TREATMENT OF NEUROSYPHILIS

A COMPARISON BETWEEN MALARIA PLUS TRYPARSAMIDE AND MALARIA THERAPY*

By W. D. NICOL, M.B., F.R.C.P.

From the Malaria Therapy Centre, Horton Emergency Hospital, Epsom, Surrey

In 1937, as a result of the investigation of 458 cases (320 men and 138 women), Dr. Hutton and I brought to the notice of the Society three aspects of the problem of neurosyphilis (Nicol and Hutton). The first was the employment of ordinary antisyphilitic treatment (mainly the use of trivalent arsenicals) with its detrimental effect on the subsequent course of the disease. The investigation of this group made abundantly clear the importance and absolute necessity of performing a lumbar puncture in all late and latent cases with a persistent seropositive Wassermann reaction. The second aspect of neurosyphilis to be examined was the evidence of syphilis in partners and in the families of patients undergoing treatment; it was demonstrated that the amount of evidence of latent neurosyphilis was surprisingly great. Lastly, a glimpse into the future was taken; we advocated the use of malaria in preference to other forms of therapy, although it was agreed that in certain circumstances treatment with pentavalent arsenic, in the form of tryparsamide, provided efficient treatment. The importance of using malaria therapy or tryparsamide for the latent case of neurosyphilis, as a prophylactic against the subsequent development of general paralysis, tabes, or both, was stressed.

Now, after nine years, Dr. Whelen† and I want to lay before you our views in the light of further experience. Although the Malaria Therapy Centre continues to work at full pressure, it is a matter for regret that six years of war have necessarily reduced facilities for research. Dattner, Thomas and Wexler¹, in their excellent work on neurosyphilis, say categorically that "for determining the choice of therapeutic methods, and for evaluation of their success, the spinal fluid syndrome is a far better guide than clinical symptomatology". With this dictum we are in entire agreement; indeed, we would say that once a complete reversal of the reaction of the cerebrospinal fluid is obtained, no further treatment is necessary.

After reviewing our clinical material, we have selected two main problems for discussion. First, should malaria therapy be supplemented by chemotherapy? Secondly, what lesson can be learned from the study of the serology of patients treated for neurosyphilis?

The material under review

When the Malaria Therapy Centre was established at the Horton Hospital 21 years ago, it was decided that the efficacy of malaria as a therapeutic agent should be given a trial; consequently no post-malarial therapy was administered. As was reported in 1937 by Nicol and Hutton, the results appeared to be satisfactory, and they compared favourably with those of other workers. The majority of clinics, however, gave chemotherapy as well, and it was decided that a trial might well be made of supplementing malaria with a course of tryparsamide. Accordingly, all patients admitted between the years 1933 and 1936 were treated with malaria plus chemotherapy; the number of cases was 127 men and 90 women. The course of tryparsamide consisted of 22 grammes, 8 injections in all; the first consisted of 1 gramme, and this was followed by 7 injections of 3 grammes at weekly intervals. Eight patients, however, received more than one course, the additional amount ranging from 30 to 50 grammes, and one patient received 96 grammes.

Because the serological data of the malaria-treated cases prior to 1933 were somewhat incomplete, especially in the matter of follow-up, it was necessary, in order to make a fair comparison, to treat a similar series with malaria only. This was carried out between 1936 and 1938; the cases were consecutive admissions

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†For Dr. Whelen's paper, see p. 121.

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and quite unselected. The total number of cases under review is, therefore, 434. Patients who exhibited an intolerance of tryparsamide, and for whom the course, therefore, had to be discontinued, are also excluded from the series. In all cases in each series the results of examination of the cerebrospinal fluid were strongly positive: Wassermann plus, increased cells and protein and paretic Lange curve. The clinical diagnosis is recorded in Table 1.

TABLE 1—CLINICAL DIAGNOSIS AND METHOD OF TREATMENT

Type of neurosyphilis	Malaria plus tryparsamide		Malaria only	
	Men	Women	Men	Women
General paralysis... ..	116	72	98	79
Taboparesis	9	11	19	5
Congenital general paralysis	2	6	9	4
Congenital taboparesis	—	1	1	2
Totals ...	127	90	127	90

With rare exceptions each patient had a course of malaria from one species only. The species employed were benign tertian, quartan, malignant tertian and infection caused by *Plasmodium ovale*; *P. knowlesi* (monkey malaria) was used for three patients. The average number of peaks of fever aimed at was 10, although this was not possible of attainment in every case. Temperatures of 103° F. and over were counted as peaks of fever. To some of the patients receiving quartan malaria infection, tryparsamide was given during the fever.

Patients have been followed up after discharge as far as possible, although the evacuation of population and the war damage sustained in London have made this difficult. In spite of these drawbacks, however, a large proportion of ex-patients have been in contact with us over periods of 10-12 years.

Clinical results

The clinical results obtained are shown in Table 2.

TABLE 2—RESULTS OF TREATMENT IN 217 CASES

Patients' histories	Malaria plus tryparsamide		Malaria only		Combined treatment	Malaria only
	Male	Female	Male	Female	Total	Total
Discharged and not readmitted	68 (54%)	42 (47%)	52 (41%)	38 (42%)	110 (52%)	90 (41·5%)
In hospital	25 (19%)	30 (33%)	19 (16%)	12 (13·5%)	55 (26%)	31 (14%)
Dead	34 (27%)	18 (20%)	56 (44%)	40 (44·5%)	52 (24%)	96 (44·5%)
Totals ...	127	90	127	90	217	217

Fig. 1 illustrates more clearly the present picture of the results of the two methods of treatment. These figures show a significant difference in favour of the malaria-plus-tryparsamide series: 9 per cent more are discharged and—what is even more remarkable—20 per cent fewer have died.

If an analysis of discharged patients relative to clinical types is made, there is no significant difference in the malaria-treated patients with general paralysis between the two sexes, but in those paralytics treated with malaria plus tryparsamide, 9 per cent more men than women recover. The figures for taboparesis and for the congenital cases are too small for comparison.

In the figures for deaths no significant difference is detectable in the two sexes in regard to cases of general paralysis, but in the taboparetics the death rate amongst the men is high (65 per cent, for both malaria-treated cases and cases treated with malaria plus tryparsamide; in women the death rate is distinctly lower, being 40 per cent for malaria-treated cases and only 28 per cent for those

treated with malaria plus tryparsamide. Combining all the clinical types treated, there is no difference between the males and females in the death rate for the malaria series, but of the patients treated with malaria plus tryparsamide 7 per cent more men have died.

Fig. 1. Comparative results of malaria therapy alone and combined with tryparsamide administration. M. = malaria alone ; M.T. = malaria + tryparsamide.

Fig. 2. Comparative study of deaths occurring in the course of treatment. Black areas = malaria alone ; hatched areas = malaria + tryparsamide.

Among the discharged patients a total of 11 are known to have died ; of these 3 were in the malaria and 8 in the malaria-plus-tryparsamide group. All those ex-patients died of intercurrent disease ; indeed, 2 men in the tryparsamide series were killed in the recent war (one in the Royal Air Force and the other in the National Fire Service during the "blitz") and one man (malaria only) was a fatal air-raid casualty. Admittedly, some of the patients retained in hospital died

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of intercurrent disease, but the vast majority have died within 5 years after treatment, the cause of death being general paralysis or taboparesis. The chart in Fig. 2 illustrates the death rate year by year.

Serological results

Coming to the serological results obtained, we are at once met by the difficulty that the second group of cases (malaria therapy only) has been much better followed up; it was not until 1937 that lumbar punctures at regular intervals became a routine follow-up at Horton, but, on the other hand, patients of the former

Fig. 3. Final assessment of cerebrospinal fluid reactions.

Black areas = cases treated with malaria only.

Hatched areas = cases treated with malaria + tryparsamide.

group who have had tests since treatment have been followed up for a longer period. We have been impressed with a recent paper by Dattner, Thomas and Wexler² and a subsequent letter by Thomas, in which the authors stress the need for rapid treatment and for the complete cessation of any further therapy if, 6 months after malaria treatment plus chemotherapy, the cerebrospinal fluid has

TABLE 3.—CEREBROSPINAL FLUID EXAMINATIONS

Reactions	Cases treated with malaria plus tryparsamide	Cases treated with malaria only
Negative	129	106
Inactive	14	36
Weakly positive	2	7
Positive	25	54
No further test	47	14
Totals ...	217	217

normal cells and normal or greatly reduced protein. This type of fluid is termed “inactive”, and in course of time (5-8 years) the Wassermann and colloidal gold reactions become negative, thus resulting in a completely normal cerebrospinal fluid.

The present state of our knowledge regarding cerebrospinal fluid examinations comprises 170 cases in the first series and 203 cases in the second series. Table 3 shows the position.

It is a matter for regret that we are not in a position to give more accurate information about the first series, but we feel justified in drawing certain conclusions in all cases of patients who have been followed up and who are out of hospital and well 3 years or more after treatment; this applies to cases with positive reactions in which the fluid was not re-tested after 6 months and to cases which were never tested. The number of cases in the first series is 72 and in the second series 68.

Among the malaria-treated cases are 20 patients who made good recoveries and whom we followed up for periods of 3-12 years; their reactions are almost certainly negative; 45 have died within 3 years of treatment and it is assumed that the fluids were still positive at death; 3 have never been followed up. Applying similar tests to the first series, the reactions in 30 cases are negative; in 25 they remain positive; 3 patients discharged in an unsatisfactory condition were lost sight of and their reactions are included in the positive group; 14 other discharged patients were not followed up. This revised estimate is shown in Fig. 3, the hatched areas representing the adjusted figures.

A further analysis was made (see Table 4) in which are recorded the examinations made at the end of 6 months and then each subsequent year. It will be noted that

TABLE 4.—EFFECT OF TREATMENT ON THE CEREBROSPINAL FLUID REACTIONS OF MEN AND WOMEN

Time after treatment	Strongly positive		Weakly positive		Inactive		Negative		Number of examinations	
	M	M+T	M	M+T	M	M+T	M	M+T	M	M+T
6-12 months ...	87	23	28	7	37	6	16	2	168	38
1 year ...	49	11	21	12	51	12	25	6	146	41
2 years ...	30	13	10	10	38	20	39	27	117	70
3 years ...	22	9	8	13	23	26	26	51	79	99
4 years ...	8	7	3	4	11	19	30	52	52	82
5 years ...	2	3		1	10	7	26	48	38	59
6 years ...	2	1	1		4	6	23	31	30	38
7 years ...		1			4	3	22	30	26	34
8 years ...		1			1	1	17	23	18	25
9 years ...							8	22	8	22
10 years ...								10		10
11 years ...								5		5
12 years ...								2		2
									682	525

M = Malaria only. M+T = Malaria + trypanamide

with the trypanamide-treated cases no serious attempt to evaluate the serological results was made until the end of the third year; nevertheless, it is possible to present in a graph the positive and negative findings as seen year by year. (See Graphs 1 and 2.) The examinations at yearly intervals do not relate necessarily to the same patients, but are rather a sample or cross-section of the patients under review year by year. If the advice of Dattner, Thomas and Wexler² is followed,

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then over 50 per cent of cases in both series should have been re-treated at the end of 6 months ; we maintain, however, that this has not been necessary in the light of experience, although we are satisfied that all patients with a positive reaction at the end of a year require further treatment.

GRAPH 1

POSITIVE CEREBROSPINAL FLUID REACTIONS EACH YEAR

PERCENTAGES

Persistently positive reactions of the cerebrospinal fluid

What factors are there which might explain these positive reactions of the cerebrospinal fluid ? Is there any relative difference according to the sex of the patients ? There is no doubt that the percentage of fluids continuing to give positive reactions is decidedly greater in women than in men, and that this tendency persists up to 4 years : in fact, at the end of 4 years a positive reaction is nearly 3 times as common in the female as in the male. Moreover, although the number of positive reactions is considerably less in the tryparsamide series, the relative ratio between women and men remains the same. Blalock and Hinsie, in an extensive review of the serology of general paresis, do not find any material difference in the cerebrospinal fluid reactions between the two sexes, but they do state that with regard to the blood Wassermann reaction twice as many men as women show negative reactions during the first 3 years after treatment, this ratio altering in favour of the women after the fourth year.

Are positive reactions in the cerebrospinal fluid more likely to occur in those patients who have had a relatively short course of malaria ? It has been customary to regard 10-12 peaks of malarial pyrexia as an adequate course of treatment. We have examined those patients who had less than 6 peaks above 103° F. One might have considered that some of those cases were inadequately treated ;

alternatively, one might expect fewer positive reactions in such patients as had had a supplementary course of tryparsamide. However, on analysis there is no suggestion that patients not so thoroughly treated as those having 10 or more peaks are more prone to retain a persistently positive fluid. Indeed, it is found that of 26 malaria-treated cases with less than 6 peaks of fever, a complete reversal of the cerebrospinal fluid reaction was obtained in half the number.

GRAPH 2
NEGATIVE CEREBROSPINAL FLUID EXAMINATIONS EACH YEAR

We know that many patients with a positively reacting fluid died within a year of treatment ; but what happens to those patients who survive and whose fluid reacts positively at the end of 2 years ? Of 13 such cases in the first series and 30 in the second, 7 and 20 patients subsequently died. Of the 10 patients remaining alive in the malaria-treated series, 6 were re-treated with a second course of malaria ; in all except one a negatively reacting fluid developed ; in the exception the reactions remained positive and the patient died soon after the second course ; the other 4 patients received no further treatment, and in 2 cases inactive reactions developed, but the reactions in the other 2 became negative. In the tryparsamide series, in the 6 patients who survived, the reactions in all cases eventually became completely negative without further treatment. It is, however, a very small percentage of patients, who, if deprived of further treatment, survive to behave in this manner and become spontaneously negative. On the other hand, it is rare to find cases resistant to additional therapy ; but such cases do occur, as is illustrated by the following example.

F.H. (M.389), aged 46 years, suffering from general paralysis, was given benign tertian fever, 7 peaks. The cerebrospinal fluid was examined at six-monthly intervals and remained persistently positive. At the end of 2 years he had a course of malignant tertian, 10 peaks. At the end of 4 years there was no change whatever in the serological reactions, so quartan was then administered, 7 peaks. It was not until 3 years later that the fluid became inactive and the last test at the end of 1944 was negative. This man has been out of hospital since the first course of therapy in 1938 and is now working in a factory.

The occurrence of serological relapses in the two series is very small : 2 in the malaria group and 3 in the other series. Of these relapsed cases, 4 patients had a single negative result, all showing strongly positive reactions a year later ;

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the fifth case had an inactive fluid, which reverted to positive, but after further treatment became inactive again. In no patient who had 2 consecutive negative results did any serological relapse occur, as recorded by subsequent tests.

Toxic manifestations

Brief mention must be made of the toxic reactions which occur in tryparsamide therapy and which give rise to considerable alarm. In our series, of 10 patients who began to receive a course of tryparsamide, one exhibited nitritoid reactions, one had jaundice, and 8 had misty vision, 2 being blind for several days. (The visual fields were not examined.) In all cases toxicity was detected before 3 injections had been given and the medicament was discontinued immediately. None of these cases has been included in the series discussed, so the incidence of toxicity is 10 cases out of 227, or about 4 per cent.

The incidence is very much lower than that reported by Downs, McDermott and Webster, who report visual reactions in 93 cases out of a series of 223; of these 41 were subjective, but contraction of the visual field was demonstrable in the other 52. Kopp and Solomon report a much larger series (829 patients); in 4.5 per cent of their cases visual disturbances developed: half the number of patients so affected had symptoms during the first 5 injections.

Discussion

On examination of both clinical and serological results, it is seen that patients treated with malaria plus tryparsamide do better than do those given malaria only. Although in both series the fluid becomes negative in a large proportion of those who survive, the fact remains that the death rate is higher in the malaria series, and that the cerebrospinal fluid reactions are apt to remain positive longer than if the patient had had a subsequent course of chemotherapy.

Solomon and Epstein reviewed a series of 173 patients treated with malaria, plus some form of chemotherapy, chiefly tryparsamide. Completely negative fluid reactions were found in 36.7 per cent of patients followed up for 3-9 years after treatment. (In our series of malaria plus tryparsamide, 52 per cent of the patients had a completely negative reaction at the end of 3 years.) These authors do not state how much malaria was given, but the post-malarial treatment was in nearly every case longer than that given at Horton.

O'Leary and his collaborators report, at the end of 3 years, only 5.8 per cent of negative cerebrospinal fluid reactions in cases treated with malaria alone, compared with 30 per cent in our series; in fact, in their cases treated with malaria plus chemotherapy, not more than 29.6 per cent are recorded as having negative reactions.

Marsh is of the opinion that tryparsamide therapy alone yields results inferior to those obtained by the use of malaria, but "its use in conjunction with malaria or other forms of artificially induced fever, seems to enhance the beneficial effects of both. Also, the unfortunate patient who is considered to be too poor a risk for some form of fever therapy, can usually be offered tryparsamide with at least a hope of benefit." The course of tryparsamide (22 grammes) given to our patients is small compared with that given in other clinics. Hinrichsen, in a review of the literature dealing with tryparsamide therapy in the treatment of syphilis, refers to the frequent necessity for giving more than 50 injections of the compound in order to produce the desired changes in the cerebrospinal fluid; this entails treatment being spread over 2-3 years.

This brings us to a very important point, and that is the duration of treatment. Dattner, Thomas and Wexler² give malaria plus 10 days' Mapharsen (0.06 gramme daily) immediately after the last fever session; they evidently prefer Mapharsen to tryparsamide. No further treatment is permitted; the question of re-treatment, if necessary, is reviewed at the end of 6 months, when the first post-treatment lumbar puncture is performed. We are in agreement with this procedure, as there is, no doubt, a great risk of overtreating patients. If, as Dattner, Thomas and Wexler¹ state, the whole treatment can be completed in hospital, much expense in further treatment is eliminated; moreover, one avoids "the inevitable delinquencies which occur during weekly routine injections". As stated above, tryparsamide therapy is not devoid of complications. Assuming that for the "active" paralytic or taboparetic patient malaria should be supplemented—at

any rate in those cases in which clinical improvement has been maintained, but in which the cerebrospinal fluid reactions are strongly positive—have we not got a good substitute in the shape of penicillin?

We mention the "active" cases of general paralysis because we still maintain that for the asymptomatic or latent neurosyphilitic, with increased cells and protein in the cerebrospinal fluid and a paretic curve, malaria therapy alone is adequate therapy. We may quote O'Leary's statement in 1937: "I still believe that malarial therapy is of more value in the prevention of general paralysis than it is in the treatment of it." Reviewing 16 cases of latent neurosyphilis treated during the period under review, but not included in either series, it is found that 100 per cent negative reactions of the cerebrospinal fluid are obtained with malarial pyrexia alone within one year of treatment. This is all that is needed; consequently it would appear that only in those cases—general paralysis, taboparesis, congenital general paralysis—in which the pathological process is much more active, is a supplementary course of chemotherapy—at any rate, sometimes—necessary.

Treatment with penicillin.—To revert to the subject of penicillin, is this new discovery going to supersede all known therapeutic procedures, including malaria therapy? These are early days to answer this question, but we would advocate the trial of penicillin in conjunction with malaria. The available reports on the value of penicillin in the treatment of neurosyphilis are somewhat contradictory. Just as it was several years before malaria was accepted as an established therapeutic procedure, so will it need time before we can assess the efficacy of penicillin in the treatment of neurosyphilis.

In the United States of America some useful papers have appeared, but the results are inconclusive and the authors quite rightly advise caution. It is agreed generally that penicillin has a curative effect on the cerebrospinal fluid, cells and protein being restored to normal limits.

Stokes and his collaborators, in 1944, reported cases from 8 clinics, to a total of 182 cases. Goldman experimented with intrathecal injections of penicillin. Neymann, Heilbrunn and Youmans draw attention to the danger of administering penicillin by the intracisternal route, but their paper refers to 5 cases only. Gammon and his co-workers give their experience in treating 89 cases with penicillin only; they found that, to observe the full effect, serological tests should be followed up for at least 120 days. They devised a plan of giving penicillin in 2 courses: a single course to be followed by the second course which is split into two parts, one given at the end of the first course and the other about 120 days later.

Rose and his co-workers find penicillin rather more attractive as an adjuvant to malaria or fever therapy; by the use of it the amount of fever therapy can be cut down to one half the total which formerly would have been considered to be necessary. In a more recent communication, O'Leary, Brunsting and Ockerley report their trials with intramuscular, intravenous and intrathecal routes of penicillin administration to 100 patients; penicillin treatment was combined with hyperthermia or malaria, and the clinical results, although good, were not superior to those obtained by pyrexial treatment alone.

In Great Britain no reports have been published, but cases of general paralysis have been treated with penicillin at a naval auxiliary hospital and a military centre. I have been able to see the work at the naval hospital, where penicillin alone was being used, and it is hoped that the results will be published. The question of dosage, the length of treatment and the method have yet to be standardized, but even if penicillin does not fulfil all expectations, the advantage of combining it with malaria, by means of which combination the amount of pyrexial treatment can be diminished, will make malaria therapy a much easier procedure than hitherto and one giving less cause for anxiety.

Summary and conclusions

(1) In the treatment of general paralysis and taboparesis, decidedly better clinical and serological results were obtained in the cases treated with both malaria and trypanamide than in those treated with malaria alone.

(2) The number of cases under review is equal in each series: 127 men and 90 women.

(3) The serological results are discussed in relation to diagnosis and to the sex of the patients.

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- (4) All positive cerebrospinal fluid reactions at the end of a year are indicative that further treatment is necessary.
- (5) The number of serological relapses was low: 2 in the malaria group and 3 in the malaria-plus-tryparsamide series.
- (6) In no case tested after 2 consecutive negative results did the cerebrospinal fluid reactions revert to positive.
- (7) In latent and asymptomatic neurosyphilis it is not necessary to supplement malaria therapy with chemotherapy.
- (8) Penicillin may well replace tryparsamide as an accessory to malaria therapy.

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CHANGES IN THE CEREBROSPINAL FLUID IN NEUROSYPHILIS AFTER MALARIA THERAPY*

By MAEVE WHELEN, M.D., D.P.M.

From the Malaria Therapy Centre, Horton Emergency Hospital, Epsom, Surrey

The results of malaria therapy in the treatment of neurosyphilis are assessable from two aspects, clinical and serological. From the point of view of the patient, of his relatives and of the community, the former is obviously the more useful and for a long time it was, and sometimes it still is, the only thing considered. This outlook was inevitable until some sort of working hypothesis could be produced to explain the action of malaria.

It is now more or less generally accepted that malaria is a spirochaeticidal agent and that its success in neurosyphilis is due to its action in bringing about the death of the spirochaetes. In order to assess the success or failure of the treatment we need some indicator of the presence of the living organism. This has been found in the cerebrospinal fluid. A positive reaction of the cerebrospinal fluid indicates the presence of living spirochaetes, a negative one of dead organisms. We have here a simple and straightforward means of telling how successful the treatment has been.

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