel growth with initial delay in one culture, or that the initially vigorous culture has ceased to grow as rapidly and that the other is catching up.

Owing to the small number of experiments in this series, true inhibition is indicated only by a relatively high S.f.. The single negative value having the highest absolute value of S.f. is $|-0.34|$; there are many positive S.f.'s with higher absolute values. Thus a figure such as .35 seems appropriate for the lowest value of the S.f. which shows inhibition with any reliably.

C. Results

Calculations attempting to evaluate Experiment I were not possible owing to contamination of a control tube. In Experiment IV mechanical difficulties with the Klett meter resulted in unstable standardization. The experiment was continued on the supposition that the density of the uninoculated

EXPERIMENT I

Organism	Tube	0	+19 hrs.	+26	+30	+41	+46	+64-1/2	+71	+89
Neisseria catarrhalis	M**	18	74	102	120	165	189			
	N**	45	97	101	120	157	187			
	c.d.**									
	s.f.**									
Salmonella paratyphi A	M	15	63	186	201	233				
	N	43	83	188	207	241				
	c.d.									
	s.f.									
Bacillus subtlis	M	17	73	116	144	202			310	
	N	41	81	101	120	168			307	
	c.d.									
	s.f.									
Bacillus anthracis	M	32	84	144	187	242				
	N	38	76	118	176	244				
	c.d.									
	s.f.									
Bacille Calmette-Guerin	M	10	27	31	39	46	56	68	70	91
	N	16	53	63	70	80	98	118	120	139
	c.d.									
	s.f.									
Clostridium tetani	M	43	99	121	196	322				
	N	85	206	238	303	435				
	c.d.									
	s.f.									
Control	M	42	*94	*113	*154	*208				
	N	47	82	95	98	133				

* Contaminated
** M = Malaria Plasma
** N = Normal Plasma
** c.d. = Controlled Difference
** s.f. = Significance Factor

EXPERIMENT II

Organism	Tube/Factor	0	+12-1/2 hrs.	36-1/2	48-1/2	62	84	110	132
Clostridium	M	45	60	126 no gas	155 no gas	222 gas			
tetani	N	51	59	138 gas	193 gas	390 gas			
	c.d.		-10	+5	+29	+152			
	s.f.		-.167	+.040	+.187	+.685			
Bacille	M	30*	50	55	63	71	95	115	146
Calmette-	N	zero	16	16	22	32	60	110	147
Guerin	c.d.	*	-7	-10	-14	-19	-22	-3	-1
	s.f.	*	-.140	-.182	-.222	-.268	-.432	-.026	-.007
Neisseria	M	13	21	24	36	47	65	142	188
caterrhalis	N	13	23	57	85	127	180	254	320
	c.d.		-1	+32	+46	+70	+98	+84	+103
	s.f.		-.048	+1.33	+1.28	+1.49	+1.51	+.592	+.548
β haemolytic	M	22	124	147	155	176	189	191	197
Streptococcus	N	16	124	167	181	192	210	234	240
	c.d.		+3	+25	+29	+12	+10	+21	+17
	s.f.		+.024	+.170	+.187	+.068	+.0529	+.110	+.086
Bacillus	M	22	47	52	45	45	54	83	93
subtlis	N	14	47	63	65	79	82	100	106
	c.d.		+5	+18	+25	+32	+19	-3	-21
	s.f.		+.106	+.346	+.555	+.711	+.352	-.036	-.226
Bacillus	M	14	85	77	81	96	86	81	91
anthracis	N	16	84	86	106	143	165	204	230
	c.d.		-6	+6	+20	+35	+60	+93	+105
	s.f.		-.071	+.078	+.247	+.365	+.698	+1.15	+1.15
Salmonella	M	17	100	146	180	214	209	232	242
paratyphi A	N	14	99	115	125	162	170	204	230
	c.d.		-1	-29	-55	-56	-53	-63	-41
	s.f.		-.010	-.199	-.306	-.262	-.254	-.272	-.169
No organism	M	15	19	6	12	26	18	18	18
(Control)	N	7	14	-1	7	28	27	38	42
	c.d.=0								

* Contaminated
** M = Malaria Plasma
** N = Normal Plasma
** c.d. = Controlled Difference
** s.f. = Significance Factor

EXPERIMENT III

Organism	Tube/Factor	0	+20-1/2 hrs.	32	43-1/2	55-1/2	70	80-1/2	92-1/2	120
Clostridium	M**	33	157	200	226	226	196	217	200	197
tetani	N**	29	152	182	201	224	216	184	188	196
	c.d.**		+8	-14	-19	+3	+27	-26	-4	+4
	s.f.**		+.053	-.070	-.084	+.013	+.138	-.120	-.020	-.020
Bacille	M	7	20	28	31	39	55	78	85	114
Calmette-	N	zero	16	21	27	39	73	88	94	138
Guerin	c.d.		+2	±0	+5	+8	+30	+20	+20	+32
—	s.f.		+.100	±0	+.161	+.205	+.545	+.256	+.235	+.281
Neisseria	M	16	15	17	16	26	45	50	63	79
catarrhalis	N	14	19	33	45	61	87	98	112	152
	c.d.		+5	+18	+23	+38	+47	+53	+55	+76
	s.f.		+.333	+1.06	+1.44	+1.46	+1.04	+1.06	+0.874	+.962
β haemolytic	M	17	131	137	143	139	151	145	149	149
Streptococcus	N	13	110	108	111	114	120	122	124	125
	c.d.		-18	-25	-26	-20	-24	-16	-17	-19
	s.f.		-.137	-.182	-.182	-.144	-.159	-.110	-.114	-.127
Bacillus	M	3	37	37	27	21	29	30	48	98
subtlis	N	7	38	37	33	30	49	64	60	103
	c.d.		-4	-5	+4	+6	+19	+33	+16	+2
	s.f.		-.108	-.135	+.148	+.286	+.655	+1.10	+.333	+.020
Bacillus	M	13	64	76	64	66	73	71	72	72
anthracis	N	37*	143	141	134	141	147	146	148	148
	c.d.	*	+54	+41	+46	+58	+53	+54	+56	+53
	s.f.	*	+.844	+.527	+.718	+.879	+.726	+.761	+.778	+.737
Salmonella	M	14	117	140	161	188	219	224	224	242
paratyphi A	N	7	127	134	160	187	214	214	222	228
	c.d.		+16	+1	+8	+7	+5	±0	+9	-6
	s.f.		+.137	+.0071	+.050	+.037	+.023	±0	+.040	-.025
No organism	M	17	19	17	15	17	22	21	22	22
(Control)	N	9	12	9	9	8	11	10	10	13
	c.d.=0									

* Contaminated
** M = Malaria Plasma
** N = Normal Plasma
** c.d.= Controlled Difference
** s.f.= Significance Factor

Experiment IV

Organism	Tube/Factor	0	+7 hrs.	+14-1/2	+37	+64	+88	+113	+136	+179
Clostridium tetani	M**	32	37	155	194	236	196	185	173	184
	N**	35	40	151	180	210	204	198	193	202
	c.d.**		+1	-14	-15	-26	+13	+16	+29	+24
	s.f.**		+.03	-.09	-.08	-.11	+.07	+.09	+.17	+.13
Bacille Calmette-Guérin	M	13	26	29	49	71	103	137	159	264
	N	zero	7	20	34	52	120	122	145	242
	c.d.		-5	-3	±0	-5	+38	+6	+7	±0
	s.f.		-.19	-.10	±0	-.07	+.37	+.04	+.04	±0
Neisseria catarrhalis	M	17	17	20	34	45	77	111	144	278*
	N	14	12	18	35	77	167	224	256	360
	c.d.		-1	-6	+6	+38	+101	+122	+132	+94*
	s.f.		-.06	-.30	+.18	+.84	+1.31	+1.10	+.92	+.34*
β-haemolytic Streptococcus	M	17	107	126	149	134	149	153	163	179
	N	21	107	132	144	140	138	150	153	173
	c.d.		-3	-5	-7	+5	-7	-1	-2	-1
	s.f.		-.03	-.04	-.05	+.04	-.05	-.007	-.01	-.006
Bacillus subtlis	M	24	25	40	51	49	89	97	103	128
	N	22	24	40	51	50	60	95	105	136
	c.d.		+2	-5	+4	+6	-19	+6	+12	+19
	s.f.		+.08	-.12	+.08	+.12	-.21	+.06	+.12	+.15
Bacillus anthracis	M	6	27	58	65	73	81	94	94	100
	N	8	24	53	43	52	57	67	64	72
	c.d.		-4	-14	-22	-20	-22	-23	-24	-21
	s.f.		-.15	-.24	-.34	-.27	-.27	-.24	-.26	-.21
Salmonella paratyphi A	M	15	92	104	126	177	174	190	202	243
	N	23	77	85	98	130	149	166	170	195
	c.d.		-22	-34	-34	-52	-25	-26	-32	-47
	s.f.		-.24	-.33	-.27	-.29	-.15	-.14	-.16	-.19
No organism (Control)	M	24	22	23						
	N	15	12	21						
	N-M				-2	-3	-8	-6	-8	-9

* Contaminated
** M = Malaria Plasma
** N = Normal Plasma
** c.d. = Controlled Difference
** s.f. = Significance Factor

Standardization of Klett meter was unstable. Therefore, only difference is recorded.

malarial culture remained constant. This assumption is reasonably valid in view of the initial lack of variation of this culture, and the similar constancy usually displayed by the analogous culture in similar experiments.

1. Clostridium tetani: Evidence of some inhibition in experiment I. Probably none.
2. Bacille Calmette-Guérin (B.C.G.): Experiment II contaminated. Significant inhibition in the 70-80 hour region. Not impressive elsewhere
3. Neisseria catarrhalis: Marked inhibition after a short initial lag phase in most experiments (not in I). All but I had some S.f.'s over one.
4. β-haemolytic Streptococcus: No significant inhibition.
5. Bacillus subtlis: Variable. Significant at about 70 hours in II and III. None in I and IV.
6. Bacillus anthracis: Variable. Significant inhibition in II and III, none in I and IV. The relative degrees, however, indicate some average inhibition.
7. Salmonella paratyphi A: Usually no inhibition. Malarial culture was even somewhat more dense in many instances.

D. Plate Experiments.

To warm flasks of agar, 5% citrated blood was added, and pour-plates made. In one series the source of blood was malarial rats, and in the other,

normal rats. The plates were then streaked with N. catarrhalis, beta-haemolytic Streptococcus, S. paratyphi A, and B. anthracis. No truly significant difference was observed in the size and number of the resulting colonies.

E. Pneumococcus III in vivo.

A blood-plate containing virulent colonies of Diplococcus pneumoniae type III was obtained from stock cultures , and sub-cultured into tubes of mouse blood-broth. 0.2 cc of culture were injected into groups of mice as follows:

Group I: 4 mice. Heavily infected with malaria 2 days ago, they were started on Chloroquine diphosphate i.p., 0.25 mg. q.d.. At the time of injection with pneumococcus, the blood had been almost cleared of parasites.

Group II: Received 0.62 cc i.p. each of the plasma of malarial mice just before inoculation.

Group III: Normal controls.

The organism was not so virulent as usual, for on the first day after inoculation, all mice were only slightly ill. On the second day, however, 2 of the post-malarial mice were dead and the plasma mice very weak. All appeared ill. On the third day, all were dead, and contained encapsulated diplococci in the peritoneal fluid.

Conclusion: No evidence of antagonism to type III pneumococcus can be found from this experiment. The earlier demise of the malarial mice can be explained by their weakness.

II. Toxoplasma

A. Method.

A mouse harboring the porcine strain of Toxoplasma was obtained from Dr. David Weinman. Peritoneal fluid was diluted, counted in a counting chamber for toxoplasma concentration and further diluted so that 0.1 cc contained 100 organisms. The total dilution was about 1:17,720. 0.1 cc (100 organisms) was injected i.p. into each of the following mice. This usually produced death in nine days.

Group I: 4 mice. Injected with malaria two days ago, now positive. Received 0.25 mg. Chloroquine i.p. on days, 2, 3, and 4.

Group II: 4 mice. Injected with 0.5 cc malarial mouse plasma i.p. on day 3. Three remaining ones got 0.67 cc on day 7.

Group III: 4 normal controls. Two of these got Chloroquine with Group I.

B. Results.

Group I: 2 died between day 7 and day 8, 11:30 p.m. - 9:30 a.m.
2 died day 8, 2:00 p.m.

Group II: 1 died day 7, 6:00 p.m.
1 died day 8, 6:00 p.m.
1 died day 8-9, 11:00 p.m. - 8:30 p.m.
1 died day 9, 2:30 p.m.

Group III: 1 died day 8, 10:00 a.m.
2 died day 8-9, 11:00 p.m. - 8:30 a.m. One received Chloroquine
1 died day 8, 3:30 p.m. Received Chloroquine

The peritoneal exudates of all dead mice contained Toxoplasma.

Conclusions: Malarial infection and malarial plasma have no significant effect on the course of toxoplasmosis in mice.

III. Leptospira

A. In vitro

Leptospira culture tubes used in this experiment contained about 2 cc of modified Noguchi's medium, and were positive for motile Leptospira icterohaemorrhagiae as shown in the following table. The filtered plasma of normal and moribund malarial mice was then added.

Table 5

Results

Tube #	Added plasma	Day 0	Day 3	Day 7	Day 10	Day 18
28	1.0 cc Malarial	4+	2+	Scarce	$\bar{0}$	$\bar{0}$
29	0.5 cc Malarial	3+	1+	1+	Rare	$\bar{0}$
31	0.1 cc Malarial	4+	4+	3+	2-3+	$\bar{0}$
32	1.0 cc Normal	2-3+	2+	2+	2+	$\bar{0}$
33	0.5 cc Normal	2-3+	3+	2-3+	2-3+	rare
34	0.1 cc Normal	4+	4+	4+	4+	2+

Conclusion: Both normal and malarial mouse plasma seemed to inhibit the growth somewhat, but the inhibition by malarial plasma appeared earlier, and was much more marked. This experiment confirms the previous findings demonstrating

a substance in the plasma of malarial mice which killed Leptospira. Here the dilutions of plasma by growing culture are much greater than they were in the former investigations. Comparison of the two experiments, therefore, in addition to the obvious data presented above, indicates that the "lepticidal activity" is increased with greater concentrations of malaria plasma.

B. In vivo

Method:

The strain of Leptospira icterohaemorrhagiae used in the above experiments proved to be non-pathogenic in 4 cc doses for hamsters and guinea pigs. A pathogenic PRD-1 strain was obtained through the great kindness of Dr. Ruth Miller of Woman's Medical College, Philadelphia. It produced a classical picture in guinea pigs with intense jaundice and many petechial haemorrhages into every organ. This strain would not grow on modified Noguchi's medium and was unfortunately lost after a few passages. Another sample of the same strain was again obtained from Dr. Miller, this time with the formula for Schuffner's modification of Vervoort's medium. This liquid medium consists essentially of a well buffered Ringer's solution and rabbit serum and haemoglobin. It supported luxuriant growth of the PRD-1 strain. Culture of a sample of heart's blood of a hamster injected with the culture from Philadelphia was positive even though the hamster was never symptomatic either before or after the sample was taken. This culture proved virulent for hamsters and guinea pigs and was the sourve of the Leptospira used in the following experiment.

The livers and spleens of two hamsters very ill with leptospirosis were ground with saline and found to be rich in Leptospira. Four hamsters which had recently been cured of P. berghei malaria with 1.25 mg. of Chloroquine diphosphate i.p. daily and sixteen normal hamsters were injected as indicated by the following table. Subsequently, each was injected with 4 cc i.p. of the leptospiral tissue brei. All plasma was fresh and had been passed through a Seitz filter for sterility and to prevent the transmission of plasmodia.

Results

Table 6

Substance injected	Hours of life after injection	Group average
1. 2.5 cc malarial rat plasma each at 0 hours	90 112	106.5
2. 2.0 cc malarial mouse plasma each at 104 hours	112 112	
2.5 cc normal rat plasma each at 0 hours	112 125 134 145	129
1.3 cc fresh malarial mouse whole blood each	102 112 112 125	113
Previously cured of malaria with Chloroquine	125 158 166 166	154
Controls	125 206 210 ∞ (living)	180

Conclusion: It is apparent from the above table that malaria has not been shown to exert a favorable influence on the course of leptospirosis in hamsters. It is difficult to explain why the control group fared so much better - especially why one is still alive. The hamsters were injected with leptospiral brei in the order shown in the chart, and perhaps the delay acted adversely on the organisms. Three of the hamsters in this group did not have the fulminating jaundice and petechiae present in the other groups. Because the control group reacted so unusually, the experiment should perhaps be repeated, this time with very fresh tissue rapidly inoculated. The inclusion of hamsters with acute malaria at the time of inoculation would be interesting.

IV. Syphilis

A. In vitro

Plasma for this experiment was collected by exsanguination of mice. 0.5 cc of 1:12500 heparin was drawn into the syringe before use to prevent coagulation. After centrifugation, the plasma was passed through a Seitz filter. Two serial dilutions were set up, one with malarial mouse plasma and one with normal mouse plasma. Guinea pig plasma was used as a source of complement. The Nichols strain of Treponema pallidum was obtained frozen in 15% glycerol from Dr. David H. Hollander, Johns Hopkins School of Public Health and Hygiene. It was passed in rabbit testicles or was maintained at -70° C. in 15% glycerol. The rabbit which provided the spirochaetes for this experiment had been inoculated with passage organisms about one month prior to use. They were extracted from the testicular tissue by mincing it into moderately small pieces with

sharp sterile scissors in a petri dish, washing it with saline, compressing the tissue against the edge of the plate, tipping the plate, and drawing off the fluid with a syringe. This produced a suspension very rich in spirochaetes but lacking in the tissue particles which made darkfield microscopy so difficult when the testicle is ground. The dilutions were set up as follows:

Tube 1: 0.375 cc mouse plasma + 0.125 cc compliment

Tube 2: 0.1875 cc plasma + 0.1875 cc compliment
0.25 cc removed, of which 0.125 cc was added to tube 3

Tube 3: 0.125 cc of the 0.25 cc removed from tube 2,
+0.375 cc saline. 0.25 cc removed.

Tube 4: 0.125 cc from tube 3 + 0.375 cc saline.
Remove 0.25 cc

Tube 5: Serial dilution in like manner.

Tube 6: Further serial dilution.

The addition of 0.25 cc of treponemal suspension to each tube produced the following dilutions of (mouse plasma) : (total) =—

1:2, 1:4, 1:16, 1:64, 1:256, 1:1024.

The solutions were thoroughly mixed and a fairly large drop placed on a slide, covered with a slip, and sealed paraffin. They were observed at intervals under the darkfield and percent motility recorded. (SEE TABLE NEXT PAGE).

Conclusions: This table indicates that in low dilutions, at least, the plasma of malarial mice exerts a distinctly detrimental effect of Treponema pallidum. The unfortunate presence of bubbles in the control slides prevents conclusions at higher dilutions. Bubbles in treponemal slides always cause rapid deterioration. The experiment was further complicated by the age of the infection in

Results

Table 7: % mobility

Dilution + Plasma	1 hour	3 hours	6-1/2 hours	12 hours
1:2 Malarial	100%	2%	0% lysis	
1:2 Normal	100	80	60 slow	
1:4 Malarial	100	95	40	0%
1:4 Normal	100	98	95	0
1:16 Malarial	100	90	50	2
1:16 Normal	100	25*	3*	0*
1:64 Malarial	100	90	50	0*
1:64 Normal	80*	35*	0*	
1:256 Malarial	100	90	60	0
1:256 Normal	80*	60*	0*	
1:1024 Malarial	100	50*	5*	
1:1024 Normal	0*	0*	0*	

* = Bubble developed.

the rabbit. At one month, certainly antibodies to the spirochaete were included in the testicular preparation. Indeed, some degree of agglutination* of spirochaetes was noticed even at the first hour on all slides. Yet this deviation from preferable technique was uniformly distributed, and hence the results are probably significant. Gradual immobilization hints that the T.P.I. antibody system is not involved. (88).

Another experiment was performed in similar fashion but instead of plasma involved red cells washed twice in saline. This experiment also differed from the above in that instead of using saline as a diluent, a mixture of one part complement to two parts saline was used. This kept the concentration of complement approximately equal in all the tubes. Also, the tubes were kept stoppered, incubated at 37° C., and samples were removed with a wire loop. The donor rabbit had just developed the first signs of orchitis, but had been infected about 20 days. The reason for the delay on the appearance of the orchitis was probably that the rabbit before it in the passage had had the infection for one month. Thus the treponemata with which this animal was inoculated, though motile, were probably more than 99% coated with antibody and only less than 1% survived. Hence there was more time for the development of antibody in the present experiment also.

The fractions in the following table indicate the number of motile treponemes over the total number which were counted. They were relatively

---

* This phenomenon has been described by McLeod and Magunson (98) who found that it occurred spontaneously with live spirochaetes but only in the presence of luetic serum when the spirochaetes had been killed. They suggested that this phenomenon would make the basis for a good test.

scarse on these slides, and were found at the rate of about one per minute.

Results

Table 8

Mobile Spirochaetes/Total number counted

Dilution + cells	4-1/2 hours	12-1/2 hours	33-1/2 hours
1:2 Malarial	6/10	0/10	
1:2 Normal	9/10?	1/10	
1:4 Malarial	5/10	0/10	
1:4 Normal	9/10	2/10	
1:16 Malarial	5/10	0/10	
1:16 Normal	5/10	2/10	0/5
1:64 Malarial	3/10	0/10	
1:64 Normal	4/10	1/10	0/10
1:256 Malarial		0/10	
1:256 Normal		2/10	1/10
1:1024 Malarial		0/10	
1:1024 Normal		1/10	1/10

Conclusions: This experiment indicates that a slight amount of inhibition of Treponema pallidum is associated with the malarial red blood cells as well as with the serum.

B. In vivo

Pilot experiments indicated that hamsters can be inoculated intratesticularly with ground rabbit testicles infected with T. pallidum and will develop a moderate syphilitic orchitis if kept at a low temperature.

Hamsters were divided into groups as indicated by the table below. Following inoculation with 0.5 cc of ground syphilitic rabbit testicle into each testicle, the hamsters were placed in a large cage at 5° C. Although the food was adequate, there was a high incidence of cannibalism to which eleven of twenty-six fell victim. As might be expected, those who were the weakest, the group infected with malaria at the start of the experiment, fared the worst and all were eaten. None of the animals were ever observed to hibernate. The hamsters were autopsied on the 17th to 19th day of the experiment and their testicles examined for spirochaetes. A piece of testicle was thoroughly mixed with a drop of saline on a slide, the large pieces removed, and the resulting extract examined. The number of spirochaetes which could be found in a fifteen minute search of the slide was recorded. The testicles of each hamster were examined for thirty minutes for spirochaetes, and the number found taken as an index of the degree of infection. In Table 9, the figures refer to the number of organisms per two testicles.

Results

Table 9

Malaria versus Syphilis *in vivo*.

Category	No. Spirochaetes/2 testes				Average per 2 testes
Malaria present at start	D	D	D	D	--
Malaria given on day 8.	3	10	70	D	28
2.5 cc malarial rat plasma i.p. each	0	1	2	0	3/4
2.5 cc normal rat plasma i.p. each	6	7	29	D	1/14
Malaria* inoc. 3 mos. ago	9	D	D		9
Malaria* inoc. 2 mos. ago	30	29	D		29.5
Controls	18	D	D	D	18
Normal uninoculated	0				0

* Treated with Chloroquine D = Died

Two things are striking about these results. The four hamsters receiving malarial plasma had only three spirochaetes amongst them, while the three receiving normal rat plasma has 42. Also, the finding of 70 spirochaetes in one of the hamsters treated with malaria is outstanding, although it must be discounted somewhat because it differs so much from the other hamsters in the group. It is unfortunate that all of the initially malarious and three of the control hamsters were devoured. We have no proof, of course, that they did not die of malaria or syphilis before they were eaten, but it seems less likely. Of the hamsters inoculated with malaria on day 8, all had parasitemia at autopsy. The heavy infection with syphilis in this group speaks against the

action of malaria against early syphilis in cases where the febrile element is minimized. Yet the marked effectiveness of malarial rat plasma in preventing the infection favors such an action. The experiment with passive transfer seems more striking and better controlled than the one with malarial infection. In an effort to explain these inconsistencies and to obtain adequate control the experiment should be repeated. The hamsters should be placed in separate cages in the cold room. These experiments indicate that previous infection with malaria has no prophylactic effect.

Appendix I

Laboratory procedures which may prove useful.

1. Leukemia

Leukemia L_{5178} was obtained through the kindness of Dr. Lloyd W. Law, Chief of the Leukemia Studies Section of the National Cancer Institute. This Leukemia has the advantage that the lymphoma which produced it has little stroma and hence is easy to grind. Injected subcutaneously, it produces a large tumor which kills in 3-4 weeks by invading the blood stream and producing an acute lymphatic leukemia. Intraperitoneally, it kills in 2-3 weeks. By both these routes, however, it tends to invade local structures. It was found that when the heart's blood of a mouse terminal with the leukemia produced by subcutaneous transfer of lymphoma tissue was injected into the tail-vein of a normal mouse, an acute lymphoblastic leukemia resulted. The intravenous injection of small amounts of finely-ground lymphoma tissue resulted in immediate neurogenic convulsions and death. The symptoms were similar to those produced by the intravenous injection of ground normal tissue or of toxotoxin. The effect was produced with small amounts too dilute to cause significant pulmonary embolization. L_{5178} has now been passed by the intravenous injection of heart's blood of a nearly dead animal about five times. As in other forms of this leukemia, the disease is specific to DBA/2 mice.* It now produces a

* Obtained from the Roscoe B. Jackson Laboratories, Bar Harbor, Maine.

lymphoblastic leukemia fatal in about 16 days. On autopsy there was vast splenomegaly, considerable hepatomegaly, and moderate lymphadenopathy. There was, however, no gross evidence of non-leukemic lymphomatous local invasion. It seems, therefore, that his leukemia is well adapted to use in studies of anti-leukemic activity.

Following these preliminary investigations, an attempt was made to study the possible antagonism of Plasmodium berghei for this leukemia. A strain of L_{5178} was obtained from the passage in DBA/2 mice of Dr. Arnold D. Welch. This strain, however, despite the identity of its original source with the leukemia studied previously, did not take well in either subcutaneous or intravenous form in the DBA/2 mice in this laboratory. Investigations with this leukemia are still in progress. It is hoped that active, passive, and prophylactic studies may be carried out.

2. Plasmodium berghei

In mice this form of malaria is acute, producing up to 70% parasitization of red blood cells. Mice usually die within eight days of inoculation with the diluted equivalent of two drops of blood. Chloroquine is effective in doses of about 0.25 mg daily if it is started before prostration occurs. In some cases, however, if administered too late, it will clear the blood of parasites but the animal will die of what is probably irreversable renal damage. The infection most closely resembles P. falciparum in man. In hamsters it produces a sub-acute infection usually fatal in about three weeks. In rats

it causes a moderate parasitemia which usually clears spontaneously.

3. Syphilis.

The method of intratesticular inoculation in hamsters may be of value. They are much less expensive than rabbits and are also more susceptible to other diseases. The results can be quantitated with relative ease. Keeping the animals at 5° C. was found to enhance the infection and was not so detrimental to the animal as might be supposed. This temperature was found more effective than 18° C. and in this experiment served the double purpose of suporting the infection and tending to counteract fever. The method of injection in the groin used by Hollander and Turner (29) was for some reason ineffective.

Appendix II

Suggestions for further study.

1. Adult rabbits are resistant to P. berghei. Hence the intraperitoneal injection of the whole blood of malarial rats should produce only antibodies. After waiting two days for any febrile reaction to subside, rabbits so injected should be injected intratesticularly with syphilis preparations. Delay in the development of orchitis as compared with rabbits injected with normal rat blood and the same syphilis preparation would indicate antagonism between malaria and syphilis on on antigenic level.

2. Further in vitro studies with malarial serum and cells should be carried out in the presence of the nutritional addatives used in the T.P.I. test.

3. The effect of Plasmodium berghei infection upon the capacity of rats to produce antibodies to various substances might be worth investigating.

4. If cell extracts of the parasite prove quite active, attempts to isolate and purify the principal might be rewarding.

5. The effectiveness in vitro of malarial preparations against Leptospira and the cure of malaria with anti-folics suggests a possible competition for folic acid. Folic acid antagonists such as Daraprim should be tried in experimental leptospirosis.

Summary and Conclusions

1. A review of the history of fever therapy indicates that spontaneous febrile diseases have frequently been reported associated with the improvement of coexisting disease. Mental disease was the condition most frequently benefited, and a good many of the symptoms of the improved cases might have been those of paresis. Many physicians produced suppurative infections in an effort to cure mental disease. Of all the febrile diseases found to have this beneficial effect, malaria was the most frequently reported. In 1876 Rosenblum may have inoculated mental patients, possibly paretics, with relapsing fever. His purpose in doing so is a matter of dispute. Yet he reported several remissions following this infection. In 1905 Schupfer achieved a remission in leukemia with inoculation malaria. In 1917 Wagner von Jauregg first inoculated a series of paretics with malaria and obtained the remissions he sought to produce. Since then malaria therapy of general paresis has been almost universally recognized as a very effective form of treatment.

2. There were many who contended that the action of malaria was dependent only upon the fever which it produces. This feeling prompted the introduction of artificial fever produced by mechanical means. Although there were many who argued to the contrary, a review of the evidence indicates that the most reliable and numerous opinions favored the results produced with malaria over those obtained with mechanical fever.

3. With the introduction of penicillin into the therapy of paresis,

the question of the value of retaining malaria therapy naturally arose. The weight of evidence indicates that in severe paresis and in primary optic atrophy, as well as in other forms of neurosyphilis refractory to other treatment, the combination of penicillin with malaria produces superior results. Penicillin plus malaria was found superior to penicillin plus mechanical fever. It should be emphasized that cases proposed for therapeutic malaria should be carefully examined and selected to make sure that there are no contraindications to its use. Thus therapeutic malaria is still a useful form of treatment, the mechanism of action of which would be well worth investigating.

4. Many have speculated as to the mechanism of action of therapeutic malaria. Action by fever alone has been discussed, and appears unlikely. What, in addition to the fever, explains the beneficial results has interested many investigators. The following theories are some of those which have been proposed: (a) stimulation by malaria of the reticulo-endothelial and haematopoetic systems promoting phagocytosis and the production of antibody; (b) further breakdown of the blood-brain barrier permitting antibody and chemotherapeutic agents to attack the causative organism; (c) forced drainage through the cerebral "lymphatics" (i.e., probably the perivascular spaces of Virchow-Robin); (d) increase in the capacity to produce antibodies caused by fever; (e) anamnistic response from malarial stimulation causing the "recall" of antibodies to syphilis; (f) conversion by malarial stimulation of a state of anergy towards the spirochaete to one of allergy; (g) stimulation of local reaction in the brain of the host tissue mechanisms to the spirochaete, the exact nature of which remains rather ill-defined by its proponent; (h) the

close antigenic relationship of malaria to syphilis has been proposed as evidence for the cross-reaction of antibodies produced to malaria with the spirochaete of syphilis; (i) nutritional competition of plasmodia with treponemata; (j) a biological antagonism of the two organisms involving cross-reaction of their antibodies and possibly the production by the plasmodia of other products toxic to the spirochaete.

Certainly the mechanism of action of malaria combines a great many of the above factors. The greatest number of these factors are best adapted to treatment of syphilis within the central nervous system. Hence the action is most noticable in this location. Precisely which of them are the most important is unclear; but fever, anamnesis, and biological antagonism have considerable in their favor.

5. Of the several attempts to investigate the action of malaria, all have involved a demonstration of antagonism for Treponema pallidum of the serum or C.S.F. of paretics who have been treated with malaria. Several have failed to demonstrate this antagonism; a few have succeeded. No studies of the antagonism for T. pallidum of the serum or infected cells of a malarial patient in whom syphilis can be ruled out are known to have been performed.

6. In addition, malaria has been shown to have a beneficial effect on other central nervous system diseases, gonorrhea, nephrosis, and leukemia. Previous studies in our laboratory have indicated that antagonism of the serum of rodents infected with Plasmodium berghei for cultures of Leptospira icterohaemorrhagiae.

Part II

The present investigations show an antagonism of malarial mouse plasma for the growth of certain bacteria, notably Neisseria catarrhalis. This finding might have significance in explaining the action of malaria against Neisseria gonorrhoeae infection. No antagonism of plasma or infection with malaria was found against Toxoplasma or pneumococcus infection in mice. The action against Leptospira was readily confirmed in vitro in even greater dilutions, but attempts to demonstrate any action against leptospirosis in hamsters were in vain. Both the plasma and parasitized red cells of mice infected with Plasmodium berghei were found to have some inhibitory effect on the motility of Treponema pallidum. Malarial rat plasma had a marked effect on inhibiting intratesticular infection in hamsters, but actual infection of the hamsters with malaria eight days after intratesticular injection of syphilis had no inhibitory effect upon the latter infection.

The advantages of intratesticular infection of hamsters with syphilis and intravenous inoculation of leukemia in mice are discussed. Further studies of the action of malaria, especially against syphilis and leukemia, are proposed.

It should be emphasized that the present studies should be regarded as pilot experiments which merely hint that the action of malaria against paresis and other conditions is partially on the level of fundamental biological antagonism of the two diseases. The numbers involved are so small and the variables so many that statistical significance of a great many of these experiments is doubtful.

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Note 1: An asterisk after an author's name indicates that his work was not read in the original, and the letter or number in parenthesis after the asterisk indicates one of the articles summarizing or making reference to this work. All of such works were not available in this library. When no reference is provided in such an article, the name of the article mentioning the fact is placed in the bibliography instead; e.g., Wagner, von Jauregg (B) mentions Galen, but gives no reference.

Note 2: The titles of all foreign articles are translated. Those of foreign books are not, in order to make reference easier.

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