NEUROSYPHILIS AND ITS TREATMENT.

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An extensive review of recent advances in the aetiology and treatment of neurosyphilis was published in this journal by one of us, E. L. Hutton (1941). While it is mainly the later manifestations with their crippling disabilities that present themselves to the psychiatrist in the mental hospital, it is becoming increasingly obvious that early treatment is imperative to obtain good results, and that neurosyphilis itself must be regarded as a preventable disease.

Asymptomatic Neurosyphilis.

Laboratory tests, the state of the blood and cerebrospinal fluid, afford us knowledge more complete than for any other diagnostic category in psychiatry. O'Leary (1939) defines asymptomatic neurosyphilis as "that manifestation of syphilis which is characterized by a positive spinal fluid test, and in which there are neither signs nor symptoms of invasion or involvement of the central nervous system." His figures give 35 per cent. of early syphilitics as having a positive fluid; some of these have spontaneous cures, others respond to usual forms of adequate treatment; even so the fluid remains positive in some 15 per cent. of cases four years after the primary attack. This smaller group he regards as a potential forerunner of clinical neurosyphilis. In some cases a definite paretic formula is revealed by examination, but in any case if the fluid remains positive after six months of ordinary routine treatment (a trivalent arsenical combined with a heavy metal), it must be assumed that the patient has a resistant type of infection (probably of a paretic type), and a change to a pentavalent arsenical or fever therapy is indicated. Adequate therapy and negative results of blood and fluid at the end of a year should guarantee the patient against any subsequent involvement of the central nervous system. A case, however, is recorded by Kopp and Solomon (1941) of a patient who developed general paralysis following essentially normal spinal fluid findings, and in spite of fairly continuous antispecific therapy over a period of 14 years. This patient was examined 14 and 22 months after treatment, with negative fluid results, but there was the significant point that in the first examination the cell content was slightly increased to 22 cells.

O'Leary reports that patients with a mildly positive fluid showed the lowest incidence of clinical progression, while those with a paretic fluid gave evidence

https://doi.org/10.1192/bjp.90.378.328 Published online by Cambridge University Press

of clinical progression four times as frequently. Again, those who received less than ten injections showed an incidence of clinical involvement three times as great as those who received 20 or more injections of arsenic plus a heavy metal.

Paul B. Jossmann (1940), in an analysis of 386 G.P.I.'s and 798 tabetics admitted between 1910 and 1924 to the Charité Hospital, Berlin, found that inadequate treatment influences the development of neurosyphilis by shortening the incubation period. He also records that cases having no treatment at all have the longest incubation, from which he draws the conclusion that inadequate treatment interferes with the resistance built up by the patient, thereby hindering antibody formation.

Diagnosis.

Too much stress cannot be laid on the necessity for doing lumbar punctures, not only in order to establish or confirm a diagnosis, but also to assess the progress of treatment, and in some cases the choice of any particular method. Augustus S. Rose (1942) classifies the changes of the asymptomatic case according to the degree of abnormality of the fluid—Group I a minimum involvement with cells ranging from 5 to 20 per c.mm., protein 30 to 50 mgm. per cent., a negative gold curve and a Wassermann either negative or weakly positive; in Group II fluid cells vary from 20 to 60, protein 40 to 70 mgm., the gold curve slightly altered, 2344321000, the Wassermann being weakly or strongly positive. Group III fluid with increased cells up to 100, protein 60 to 150 mgm., a paretic gold curve, 5555543200, and a strongly positive Wassermann is the most resistant to treatment. Patients with the Group III or paretic formula are liable to develop general paresis. Patients with Group I fluid react well to ordinary treatment, the changes are frequently seen in late cases of vascular neurosyphilis, while those with Group II respond less satisfactorily to routine methods and require tryparsamide or even fever therapy. The third group demand more energetic treatment, such as tryparsamide, malaria or other artificial fever agent.

Dattner and Thomas (1942) consider that: (1) In untreated syphilis a positive Wassermann of the cerebrospinal fluid with negative findings in other tests does not prove activity, whereas if it is associated with increased cells and protein, activity must be assumed. (2) In cases receiving specific therapy, normal cell count and protein content merely indicate that the infectious process is inhibited; it may become active again six months after treatment is terminated. (3) If, six months after treatment has been discontinued, the cerebrospinal fluid shows no more than three to four cells and definite diminution in protein, in all probability the activity of the syphilitic process in the central nervous system has been permanently checked. These authors maintain that in many cases the differentiation between meningovascular and parenchymatous involvement is extremely difficult, and even when a meningovascular lesion is clear, they claim that fever combined with chemotherapy is vastly superior to chemotherapy alone. The fever agent recommended is malaria.

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Aetiology of Neurosyphilis.

Fleming and Moore (1941) present three possibilities for variations in the course of the untreated syphilitic infection: (1) the infecting organism, (2) extraneous factors, such as intercurrent disease, nutritional deficiencies, pregnancy, and (3) the defence mechanism of the host. Much has been written on the possibility of a neurotropic strain of spirochaete as opposed to a dermatotropic strain. As far as extraneous factors are concerned, the evidence of any influence effected by associated tuberculosis is unconvincing, but pregnancy appears to exert a favourable influence on the syphilitic infection, while nutritional deficiency, especially in vitamins A, B, or both, may predispose to development of certain forms of neurosyphilis, especially tabes. Regarding the defence mechanism of the host, early tissue reaction is found more commonly in negroes, whereas in white races and in experimental animals the late manifestations, cardiovascular or parenchymatous neurosyphilis are more frequent. Some speculative theories are put forward with regard to the relation of infection to the habitus of the host—the sthenic or hyper- and hyposthenic individual. Patients with Group O blood become sero-negative more rapidly than those belonging to other groups. All these results are rather vague, and one is still at a loss to explain why one patient gets neurosyphilis and another does not.

The association of lesions of skin and mucous membranes in neurosyphilis is recorded in a paper by Clarence Shaw (1940). Among his own group at Chicago of 70 patients with late syphilitic skin, mucous membrane and bone lesions, 15 (21·4 per cent.) had a positive fluid, and 7 had asymptomatic neurosyphilis. Besides these he quotes figures from other workers; among 1,515 patients with tertiary lesions, the average percentage involvement of the central nervous system was 22·6. With control groups the incidence of a positive fluid was twice as great, thus indicating a possible difference in immunity in patients who have benign late syphilis.

Diagnosis of General Paralysis of the Insane.

An interesting account by Herman and Rosenblum (1940) gives some data on acute general paresis. These authors, while agreeing that G.P.I. is usually a chronic disease, present four types, fulminating, convulsive, catatonic, and acute confusional, with an acute onset and a rapidly fatal termination. The fulminating type is characterized by acute delirium with marked hallucinosis, physical signs are prominent, and the patient runs a febrile course, death supervening in one to three weeks. The convulsive and acute confusional varieties describe themselves, but the latter is more prone to subside, the patient assuming a chronic type with dementia. The catatonic type, with mutism and negativistic behaviour strongly suggestive of an acute schizophrenic process, gives rise to some difficulty in diagnosis, apart from the fluid findings, because according to Schilder and Parker (1931) fixed pupils are found under certain conditions in catatonic schizophrenic patients, especially negroes. For all cases treatment is urgent and imperative, and a course of tryparsamide has been recommended to improve the patient's general condition prior to malaria.

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Weinberg (1941) describes tumour syndromes in association with general paresis, one a meningioma in the spinal cord, and the other with a gumma in the cerebrum. Wexberg (1940) analyses 256 cases of cerebrospinal syphilitic affections: in addition to 38 cases of G.P.I. and 6 cases of cerebral syphilis with psychosis, there is left a group of 20 cases in which the differential diagnosis between G.P.I. and cerebral syphilis was not possible with present clinical methods. The author continues, "The insufficiency of our diagnostic methods is responsible for overlapping interstitial types, thus leaving the differentiation between interstitial and parenchymatous forms of cerebral syphilis in doubt in about 30 per cent. of patients with mental symptoms." In all these doubtful cases the cerebrospinal fluid examination remains the only test decisive in the determination of therapeutic application. A case of paralysis agitans with syphilis as a causative factor is described by Harris (1940), who quotes Jelliffe and White, "Neurosyphilis is so kaleidoscopic in its clinical manifestations, that the significance of the *Treponema pallidum* infection as a primary aetiological factor in the production of nervous disorders is frequently overlooked."

Treatment.

Malaria, artificial fever and chemotherapy have been employed singly and in combination, and their relative merits still afford much controversy. Before trying to assess the value of these different methods, we propose to review the literature of each method separately.

Malaria.

In two papers Bruce Mayne and Young (1941) and Gerstmann (1941) outline procedure and general indications for therapeutic malaria. Bruce Mayne enumerates the following contra-indications: (*a*) presence of any chronic infectious disease, (*b*) cardiovascular or renal disease, (*c*) severe emaciation, (*d*) galloping paresis, (*e*) severe anaemia, (*f*) liver dysfunction, (*g*) senility, (*h*) extreme obesity.

Quartan malaria is claimed by Fong (1940) as a useful agent for patients, especially negroes, who are immune to benign tertian, but even in negroes successful inoculations were obtained in only 53·2 per cent. of cases in a series of 436. He notes that the serologic results following induced quartan malaria corresponded in general to those obtained by benign tertian; the blood Wassermann, however, was much more resistant with quartan. Kroll (1940) gives an account of 62 patients, of whom 46 were coloured; he finds quartan of value for the case which requires a second course. Only seven inoculations were unsuccessful.

A study of febrile paroxysms resulting from induced infections of benign tertian is published by Coatney and Young (1942); 338 paroxysms in 21 patients were analyzed. The average duration of temperature of 100° F. and over was 10 hours 10 minutes per paroxysm with a height of 104·8° F. It was found that 201 paroxysms were accompanied by rigors, there being 137 without; the fever peak average was 0·7° F. higher in the rigor group; moreover the average rate of fever rise was 3·3 times faster during the rigor (1° F. in 17 minutes) than during any other period of fever rise (1° F. in 56 minutes).

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The almost constant feature of a quotidian type of fever in primary benign tertian malaria has always been a source of anxiety in the management of a case, and it has long been the practice in this country to give malaria in two stages by aborting the fever with a small dose of quinine (Nicol, 1942). A useful therapeutic procedure has been introduced from America by which 0·2 grm. of thiobismol is given to the patient after the fever has become established; this destroys one generation of parasites, and with unfailing regularity produces tertian fever, thereby giving the patient a rest every other day without fever. Papers relative to this action have been published in America by Schwartz (1939), Brunsting and Love (1940), Cole and others (1930), and in this country by Whelen and Shute (1943).

An analysis of deaths following therapeutic malaria is given by Wile and Mundt (1941 and 1942). These workers treated 1,026 patients between 1925 and 1940; the mortality-rate was low, only 29 deaths occurring during the paroxysms or immediately following their termination. The authors state, "The hazard may be reduced by a careful selection of cases, which presupposes a clear comprehension of the many indications and contra-indications, and by close observation of the patient during the course of the malaria . . ." They think that the mortality should have been lower, as included in the total are two suicides, which might have been prevented, and five cases with lung complications, who, with the advent of sulphonamides, might well have survived. Half the number died before the fifth paroxysm. The condition responsible for the largest number of deaths was circulatory failure or vascular collapse—symptoms identical with those seen in true medical shock. In five patients death was attributable to hyperpyrexia. Only in one case is rupture of the spleen recorded; this is a rare complication, though isolated cases have been recorded in the literature from time to time. Büttner and Hauer (1938) report a spontaneous rupture in a case inoculated with *Plasmodium ovale*.

It is interesting to note that 80 per cent. of the deaths recorded were in general paralytics (19 deaths out of 358 treated) and taboparetics (4 deaths out of 118 treated).

Hallucinatory psychosis and epilepsy are both unpleasant sequelae; a brief review of the literature regarding the former phenomenon is given by Tcherniak (1938), who reports 22 female cases, the prognosis being considered unfavourable. Roger and Alliez (1938) discuss the theories of pathogenesis of epilepsy; they adopt the view that ultimately syphilis will cause epilepsy, as occurs in the untreated paretic. Many developing epilepsy are those in whom life has been prolonged by therapy, who before its advent would have died.

An interesting account is given by Kopp and Solomon (1939) on the relation of the height, duration and frequency of fever to the clinical and serological results. 302 patients with various forms of neurosyphilis were given malaria with or without other methods of therapeutic fever. A subdivision of this group, 182 patients, all general paralytics, received malaria only and were under observation from 6 months to 13 years. The total amount of fever above 100° F. experienced varies widely, even for the same number of paroxysms. In the group of 182 general paralytics the amount of fever at different temperature levels, 104°, 105° or 106° and above, did not make any significant statistical

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difference in the clinical results. The best clinical results were obtained in those patients who had more than 150 hours of fever above 100°. Moreover, patients with less than ten paroxysms did not show such good clinical improvement as those who had more than ten.

Fever Therapy by Physical Methods.

An excellent critical review of developments in the treatment of syphilis with artificial fever combined with chemotherapy during the past decade is given by Simpson, Kendell and Rose (1941). The results of various workers are related, of which the more recent ones are recorded elsewhere in this paper. The author relates his personal experiences in the treatment of neurosyphilis, having tried hot baths, hot-air cabinets, electric blankets, diathermy electrical currents, and ultra high frequency electrical currents, until finally he adopted the Kettering hypertherm. Rather surprisingly it was found possible to treat general paralytics, who may be extremely uncooperative at times. Advantages adduced are that the fever is easily controlled, chemotherapy can be given almost at the same time as the fever, and finally the death-rate is practically negligible. In all methods an optimum temperature of 105·8° F. (41° C.), usually at weekly intervals, is aimed at, there being ten 5-hour sessions in all. In 1937 an experiment in the reduction in the total number of hours of fever together with a decrease in the number of hours for each treatment was made. Consequently twelve 3-hour sessions at an average temperature of 105·8° F. or a total of 36 hours were given. Serological and clinical results were equally good with this reduction in amount and duration of fever. Moreover, if necessary on account of travelling, patients could be hospitalized and given three treatments weekly for four weeks. On the other hand all local patients were treated as out-patients at bi-weekly or weekly intervals. Modifications of this programme were applied to the more debilitated type of patient.

A hypo-hyperthermia method is described by Solomon, Kopp and Rose (1941), in which the patient's temperature is lowered to 95° F. first, and then the patient is put in the inductotherm and the temperature raised to 103°–105°.

Tryparsamide.

Complications in tryparsamide therapy are described fully by Kopp and Solomon (1940), and other relevant papers are by Henrichsen (1939), Beerman and Shaffer (1940), and Downs *et al.* (1941). The most serious toxic effect is visual disturbance, and most observers agree that these changes are particularly liable to occur during the first eight to twelve injections. Kopp and Solomon advise permanent omission of the drug if disturbance of vision occurs during the first ten injections. Between 1923 and 1929 visual complications were reported in 4·5 per cent. of cases. In 13 patients in whom the drug was continued, optic atrophy resulted in 6; in 16 patients with immediate omission of the drug, optic atrophy resulted in 3 only. When visual complaints occurred after 17 to 61 injections optic atrophy did not result, even though the drug was continued in six or seven patients. Nitritoid reactions, flushing of face and neck, suffusion of conjunctivae, sense of oppression in chest, pruritus

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and sometimes nausea and vomiting are reported as being more frequent; these authors during the first five years of tryparsamide therapy, 1922 to 1926, had one case; in 1939 they reported 8·6 per cent. of their patients. The reactions last twenty minutes to half an hour; they have never been associated with optic atrophy. In this series of 829 patients with 43,308 injections, gastro-intestinal upset is recorded in 7 per cent. Here again the incidence seems to be increasing of late years; the condition was rarely seen during the first ten injections; nausea, vomiting, diarrhoea, abdominal cramps with profuse sweating are described. Jaundice, a benign type and of short duration with no sequelae, occurred in 3·6 per cent. of the entire group of patients. Batchelor (1941) suggests that tryparsamide may exert a more favourable influence when persisted with for prolonged periods and given up to a very large dosage. One of his cases received over 600 grm. of the drug and others from 300 to 500 grm. with apparent benefit.

Forman (1939) reports the results of treating 38 female cases of general paresis with continuous intensive tryparsamide and bismuth. To 32 of the patients, however, malaria therapy was also given, but the main interest lies in the administration of tryparsamide 3 grm. each week, except for two weeks twice a year. Thiobismol 0·2 grm. was given twice weekly for six weeks, alternating with rest periods of the same duration. Complete reversal of the fluid was obtained in every case, but it is noteworthy that 3 per cent. of the entire group, after showing negative results of the cerebrospinal fluid, reverted to positive.

Spiegel *et al.* (1941) give an account of a new pentavalent arsenical, aldarsone. 133 patients were treated during five years with a total of 6,702 injections. This drug was effective in the treatment of neurosyphilis, especially the meningo-vascular type. Serological improvement was noted in various spinal tests. There was no contra-indication for its use in optic atrophy—in fact visual fields showed improvement. The drug can be used continuously over a long time.

Results of Treatment and Selection of Treatment.

It is difficult to evaluate the efficacy of any one particular therapeutic agent, since a combination of one or more forms of treatment is invariably used. Much controversy exists as to whether artificial fever therapy is superior to malaria. Reports differ widely as to the relative merits of the different forms of therapy, but there would appear to be almost unanimous agreement that chemotherapy must be given as well. The aim of all therapy is to arrest the progress of the disease, in the asymptomatic neurosyphilitic to eliminate the infection, and in all forms to produce if possible a reversal of the spinal fluid. Indeed it is only by repeated lumbar punctures that one can assess the degree of improvement, if any.

Bower (1938–39) maintains that acute primary malaria with only 12–14 paroxysms is insufficient to kill all spirochaetes, and that in no instance has he seen a complete cessation of symptoms without the addition of chemotherapeutic measures. This would appear to be a sweeping statement, and does not conform to our results at the Horton malaria unit.

A serious attempt has been made by Blalock and Hinsie (1938) to assess the

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relative value of different modes of therapy. The patients under review were 300 general paralytics treated between 1923 and 1935. With all procedures it was found that a reduction in the cell count is the first change in the cerebrospinal fluid; this generally takes place soon after treatment. The globulin content becomes modified in the early months and years following treatment, but lags behind the improvement noticed in the cell count. At the end of ten years 64·3 per cent. of the males had a negative globulin reaction, in contrast to 90 per cent. of the women, whereas at the end of five years there was no sex difference. The gold curve was negative in 14 per cent. of cases at the end of the first year, in 53 per cent. after five years, and in 73 per cent by the tenth year. The Wassermann was negative in 11 per cent. at the end of the first year, and in 49 per cent. at the end of five years, when 98 patients were examined; this was increased to 89 per cent. at the end of ten years, when 28 patients were available. Still, taking all patients as a group, it was found that the reversal in serology varied with the clinical condition; at the end of a four-year period negative reactions were twice as frequent in the remitted as in the improved group. In the remitted group the cell count was normal in 100 per cent., whereas in the unimproved group this percentage was reduced to 85. Many patients who maintained an abnormal cell count during the early years following therapy had a fatal outcome.

To come to serological results in individual forms of treatment, in malaria, of 68 patients who showed clinical improvement there was a much higher rate of serological improvement than there was among 49 patients who showed no clinical remission.

Tryparsamide therapy was applied to 55 patients, 29 of whom showed clinical improvement, and 26 were unimproved. At the end of five years there was a decided difference in the improved group compared with the unimproved; a negative result was obtained in 91 per cent. for the blood Wassermann, in 82 per cent. for the spinal fluid Wassermann, and in 90 per cent. in the gold sol reaction, in contrast to 20 per cent., 33 per cent. and 40 per cent. respectively in the clinically unimproved patients.

The figures for electropyrexia are not quite so reliable, as many patients had bismuth and tryparsamide as well. 116 patients were treated, 73 being improved, and 43 with no clinical improvement. Again the percentages of negative responses are distinctly superior in the clinically improved group. At the end of four years the percentage of negative fluids for 22 patients treated by electropyrexia was 63·6, compared with 57·2 per cent. in 14 cases receiving malaria.

Combining improved and unimproved groups, it is evident that the earliest serological changes occur in the cell count of the spinal fluid, and here it is significant that at the end of three years a normal count is revealed in 92·5 and 93·9 per cent. of cases treated respectively with malaria only and with tryparsamide only, in contrast to merely 58·8 per cent. with electropyrexia only, though when combined with tryparsamide a return of 88·9 per cent. negative is obtained.

Although a most careful analysis is presented by these authors, it is unfortunate that the numbers of patients are relatively small, nor is there any

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indication of what type of paresis they are suffering from, which in most cases has an important bearing on the prognosis. The authors conclude that the safest time, if there is any, to estimate the future course of the patient's condition, from the standpoint of serology, is three to four years after treatment has been started. Serological improvement is in general independent of the clinical condition of the patient. However, a persistently positive ensemble is usually associated with a poor clinical condition. The most favourable clinical and serological results were observed in those patients who received some form of fever therapy followed by chemotherapy. A further analysis by the co-operative clinical group—O'Leary *et al.* (1940)—is presented: 1,100 patients received malaria and 320 artificial fever, both forms of treatment being supplemented by chemotherapy. Clinical remission in early or mild paresis can be obtained by either method, but as the severity of the disease progresses, there is a striking advantage in favour of electropyrexia, ten in a hundred remitting compared with only one in a hundred treated by malaria. Reviewing the serological results, the reversal rates at the end of four years were not only more rapid, but approximately twice as frequent under malaria as under artificial fever; the authors state, however, that this may have been due to more chemotherapy being given to the malaria series. Deaths, regardless of cause, provided death occurred within three months of fever therapy, were higher with malaria (13 per cent.) than with artificial fever (8 per cent.). Clinical relapses occurred in 3·3 per cent. of the malaria-treated group, and in 5·5 per cent. of the artificial fever group. The highest percentage of clinical remissions was obtained in patients treated with an average of 69 hours' fever above 101° F., of which fever time 70 per cent. was at a level above 105° F., with a maximum temperature of 106·9° F. This high temperature cannot be obtained in malaria, and the conclusion was arrived at that equally good results were obtained with an average of 44 hours of fever above 101° F., of which total time 57 per cent. was above 106° F.

A further study by Ewalt and Ebaugh (1941) was made in 232 cases of general paresis, treated alternately by either artificial fever or malaria, and observed over a five-year period. Here the authors state that the malaria series in most instances received fifty hours' fever at 104° F. or more. In the first three years patients receiving artificial fever had 50 hours between 105° and 106°, given as ten treatments of five hours each. During the last two years this was reduced to 36 hours of fever at a rectal temperature of 105·8° in twelve treatments of three hours each. No difference in results was noticed with the shorter treatments. Both treatments were supplemented by chemotherapy spread over three years, each year comprising six months of tryparsamide 3 grm. weekly, four months of bismuth salicylate 0·26 grm. weekly, and two months of neoarsphenamine 0·6 grm. weekly. Remission or improvement in this series was 69 per cent. in the artificial fever group, compared with 58 per cent. in the malaria group.

A more recent communication on the results of artificial fever therapy is given by Barton *et al.* (1942). They report that the optimum temperature should be raised to 106°, and held during the several fever periods more than 20 hours above 105° F., the recovery-rate being highest three years after treatment.

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Kopp (1942), with a series of 173 patients treated by malaria, 118 by mechanotherapy, and 81 by tryparsamide, the two first modes of therapy being supplemented by prolonged chemotherapy, reports that malaria is superior to artificial fever, while tryparsamide is superior to both; this latter statement can be explained by the fact that tryparsamide was given to very early cases with mild parenchymatous involvement and not requiring hospitalization.

Freeman (1942), in an analysis of 840 general paralytics admitted to the Worcester State Hospital during twenty years from 1920 to 1940, advocates immediate chemotherapy with subsequent fever therapy. His experience is based on different forms of therapy. From 1920 to 1924 chemotherapy was employed; from 1925 to 1929 malaria was the method of choice in conjunction with chemotherapy, while during the last decade diathermy supplemented by various combinations of chemotherapy replaced malaria. This worker reports diathermy as giving the best results.

An interesting observation is made regarding the untreated general paralytic who is physically unfit to withstand therapy. 84·4 per cent. died. Since the advent of therapy the death-rate has fallen to 28·7 per cent. It is also recorded that the "physical wreck" seen on admission is becoming rare; during the period 1920–24, 37·8 per cent. of admissions were physical wrecks and unfit for treatment; for the period 1937–40 this figure has become reduced to 8·5 per cent.

The general practice seems to be the prolonged administration of some drug such as tryparsamide following fever therapy; the period of administration varies from 20 weeks to several years. Dattner and Thomas (1942), however, raise this question. In the past at the Bellevue Hospital it was the practice to administer routine chemotherapy for one year after malaria; now a daily intensive course of mapharsen is given for ten days. Dattner states that in the Vienna Clinic chemotherapy after fever was seldom given for more than six weeks. Provided the cerebrospinal fluid is examined six months after all treatment is stopped, there is no doubt that much of this prolonged after-treatment would become unnecessary.

Artificial fever and malaria both have their place in the therapeutic programme of neurosyphilis. The death-rate of the former is lower, but with skilful management of malaria, which is equally necessary for the other method, the death-rate from malaria therapy should be greatly reduced. More patients can be treated at one time with malaria than with the artificial fever methods.

Optic Atrophy.

A review of the literature of neurosyphilis would be incomplete if the problem of optic atrophy were not included. In all contributions to this vexed problem there appears to be much confusion and disagreement. On two points, however, all workers are agreed: (1) Untreated syphilitic primary optic atrophy always involves both eyes. (2) It always leads eventually to permanent and complete blindness.

https://doi.org/10.1192/bjp.90.378.328 Published online by Cambridge University Press

There are many theories of the pathogenesis, which are summarized by Moore and Woods (1940). (1) Optic atrophy may be due to the co-existence of syphilis and lymphogranuloma inguinale. (2) It depends on a nutritional disturbance of the optic nerve, due to syphilitic involvement of the blood supply of the nerve. (3) It depends on a disturbance of the relationships between systemic blood pressure, retinal blood pressure and intra-ocular tension, with resultant disturbance in nutrition of the optic nerve. (4) A meningeal inflammation with development of chiasmal arachnoiditis constricts the nerve or its blood supply. (5) It may be due to a combination of nutritional (vitamin) deficiency and neurosyphilis.

There does not appear to be any good pathological support for the first two theories. Benedict and Wagener (1940) discuss the third theory relating to systemic blood pressure and intra-ocular tension, which has been put forward by Lauber (1938). This worker maintains that all tabetics with optic atrophy suffer from peripheral hypotension, diastolic at least, if not systolic as well. As a result, retinal diastolic arterial pressure, which averages about 45 per cent. of diastolic pressure, approaches the level of intra-ocular tension, with resulting circulatory failure in the optic nerve and development of optic atrophy. Consequently, as arsenic, bismuth, mercury and iodides tend to lower the blood pressure, and as it is impossible to maintain an elevation of blood pressure, the treatment of syphilitic optic atrophy should be essentially that of glaucoma, by the use of miotics. Although some good results are reported, this theory is not confirmed by other workers.

The fourth theory again is not supported by much evidence; it may explain the occasional case, and operative interference has been pursued. The post-mortem findings of such a case are described by Epstein (1940).

The last theory, that of vitamin deficiency, has considerable clinical and experimental backing. Subacute combined degeneration and vitamin B deficiency exhibit neurological signs which correspond in many ways with those seen in tabes. Experimental work in feeding young pigs on vitamin A deficient diet has produced blindness, inco-ordination and spasms. Mellanby's work (1931) is also quoted, in which he reported neurological degenerative changes in the spinal cords of puppies fed with amounts of cereal other than yellow maize and deficient in vitamin A.

Treatment and results are presented by Moore, Woods, Hopkins and Sloan (1938), and Moore and Hakin (1942). These workers are in agreement that trivalent arsenical drugs and heavy metals do not possess any direct toxic affinity for the optic nerve, as is the case with the pentavalent tryparsamide. Inadequate routine treatment (less than ten injections of a trivalent arsenical and heavy metal) results in blindness, occurring approximately within the same time period as if no treatment at all had been given; 28 per cent. are blind within one year of onset of symptoms, and all are blind by the seventh year. The most favourable results are recorded with malaria; only 9 per cent. of patients given malaria were blind one year after the onset of symptoms, 14 per cent. after two years, and 18 per cent. after three years. Thereafter for observation periods up to 15 years no additional blindness ensued.

https://doi.org/10.1192/bjp.90.378.328 Published online by Cambridge University Press

Experimental Syphilis and the Mechanism of Action of Malaria Therapy.

Himwich *et al.* (1940) give an account of experimental work relating temperature and brain metabolism. The method employed was the estimat of the metabolism of the brain *in vivo* by chemical analysis of arterial a venous blood entering and leaving the brain. This study was applied 15 patients with G.P.I. Further studies in excised cerebral tissues estima at various temperatures ranging from 25° C. to 45° C. were made on the cereb cortex of rats, the oxygen uptake being measured by the Warburg apparat The metabolic A : V oxygen differences increased irrespective of whet malaria, inductotherm or T.A.B. were used. The increase of respirat between 30° C. and 37° C. is 90 per cent., but within the range of 37° C. 44° C. was only 66 per cent.; the damaging effect of high temperature increased with duration. In 11 out of 15 G.P.I.'s examined the A : V differe increased by more than two volumes per cent.; in most cases the increase v greater than could be explained by the temperature. It is significant that increase of temperature which is critical may cause an irreversible change the thermolabile portion of enzymes, which no doubt explains the cause death occasionally observed in hyperpyrexia.

Pötzl (1938) gives an interesting account of the mechanism of the action malaria therapy, though no final decision has yet been reached concerning the w in which fever therapy effects its curative results in neurosyphilis. It has b claimed that the destruction of the spirochaete is achieved solely by the rise temperature, that it is so thermo-sensitive that it is unable to survive expos to temperature of the height and duration produced by the various meth of fever therapy. Nevertheless there is considerable evidence that ot factors are involved, and that even physical methods of inducing pyrexia by stimulating the immuno-biological responses of the patient.

Wagner-Jauregg himself favoured the immuno-biological theory, and following experimental findings support this view:

(1) The non-specific methods of treatment of general paresis can be arran in a definite series; the weakest are substances like milk, albumoses, phloget etc.; more active are tuberculin or vaccines, and most active are those disea produced by micro-organisms.

(2) The opsonic index for staphylococci, streptococci and *B. coli* increa in the blood during the first rise of malarial fever and in the cerebrospi fluid during the third, and remains increased from the fifth.

(3) The histological changes found in the brain during malarial attacks those of reticulo-endothelial activization.

(4) During the febrile attacks there is a very definite increase of peptida in the blood, and in the intervals a very considerable excretion of these in urine; this is a well-known result of immunization therapy.

(5) In malaria, even with high fever, there is no noticeable increase in amino-acid content of the blood, while that of the cerebrospinal fluid is app ciably higher than in fever produced by protein substances or vaccines, althou in these latter there is regularly found an increase in the amino-acid conten the blood; this indicates that in malaria there is a greater destruction

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protein in the cerebrospinal fluid than in the blood. This increase of the amino-acid content of the fluid only occurs, however, in patients with neuro-syphilis; in patients with natural malaria or those treated for gonorrhoea it does not occur.

(6) Alterations in the permeability of the blood-brain barrier are also associated with these immuno-biological responses:

(*a*) Weil-Kafka haemolysis reaction: Sheep's blood amboceptors are present in the blood of most healthy men, but never in the cerebrospinal fluid. In general paralytics when seizures are frequent these amboceptors can be demonstrated in the fluid. After fever therapy these disappear, and their disappearance and reappearance often run parallel with remissions and recurrences.

(*b*) After injections of dead cholera, virus immunity, substances are found in the blood, but not in the cerebrospinal fluid. If the same patients are then given malaria and subsequently injections of typhus vaccine, agglutinins are found in the fluid as well as in the blood. Reversal of the procedure shows the same result.

The effect on the blood brain barrier cannot be purely mechanical, since it hinders the passage of the sheep's blood amboceptors and facilitates that of the agglutinins.

(7) There is some evidence that a brain specific antibody is produced in the cerebrospinal fluid of tabetics and general paralytics; if one uses a brain extract instead of the heart extract as antigen in the Wassermann reaction one usually obtains a positive reaction in cases of parenchymatous neurosyphilis, but never in meningo-vascular syphilis. With the heart extract as antigen the Wassermann in the fluid remains positive after malaria, but when brain extract is used it has become negative in several cases, suggesting that the production of brain specific antibodies has stopped.

(8) The leucocytosis which occurs with physical methods of fever therapy makes it probable that these methods produce changes in the organism similar to those produced by many kinds of infection and fever therapy. The leucocytosis cannot itself be the main factor, however, for malaria produces a leucopenia, and is much more effective than methods which produce a marked leucocytosis, such as phlogetan.

Prophylaxis.

Though this review of recent literature is somewhat restricted on account of many papers from Europe not being available, there are two outstanding features: (1) Neurosyphilis is a preventable disease. (2) Neurosyphilis when it manifests itself should receive immediate and energetic treatment; the choice of method should be made after a lumbar puncture has been performed, in order that the degree of activity of the disease process may be assessed. The general consensus of opinion is that fever therapy, whether malaria or artificial fever is employed, must be supplemented by chemotherapy. Prophylaxis should be started from the beginning; adequate antispecific treatment of the primary case resulting in a negative blood and cerebrospinal fluid should guarantee against any subsequent development of neurosyphilis. For the

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detected latent neurosyphilitic or the asymptomatic neurosyphilitic, fe therapy plus chemotherapy is indicated. Finally Hutton (1941) stresses t importance of the investigation of the families of neurosyphilitics, in wh the incidence of neurosyphilis is sufficiently high to warrant the investigati of all marital partners. It is in these asymptomatic cases that one loo forward to a complete cure, by applying a prophylactic course of treatme long before the grosser manifestations of disease become evident.

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