MALARIAL TREATMENT IN THE EARLIER STAGES OF NEUROSYPHILIS *

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Modern methods in the treatment of neurosyphilis before the onset of dementia paralytica have met with a measure of success. Thus, signs of clinical activity may disappear and even a return of function can occur in nerve tissue provided that irreparable damage has not been done. But for patients who are totally or partially resistant to this treatment, alternative therapeutic measures should be sought and adopted.

By accepting the fact that non-specific fever therapy such as infection with malaria is the most effective form of treatment for dementia paralytica, the natural conclusion seems to be that this treatment might be as efficacious in the earlier stages of neurosyphilis, before the greater damage has been done to the nerve tissue by *Spirochaeta pallida*. Nicol (1942) has made the apposite remark that it is somewhat Gilbertian that this most helpful method of treatment should in the majority of cases be withheld from the patient until he has acquired the stigma of insanity and thus does not get his one chance of salvation until he falls into the dread hands of the psychiatrist.

From a review of the literature it appears that in Great Britain at any rate malarial treatment for the earlier forms of neurosyphilis, namely before the onset of dementia paralytica, has not been extensively employed. We have been unable to find any useful records in British literature, except those by Lees (1936), Nicol and Hutton (1937) and Nicol (1942). A few articles on this subject published in France and Germany have been reviewed by Driver, Gammel and Karnosh (1926), Ebaugh (1928) and Wile and Davenport (1931).

Rather more work in this direction has been done in the United States of America. Driver and his colleagues, Ebaugh, Wile and Davenport, Wile and Hand (1936), O'Leary (1937) and O'Leary, Cole, Moore, Stokes, Wile, Parran, Vonderlehr and Usilton (1938) have used malaria in the treatment of the various types of neurosyphilis before the onset of dementia paralytica. Most of the patients had had chemical treatment beforehand. These observers have claimed some success in the amelioration of the lightning pains and crises in tabes. O'Leary and Welsh (1933) consider that this treatment is especially useful for patients with progressive neurosyphilis who show negative reactions in the spinal fluid. On the other hand, Stokes and his colleagues (1932) have shown that at any time during the life history of *S. pallida* in the human body the spinal fluid may show abnormal changes without clinical evidence of disease (the so-called asymptomatic neurosyphilis) and that this condition was present in no less than 33 per cent of patients in the secondary stage of syphilis. O'Leary (1930, 1931), O'Leary and Welsh, Simpson (1935) and Kroll (1940) found that improvement or even reversal in the abnormal reactions of the spinal fluid occurred after malarial treatment in many patients who had proved resistant to ordinary antisyphilitic measures. O'Leary (1931), Simpson and Nicol and Hutton even recommend this treatment as a prophylactic measure in asymptomatic neurosyphilis.

The treatment of neurosyphilis with malaria

There is a mortality rate of from 2 to 10 per cent (Solomon 1928), associated with the malarial treatment of neurosyphilis, and this knowledge may be responsible for the lack of enthusiasm shown for the treatment. However, it should be

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remembered that the figures have been estimated from results obtained in patients actually suffering from dementia paralytica, which is a fatal disease. It was reasonable to suppose that if patients suffering from neurosyphilis before the onset of dementia paralytica were treated with malarial fever, the mortality rate should be much less than the figures already quoted. With this in mind we have used malarial therapy in a series of twenty cases of neurosyphilis before the onset

FIG. 1.
COMPOSITE AVERAGE HOURLY TEMPERATURE CHART
DURING A PAROXYSM OF MALARIA
(MADE FROM THE PATIENTS IN THIS SERIES).

of dementia paralytica. Three were of congenital type and five were of the acquired meningovascular type. Twelve patients suffered from tabes of whom two had additional optic atrophy. The majority of the patients had been thoroughly treated with tryparsamide and bismuth with little or no clinical or serological improvement. Before embarking on malarial therapy care was taken that patients were well nourished and were not suffering from infective or debilitating diseases. Especial care was taken to exclude patients who had gross infection of the bladder or in whom there was evidence of damage to the cardiovascular, renal, or hepatic systems.

A therapeutic malarial attack can be induced either by the bites of mosquitoes infected with the parasite of benign tertian or quartan malaria, or by the injection intravenously or intramuscularly of about 4 cubic centimetres of blood taken from a patient infected with one of these two types of parasite. If a suitable donor is not available locally, infected defibrinated blood will be sent on request to the Medical Superintendent, Malarial Laboratory, Horton Emergency Hospital, Epsom. It should be used immediately it is received. Neither method of infection has any real advantage over the other and we relied solely upon the latter. Care should be taken to ensure that the syringe used for injecting the infected blood is dry-sterilized or is thoroughly washed out with cold sterile normal saline solution in order to avoid traces of antiseptic which might kill the parasite. Not one of our cases failed to become infected, although two had to receive a second inoculation. The incubation period varied from eight to fourteen days. The questions of the degree of pyrexia and the number of paroxysms allowed, as affecting the final results, were studied. In some instances the paroxysms occurred every day or every second day, occasionally every third day, depending presumably on the presence of plasmodia of different life cycles. The highest temperature rarely exceeded 105° F.

Difficulty was not experienced in maintaining the infection for as long as was desired. We did not notice that the onset of the febrile course was delayed or that the temperature curves were lowered on account of the previous arsenical therapy. Examination of blood smears for a sudden increase in the number of parasites gave useful information concerning the intensity of the infection. Interruption or modification of the paroxysms with small doses of quinine owing to untoward symptoms such as a rapid fall in blood pressure or a rise of urea in the blood were found to be unnecessary. There were not any signs of marked debility or of loss of weight; severe vomiting, diarrhoea, severe anaemia and jaundice did not occur. Mild delirium developed in a few patients at the height of the paroxysms. Several suffered from herpes, and one or two from a transient

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albuminuria. Driver and his colleagues have called attention to a state of toxic psychosis which may develop during the malarial infection. One of our patients was an example of this, and although symptoms such as lightning pains improved, a month later he made a half-hearted attempt to commit suicide. Although during a paroxysm some patients appeared to be ill, rapid improvement took place when the temperature subsided and at no time did the condition of any patient give rise to serious anxiety.

Difficulty was not experienced in finally terminating the malarial infection. This was effected by giving quinine hydrochloride, 10 grains, twice daily for three days, and half this dose daily for two weeks longer. Recurrence of the malarial infection did not take place. Iron was always given for the slight degree of anaemia which invariably occurred.

After leaving hospital all the patients thus treated attended for regular clinical and serological examinations. O'Leary and his colleagues (1940) have found that serological reversal rates in the cerebrospinal fluid and blood in dementia paralytica treated with malaria are nearly twice as great with the use of subsequent chemotherapy. Therefore we thought it advisable to follow up the malarial infection with chemical treatment, regulating the dosage and frequency of its administration by periodical clinical and laboratory examinations. Whether the final results in our series are due to the malaria alone, or whether it is possible with malarial treatment to render an arsenic-resistant patient sensitive to subsequent chemical therapy is still obscure.

The most striking clinical improvement occurred in the congenital and acquired types of meningovascular syphilis. In the former the most notable feature was the marked intellectual improvement which became apparent soon after the termination of the infection, together with a diminution in number or even an actual cessation of the convulsions. Thus within a reasonable time these patients were able to begin responsible work. On the other hand, O'Leary and Welsh and Wile and Hand have found infection with malaria disappointing in congenital neurosyphilis, and they consider that its use in this type of syphilis as a regular therapeutic measure is not justified. In the tabetic group the outstanding feature in patients who did improve was the rapid amelioration and often the disappearance of the lightning pains and crises which took place during or soon after the course of the malarial infection. Yet Driver and his colleagues have called attention to the aggravation of these symptoms during the pyrexial period. Three patients suffered from difficulties of micturition, but these cleared up after malarial treatment. This does not agree with the findings of Moore (1931) and Wile and Hand, who have called attention to the likely ill effects of malarial treatment on patients with urinary affections. Marked ataxia was a prominent condition in six patients in our series. Improvement or even disappearance of this occurred in all but one after malarial treatment with subsequent physiotherapy. We have found however that this condition so often improves with re-education and suggestion that a functional element may be a factor. Libido once lost was not regained in any of our patients. Two suffered from tabes accompanied by diminished vision due to optic atrophy. Whereas the lightning pains improved after malarial therapy, the vision continued to deteriorate; this is an experience common to many observers. O'Leary (1931), however, had better fortune. He treated with malaria nine cases of syphilitic optic atrophy; at first the condition progressed in all patients, but later clinical arrest occurred in four. Clark (1936) reported twelve similar cases in which the patients were treated in an identical manner, eight benefiting.

Change did not occur in physical signs such as fixed irregular pupils and pathological reflexes. This is not surprising because a therapeutical agent is not likely to regenerate nervous tissue which has undergone actual destruction.

The second criterion in assessing the value of malaria in the treatment of neurosyphilis is the extent of the change which may take place in the cytology, chemistry and serology of the cerebrospinal fluid. For the state of a patient

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cannot be considered really satisfactory unless the laboratory findings assume and retain a normal picture.

In the majority of the cases in this series a marked improvement in the cerebrospinal fluid, amounting in some patients to a total reversal, occurred after malarial infection and subsequent chemical treatment. The correlation, however, between the clinical and the laboratory findings has not been the experience of all observers. Thus, O'Leary (1927), Wile and Davenport and Wile and Hand find that no

TABLE
Results of treatment with Malaria in 20 cases of Neurosyphilis

Result of treatment	Meningovascular Syphilis		Tabes	Tabes with optic atrophy
	Congenital	Acquired		
<i>Clinical—</i>				
Much improved ...	3	5	4	—
Improved ...	—	—	3	—
Not improved ...	—	—	3	2
<i>Cerebrospinal fluid—</i>				
Reversed ...	—	4	2	—
Improved ...	3	—	4	2
Not improved ...	—	1	4	—
<i>Blood—</i>				
Reversed ...	1	1	3	—
Improved ...	2	2	6	—
Not improved ...	—	2	1	2

constant parallelism exists between the clinical improvement and the change in the state of the spinal fluid. On the other hand, Matz (1928) found that after malarial treatment followed by chemotherapy with satisfactory clinical results, the cytology of the spinal fluid was benefited in 82 per cent of 279 patients. Thus the globulin content became negative or was reduced in 70 per cent; the Wassermann reaction changed to negative or was modified in 60 per cent and the colloidal gold curve improved in 54 per cent.

So long as active syphilitic processes are taking place in the nervous tissue they will be reflected as a rule in the state of the cerebrospinal fluid. On the other hand even a reversal in the reactions of the spinal fluid is no guarantee that active disease is not present, for a negative serological reaction in the fluid may be recorded even when there is a localized gummatous lesion or a smouldering plaque of meningitis in the more remote parts of the brain or of the spinal cord. O'Leary and his colleagues (1938) reported on a group of tabetics who showed a satisfactory serological response in the spinal fluid; and yet in only 26 per cent of the patients was the disease clinically arrested. Solomon and Epstein (1936) have experienced similar results. In five of our patients the clinical condition progressed unfavourably in spite of improvement in the spinal fluid. Nevertheless periodical examinations of the spinal fluid must be regarded as one of the best guides with which to direct the therapeutic course in neurosyphilis.

O'Leary and others (1938, 1941) have found that clinical and pathological progress of the disease is greater among patients in whom are present the more severe abnormalities of the spinal fluid which occur in the so-called "paretic" type. In our series thirteen patients showed a paretic change in the spinal fluid before malarial and chemical treatment, yet afterwards an improved clinical state occurred

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in eleven, with improvement in the condition of the spinal fluid in ten. After malarial treatment a change in the serology of the blood towards negativity occurred in fifteen of our patients. Such a reaction in the blood does not of course necessarily reflect the true state of the spinal fluid. Hence, the information obtained from serological examinations of the blood alone in an effort to establish or to confirm the diagnosis of neurosyphilis or to control treatment can be fallacious. It is, however, important to obtain a reversal if possible of a positive serological reaction in the blood because this indicates that the further spread of infection may be prevented.

Summary and conclusions

(1) Twenty cases of active neurosyphilis before the onset of dementia paralytica have been treated by infection with malaria. Previously, most of the patients had been treated energetically with antisyphilitic measures without material clinical or serological benefit.

(2) Progress of all the patients has been followed and they have been examined periodically, both clinically and pathologically. Further chemical treatment has been given when considered necessary.

(3) After combined malarial and chemical treatment, clinical improvement has taken place and has been maintained in fifteen patients, together with improvement in the condition of the cerebrospinal fluid and in the blood serum reactions.

(4) It is suggested that malarial therapy has a place in the treatment of selected patients suffering from the earlier forms of neurosyphilis and that venereal disease clinics should be situated at or affiliated to hospitals where facilities for this form of treatment are available.

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Penicillin used in the treatment of early syphilis

J. F. Mahoney, R. C. Arnold and Ad. Harris report that after proving the usefulness of penicillin in treating syphilis in animals, they decided to study the drug's effects on early syphilis in human beings. Four men, each having a single penile ulceration, were given intramuscular injections of 25,000 units of penicillin at four-hourly intervals for eight days. Forty-eight injections were given and 1,200,000 units of the drug were used. The gluteal muscle was the site for the injections. During the first eight hours of treatment some clinical manifestations were observed, but the symptoms did not show any toxic response to the drug. A comprehensive routine of serodiagnostic tests was employed. After treatment, a long period of observation is essential. If the satisfactory results are confirmed, it may become necessary to change syphilis therapy using penicillin as the base.—*Venereal Disease Information, Washington*, December, 1943.