THE MODERN TREATMENT OF NEUROSYPHILIS

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During the last eight years over 50 patients suffering from various types of neurosyphilis, chiefly in the earlier stages, have been treated in this clinic by three different methods. Twenty-five who had not responded satisfactorily to pentavalent arsenic and bismuth were treated by infection with tertian malaria, followed by chemotherapy (Lescher and Richards, 1944). Ten more were given penicillin alone; and a further 19 were treated by malaria combined with penicillin. Forty-seven have been followed up both clinically and serologically, examinations of the spinal fluids having been made at definite intervals. It is our intention here to try to compare the results of these three different methods of treatment.

Treatment of Neurosyphilis with Malaria and Chemotherapy

Until recently it was considered that the most satisfactory method of treatment of neurosyphilis was with malaria, followed by trypanamide and bismuth. The latest review is by Nicol (1946), who treated and followed up 217 patients suffering from taboparesis or dementia paralytica. Over 50% improved clinically, and in 70% the spinal fluids became negative. Of the 25 patients in our series who were treated by this method, 20 have been followed up for from five to eight years (Tables I and II).

TABLE I.—Clinical Results after Treatment with Malaria and Chemotherapy

Type	No.	Much Improved	Improved	Stationary	Worse
Meningovascular ..	5	4	1	—	—
Tabes ..	10	2	4	—	—
Tabes with marked optic atrophy	4	—	—	2	2
Dementia paralytica	1	—	1	—	—
Totals ..	20	6	6	4	4

TABLE II.—Serological Results after Treatment with Malaria and Chemotherapy

Type	No.	Cerebrospinal Fluid				Blood		
		Strong Pos.	Weak Pos.	In-active	Neg.	Neg.	Im-proved	Pos.
Meningovascular ..	5	—	—	2	3	3	2	—
Tabes ..	10	1	2	1	6	6	2	—
Tabes with marked optic atrophy	4	—	—	3	1	1	1	2
Dementia paralytica	1	—	—	1	—	—	1	—
Totals ..	20	1	2	7	10	10	6	4

In classifying the spinal fluids in neurosyphilis Dattner's method (Dattner *et al.*, 1944) has been adopted. The various groups may, however, merge one into another.

(1) *Strongly Positive*.—Cell count and total protein increased. Paretic gold curve (first zone). Strongly positive W.R.

(2) *Weak Positive*.—Cell count normal or slightly raised; amount of protein increased. Paretic gold curve. W.R. strongly positive to positive.

(3) *Inactive Fluid*.—Cell count normal; marked reduction in the total protein. Gold curve may or may not be positive. W.R. positive.

(4) *Negative Fluid*.—Cell count normal; normal amount of protein. Normal gold curve. Negative W.R.

Each patient in the series was infected with tertian malaria, and ten bouts of fever were generally allowed. The duration of each bout averaged from eight to twelve hours, and no difficulty was experienced in stopping the infection by means of quinine. During the stage of fever the intake of fluids and the output of urine must be watched, and the urine should be tested for its salt content, as there is a danger of salt depletion. No complication occurred. Care was taken, however, not to employ malarial therapy in any patient of poor nutrition, or in those suffering from debilitating diseases or infections, especially those of the kidneys and bladder. Further, malarial therapy was not given to those in whom there was evidence of damage to the cardiovascular, renal, or hepatic system.

To assess accurately the clinical results in a chronic disease so complex as neurosyphilis is far from easy, for clinical improvement depends not only on the death of the spirochaete and the subsidence of the inflammatory reaction but also on the extent of destruction of nerve tissue. It cannot be expected, then, that scarred and destroyed nervous tissue can ever be restored to normal by treatment, or that nervous wrecks can be rehabilitated. The results of treatment in the present series (Table I) conforms in most respects to the results obtained by others. There is often improvement in the general health, as well as in such symptoms and signs as lightning pains, ataxia, and disorders of micturition, and in libido. In some, arrest of failing vision was noted.

However, the clinical disappointments are to some extent offset by the almost mathematical accuracy of the information on the activity of the disease and the need for further treatment gained by serial examinations of the spinal fluid. For in neurosyphilis there is a definite relationship between the pathological state of the nervous system and its reflection in the spinal fluid. Dattner *et al.* (1944) say that "for evaluating the success of treatment in neurosyphilis the spinal fluid syndrome is a far better guide than clinical symptoms." Whelan (1946), after examining a series of patients suffering from dementia paralytica and taboparesis, found that the majority of spinal fluids became inactive within six to twelve months after the termination of treatment with malaria, and, further, that there was a strong probability that the reactions would become negative in from one to three years without any further treatment. She found also that these fluids seldom reverted. Our experience, on the whole, bears out these conclusions.

Treatment of Neurosyphilis with Penicillin

Although penicillin is being used alone or combined with malaria in the treatment of neurosyphilis in many clinics in this country, few detailed accounts have as yet appeared in the medical press; a number of communications have, however, come from the United States. The earliest was from Stokes and his fellow workers (1944), but as it was a preliminary report no definite conclusion could be reached except that of encouragement. Later the same authors (Stokes *et al.*, 1946) claimed successful clinical and serological results from treatment with penicillin in 197 patients suffering from various forms of neurosyphilis. They found that the maximum improvement occurred in the first 120 days after its use, although it could continue beyond this time. Relapses were infrequent; little difference was found between high dosage (5–8 mega units) and low (1–4 mega units); no better results were obtained from a repetition

of the course. Gammon and his associates (1945), Nelson and Duncan (1945), Rose (1945), and Smith (1947) also reported successful results. O'Leary, Brunsting, and Ockuly (1946) and Mohr and Moore (1946) observed great serological improvement after the use of penicillin, but clinically the results were not so striking. No significant advantage was found to occur with amounts greater than 5 mega units. Marshall (1946) gives two courses of penicillin, followed by chemotherapy, with clinical improvement. Callaway and his associates (1946) consider that treatment with penicillin is more effective than with malaria. On the other hand, Rose and his colleagues (1945) concluded that there was little to choose between malarial therapy followed by tryparsamide and that of penicillin alone. Bruetsch (1946) found that penicillin is not so efficacious as malaria in the treatment of syphilitic optic atrophy.

In the above reports a total of 1-10 mega units of penicillin was given in divided doses, intramuscularly, every three hours. The intrathecal route has also been employed. Goldman (1945) considers that the results justify further study, but he gives no account of a follow-up. O'Leary, Brunsting, and Ockuly (1946) and Thrasher (1945) also claim more rapid serological reversals with this method. McDermott and Nelson (1945), Marshall (1946), and Neymann, Heilbrunn, and Youmans (1945), however, consider that this route is dangerous. But as penicillin which contains at least 90% penicillin G (II) and is free from impurities has been issued for special purposes—for example, for intrathecal injection—since these reports, any irritant property that it formerly possessed should be of a lower degree.

Ten patients in our series were treated each with intramuscular injections of penicillin in oil, 125,000 units twice daily, until four mega units had been given. The course was preceded by smaller doses for the first two days to avoid the possibility of a Herxheimer reaction (Tables III and IV). They have been followed up both clinically and

give the answer to this problem; most investigators have certainly stressed this.

Treatment of Neurosyphilis with Malaria and Penicillin

It is now established that penicillin is a definite spirochaetocidal agent; and malaria has stood the test of time as an effective therapeutic method in the treatment of neurosyphilis, very probably by raising in some manner the immunity of the host, besides having itself a spirochaetocidal action. Eagle and Musselman (1944) have found that the rate at which spirochaetes were killed *in vitro* by penicillin increased with a rise of temperature, the optimum being 39-40° C. It seems reasonable, therefore, to expect that owing to their complementary action a combination of these two methods may be likely to enhance the beneficial effects of either.

A few papers giving preliminary results of this combined treatment have appeared in the United States. However, no reports have yet been published in Great Britain, although the method is being employed in some clinics in this country. Rose and his associates have so treated 70 patients with clinical and, to a greater extent, serological improvement. Reynolds, Mohr, and Moore (1946), and Rose and Solomon (1947) consider that this combined method is superior to that with penicillin alone; Nicol (1946), despite his success with malaria and tryparsamide, advocates treatment with malaria together with penicillin. O'Leary, Brunsting, and Ockuly (1946), however, have found no appreciable difference either clinically or serologically with the combined treatment, compared with that of malaria alone, except in the asymptomatic and meningeal forms of disease.

We started in August, 1945, to use penicillin combined with malarial therapy. Nineteen patients suffering from various forms of neurosyphilis, mostly in the earlier stage, have been so treated and followed up (Tables V and VI); others are at present undergoing this method of treatment, but are not included in this review.

TABLE III.—Clinical Results after Treatment with Penicillin

Type	No.	Much Improved	Improved	Stationary	Worse
Meningovascular ..	2	2	—	—	—
Tabes ..	6	1	2	2	1
Taboparesis ..	2	1	1	—	—
Totals ..	10	4	3	2	1

TABLE IV.—Serological Results after Treatment with Penicillin

Type	No.	Cerebrospinal Fluid				Blood		
		Strong Pos.	Weak Pos.	In-active	Neg.	Neg.	Im-proved	Pos.
Meningovascular	2	—	—	2	—	—	1	1
Tabes ..	6	—	1	2	3	2	1	3
Taboparesis ..	2	—	—	2	—	—	1	1
Totals ..	10	—	1	6	3	2	3	5

serologically. There is a difficulty, however, in comparing the results obtained at the present time with penicillin with those obtained with the earlier preparations, for penicillin has been a changing mixture. Formerly much of it contained an appreciable amount of penicillin K, which is inefficacious against *Treponema pallidum*, and this may have been responsible for the poorer results obtained in the treatment of syphilis. At present penicillin of a purity of 90% can be produced, and it does not contain K substance in any significant amount; but to assess accurately the value of penicillin in the treatment of neurosyphilis more knowledge is required, especially as regards the dosage and the duration of treatment. Time and experience should

TABLE V.—Clinical Results after Combined Treatment with Malaria and Penicillin

Type	No.	Much Improved	Improved	Stationary	Worse
Asymptomatic ..	3	3	—	—	—
Meningovascular ..	1	1	—	—	—
Tabes ..	8	3	2	3	—
Dementia paralytica	7	2	3	2	—
Totals ..	19	9	5	5	—

TABLE VI.—Serological Results after Treatment with Malaria and Penicillin

Type	No.	Cerebrospinal Fluid				Blood		
		Strong Pos.	Weak Pos.	In-active	Neg.	Neg.	Im-proved	Pos.
Asymptomatic ..	3	—	—	1	2	1	—	2
Meningo-vascular	1	—	—	1	1	—	1	—
Tabes ..	8	—	1	4	3	3	—	5
Dementia paralytica	7	1	—	5	1	2	1	4
Totals ..	19	1	1	10	7	6	2	11

A wax-oil preparation of penicillin was given just before and during the acute stage of the malarial infection, 250,000 units being injected twice daily, to a total of 4 mega units. To avoid the possibility of a Herxheimer reaction, a smaller dose was given for the first two days. It was confirmed that penicillin had no inhibiting effect on *Plasmodium vivax*. These patients attended the follow-up department at regular intervals afterwards, and the changes in the spinal fluids were carefully watched. One problem has been practically solved. A patient will not submit willingly to

periodic lumbar punctures if each is followed by a severe headache; but since we have started to use the fine Dattner needle the complaint of post-puncture headache has rarely been made. Follow-up lumbar punctures are performed in the out-patient clinic, and the patient leaves shortly afterwards.

Comparison of the Three Methods of Treatment

Two difficulties are apparent in attempting a just comparison between these three different methods of treatment. The number of patients in each series is too small to draw an absolute conclusion; and enough time has not elapsed to complete a thorough follow-up of those who have been treated with penicillin or with penicillin combined with malaria. This paper must therefore be considered rather as an interim report.

In comparing the various tables, after reducing the figures to percentages, the best clinical results are seen to have been achieved with malaria and penicillin, closely followed by those obtained with penicillin alone; the results obtained by combined treatment with malaria and chemotherapy come last.

Serologically there are several points to notice. In our series a greater number of positive spinal fluids became inactive within six months after the combined treatment with malaria and penicillin than with the two other methods. So rapidly may this change occur that some fluids have been found to become inactive directly after the termination of this form of treatment. The total number of spinal fluids that have become inactive and negative is higher in those treated with malaria and penicillin and with penicillin alone; but more fluids have become negative and remained negative after malaria and chemotherapy. It is possible, however, that it is merely a question of time, since those patients who have been treated with the latter therapy have been followed up for a longer period; and there is reason to suppose that in time more spinal fluids of these patients treated with malaria and penicillin will eventually become negative. After treatment with malaria and chemotherapy a greater percentage of spinal fluids remain positive than with the two other methods.

It seems, therefore, that in active neurosyphilis the method of choice, at least for the present, is to treat the patient immediately with penicillin and malaria (provided there is no contraindication to the latter). If at the end of twelve months from the termination of this method of treatment the spinal fluid is still found to be positive, or if it remains inactive after two years, treatment with penicillin or with penicillin and malaria can be repeated. Even in "burnt-out" cases of neurosyphilis with subjective sensations and objective signs, but with negative spinal fluids, clinical improvement may still occur with further treatment.

Treatment of Latent Neurosyphilis

There is enough evidence to show that *Treponema pallidum* may invade the central nervous system early in the septicaemic stage of the disease, yet the organism can remain latent for a varying period without showing clinical evidence. In asymptomatic neurosyphilis, which can easily be detected by the examination of the cerebrospinal fluid, correct therapy is of the greatest importance, for by it further progress can be prevented. Thorough treatment with trivalent arsenic, together with bismuth, will often at an early stage cause a positive fluid to revert permanently to normal. For in dealing with neurosyphilis it is not enough to wait for obvious clinical signs of disease, as by this time irreparable damage has been done. The spinal fluids of all patients who have received adequate treatment

for early syphilis should therefore be examined at the end of the first year of treatment. A positive fluid will mean that there is a danger that the patient may at any time develop clinical neurosyphilis, with pathological changes in the brain or spinal cord. In our opinion intensive treatment, preferably with penicillin and malaria, should under these circumstances then be started.

It is also advisable to employ the latter method of treatment in those who show evidence of latent neurosyphilis of longer standing. If a positive Wassermann reaction in the blood is found in a person with no other signs of syphilis, and who has not had adequate treatment, it will often be observed that the spinal fluid is also positive. (We have seen this a number of times in prospective blood-donor volunteers on whom a blood Wassermann reaction has been performed as a routine.)

Summary

Forty-nine patients suffering from neurosyphilis in varying forms and degrees have been treated by one of the following three methods: 20 with malaria and chemotherapy, 10 with penicillin, and 19 with malaria together with penicillin.

Each patient has been followed up clinically and serologically.

An attempt has been made to compare the results of these three different methods of treatment.

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The Communist Party has issued a pamphlet entitled *Health Centres* (3d. post free from Central Books, Ltd., 2-4, Parton Street, London, W.C.1). This memorandum outlines advantages to the general public to be obtained from health centres, as well as those to the medical profession, such as regular hours off duty and periods for postgraduate study. It suggests that the most suitable size for a health centre in an urban area covering a population of 10-20,000 would be for 5-10 doctors. There would be individual consulting rooms, one comfortably furnished waiting room, a large treatment room providing facilities for minor surgery, a rest room, a reception office, and a dispensary. In addition there would need to be W.C.s, store rooms, a kitchen, and accommodation for staff. Such a centre would require 4-8 nurses, 2-4 clerks, 1-2 dispensers, a cook, and several domestics. Ancillary diagnostic and therapeutic aids could be obtained at the nearest hospital, the patient being sent direct from the centre with a request for the desired examination without having to see a specialist at the hospital. In country areas health centres would be smaller, being staffed by perhaps 2-4 doctors. The memorandum contends that "there is an urgent need to get the idea of health centres realized in practice immediately following the inception of the National Health Service," but it recognizes that it will be necessary to improvise in view of the resources available.