subjective or objective, should be carefully recorded and analysed. Many of them appear to be common to a number of different conditions, but it is hoped that they will eventually be capable of classification, and thus provide the material for an early diagnosis of the conditions producing them.

THE TREATMENT OF GENERAL PARALYSIS BY INFECTION WITH MALARIA.

BY

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This paper is intended to give a preliminary account of an experiment in the treatment of general paralysis of the insane which has now been in progress for several months in the Royal Hospital at Morningside under the supervision of Professor George M. Robertson. Despite the fact that the etiology and the pathology of the disease—at least in their more significant details—have been successfully worked out, treatment has lagged far behind. Indeed, for the time being an impasse has been reached in the approach to the problem along the accustomed lines, and resort is being had to more empirical modes of treatment. Not that these are to be despised—if their fruits justify them, few will be found to cavil at their use.

In this latter category of reputed remedies one must place the treatment of general paralysis by inoculation with the plasmodium of malaria. The method has been used for a few years by Wagner von Jauregg in Vienna and by Weygandt in Hamburg, with results which, if confirmed, can hardly fail to arrest attention. It is claimed, for example, that out of a large number of patients treated in the course of twelve months no fewer than 41 per cent. can be regarded as completely cured; 20 per cent. sufficiently recovered to be able to resume their occupation though still retaining minor disabilities; and 10 per cent. as improved but not sufficiently so to warrant their discharge. The remainder failed to respond adequately to the treatment. The difference in the response to treatment seems to vary with the length of time the disease has been in progress before inoculation with malaria is resorted to. Thus, among the "cures" the duration was never more than two and a half years; among the "improved" the period was three and a half years; while in the case of the others the disease was of old standing. In practically every case, however, some improvement followed the treatment. In the most successful cases the physical signs of the disorder are said to have disappeared completely, though the laboratory findings—for example, the Wassermann reaction in the blood and cerebro-spinal fluid and the cell count and globulin content of the latter—remained unchanged. On the mental side there is reported a corresponding improvement. In other cases, though the results have been less satisfactory, there has apparently been some alleviation of the severity of the symptoms and a retardation of the rate of deterioration so characteristic of the disease. Such claims, confirmed as they were by the testimony of visitors to Wagner von Jauregg's clinic, seemed eminently worthy of practical investigation, and so the experiment was set in train.

Mode of Inoculation.

The first difficulty encountered at Morningside, when the experiment was resolved upon, was to procure a suitable supply of the virus. The help of the local health authorities was enlisted, but an exhaustive inquiry elicited the surprising fact that there was not at that time within the Edinburgh area an uncomplicated case of benign tertian malaria. The London School of Tropical Medicine was then approached, but even had a supply of the organism been available from that source, the practical difficulty of transporting it alive to Edinburgh was deemed insuperable. Just then there was admitted to Craig House from Burmah a young man whose mental breakdown was attributed to recurrent severe attacks of malaria, though no accurate information as to the type could be gathered. In due course this patient had a bout of fever which on clinical grounds appeared to be benign tertian malaria, and this was confirmed in the laboratory. As an additional precaution Colonel Marshall, Lecturer in Tropical Diseases in the University of Edinburgh, was called in consultation and confirmed the laboratory findings. But for this fortunate coincidence the initiation of the experiment might have been indefinitely postponed.

On March 29th of this year the patient referred to had a paroxysm, at the height of which venipuncture was performed and sufficient blood withdrawn in an ordinary syringe to inoculate twelve cases of general paralysis. Each of these received a subcutaneous injection of approximately 2 c.cm. of infected blood. The site of the injection was the loose skin just below the angle of the scapula. When the needle was inserted the subcutaneous tissues were probed in all directions to a distance of about 1½ inches so as to diffuse the plasmodium and promote absorption as rapidly as possible. A simple dressing of sterile gauze was affixed to the puncture by means of collodion, and any swelling resulting from the injection gently massaged. The patients immediately resumed their normal mode of life, but careful records were kept of their temperatures.

On reflection it would appear more prudent, in view of the difficulty of obtaining supplies of the virus, to substitute individual inoculation for the mass inoculation practised in this instance. In this way the virus can be kept alive for a long period of time by the inoculation of one patient from another in series. The one drawback would be that results would take longer to accumulate.

Incubation Period.

In every case the infection "took," though there were considerable variations in the length of the incubation period. The earliest cases had their first definite attack after eight days; a group followed the next day, and the others were spread out at irregular intervals till the sixteenth day. One case did not react till twenty-eight days had elapsed; while in another the interval was thirty-two days. Whenever a case was reported as having developed malaria a microscopic examination of the blood was made to confirm the diagnosis.

Subsequent Treatment.

The infection was allowed to run its course unimpeded for any number of paroxysms up to twelve—the average number being ten. During this time sponging was resorted to when required, but nothing more was done so long as the patient tolerated the condition well. In only two cases was it considered advisable to kill off the infection before the regulation number of paroxysms had occurred. In one of these an intercurrent affection occurred two days after the inoculation (and in no way dependent on it) and ended fatally, while in the other the decrepit condition of the patient before inoculation held out little hope that he would successfully carry the additional burden of a series of severe malarial attacks. He was therefore allowed to have only three paroxysms. To arrest the infection quinine hydrochloride was given in doses of 10 grains four-hourly for three days, and thereafter 5 grains thrice daily for fourteen days. In every case the temperature began to subside immediately after the administration of quinine was commenced, and by the fourth day was as a rule stabilized. In none of the cases has there been to date any recurrence of the malady.

The manifestations of malaria were in no way modified by its occurrence in cases already suffering from general paralysis, except that its discomfort was as a rule borne with forbearance which was as praiseworthy as it was unusual. On the fourth day after the subsidence of the temperature an intravenous injection of 0.3 gram novarsenobillon was given. This was repeated at weekly intervals for six weeks. There was generally a well marked degree of secondary anaemia after the infection had run its course, treatment for which was given simultaneously with the antispecific remedy.

Following is a brief account of the twelve cases treated:

Case I.

An advanced case of general paralysis lasting for two and a half years. The patient died of peritonitis three days after inoculation.

CASE II.

An advanced case lasting for three years, having previously had tabes dorsalis for three years. The patient was so infirm that only three paroxysms were allowed to develop. He did not seem to be affected by the treatment; decline was continuous thereafter, death occurring on May 30th, 1923.

CASE III.

Transferred to Bangour Hospital, where the infection "took." This case formed the starting-point of a similar experiment at Bangour.

CASE IV.

Duration of disease, eleven months.

Before Inoculation.—Mentally the patient was highly elated; had numerous tawdry delusions of grandeur—for example, could run 100 yards in six seconds; was imperial ruler of the universe; the greatest poet, preacher, and statesman in history. Facile and generally enfeebled; memory defective; frequently confused and disoriented. Physical state: Pupils unequal, right fixed; tongue and lower facial muscles tremulous; amimia; gait ataxic; other stigmata of general paralysis marked. Wassermann reaction in blood and cerebro-spinal fluid strongly positive.

Inoculation.—Incubation period, twenty-eight days; number of rigors, eight.

Present Condition.—Tolerated the treatment well, but was markedly anaemic at the end of it. Physical signs of general paralysis less obvious, but can be elicited on examination. Mentally is distinctly better. Is not now delusional and has a large measure of insight into his former state. His recent memory is now more dependable. There still remains a slight degree of euphoria and general mental enfeeblement, but the general improvement is striking.

CASE V.

Duration of disease, three and a half years.

Before Inoculation.—Mentally the patient was always dull and apathetic; habits faulty; distinctly enfeebled. Physically he was thin and enfeebled; pupils unequal and did not react to light; deep reflexes diminished; speech movements much impaired. Wassermann reaction in blood and cerebro-spinal fluid strongly positive.

Inoculation.—Incubation period, twelve days; number of rigors, nine.

Present Condition.—Tolerated the treatment well considering his condition. Highest temperature recorded 105°. Physical signs of general paralysis unchanged, but general condition better. Mentally there is little, if any, improvement.

CASE VI.

Duration of disease, one and a half years.

Before Inoculation.—Mentally the patient was stupid and mildly confused; had an exaggerated sense of well-being, with absurd delusions of grandeur, which, however, were beginning to fade before treatment; was silly in manner and speech; judgement obviously impaired and self-control diminished. Physically, he was fat and gross; pupils irregular, unequal, and unresponsive to light; marked impairment of speech—slurring and hesitant; great difficulty with test phrases.

Inoculation.—Incubation period, thirty-two days; number of rigors, eleven.

Present Condition.—Tolerated the treatment well, and improved under it. Had a severe degree of secondary anaemia from which he has now recovered. Trombone movement of tongue and difficulty in articulation not so prominent as before. Pupils now almost equal, and both react to light and accommodation. Physical health generally better. Expresses no delusions, but will concur in any imputation of great wealth, power, etc. His bearing as a whole is less aggressive.

CASE VII.

An early case; duration of disease, six months.

Before Inoculation.—Mentally, he was euphoric, lacking in common sense, full of impossible projects; deficient in self-control, especially when thwarted; there was slight impairment of recent memory. All these symptoms were present in a mild form. Physically, he presented all the characteristic signs—pupils very unequal and did not react to light; tremor of lips and tongue; failed at test phrases, etc. Wassermann reaction in blood and cerebro-spinal fluid positive.

Inoculation.—Incubation period, nine days; number of rigors, eleven.

Present Condition.—Devoid of insight into his condition, and intolerant of opposition to his whims. Always slightly elated. Physically much improved, and mentally has not lost any ground since inoculation.

CASE VIII.

Duration of disease, two years.

Before Inoculation.—The patient was silly and facile; memory much impaired; garrulous and incoherent; numerous grandiose delusions. Physically he was obese; musculature flabby; pupils unequally contracted and did not react to light; deep reflexes exaggerated; marked tremor of tongue and facial muscles; failed badly at test phrases. Wassermann reaction strongly positive in blood and cerebro-spinal fluid.

Inoculation.—Incubation period, nine days; number of rigors, nine.

Present Condition.—The patient is almost exactly as described above.

CASE IX.

Duration of disease, two years.

Before Inoculation.—Mentally, this case had advanced rapidly and had every appearance of terminal dementia. The patient could not be roused to answer questions except at rare intervals; his replies were almost unintelligible. Habits very faulty. So enfeebled in body and mind as to be practically bedridden. His physical state was comparable to his mental state. Had had numerous series of seizures, all of which produced further deterioration. Had lost weight progressively. All the stigmata of general paralysis prominent. Wassermann reaction in blood and cerebro-spinal fluid positive.

Inoculation.—Incubation period, nine days; number of rigors, eight.

Present Condition.—Distinctly improved physically, though the signs of general paralysis may still be elicited. Is rapidly making good his loss of weight. Mentally is very taciturn, but he now takes more interest in his surroundings. When induced to speak he shows a great improvement in articulation. Habits quite reformed.

CASE X.

Duration of disease, two years.

Before Inoculation.—Mentally the patient was stupid, amnesic, silly, and facile; had no definite delusions, but was unwarrantably happy and self-satisfied. Physical state: Pupils contracted and fixed to light; marked tremor of tongue and lower facial muscles; speech slurring; great difficulty with test phrases. Wassermann reaction positive in blood and cerebro-spinal fluid.

Inoculation.—Incubation period, eleven days; number of rigors, twelve.

Present Condition.—Less confused and does not obtrude his silly notions. Memory improved. Tidy in his habits and more active and alert. Speech difficulties remain quite marked. Pupils still unequal but react sluggishly to light.

CASE XI.

Duration of disease, four years.

Before Inoculation.—The patient was simple and demented; vaguely delusional; amnesic. Examination showed the deep reflexes to be exaggerated; pupils contracted and very sluggish in their reactions to light There was tremor of lips and tongue; speech slurring. Wassermann reaction strongly positive in blood and cerebro-spinal fluid.

Inoculation.—Incubation period, eight days; number of rigors, twelve.

Present Condition.—Treatment has had a general bracing effect, both mentally and physically. Mental attitude more alert and responsive. Little change physically.

CASE XII.

Duration of disease, four years.

Before Inoculation.—Mentally the patient was facile, amnesic, and becoming progressively more demented; inert and indolent. Physical state: Pupils R. > L.; both irregular in outline and sluggish in reaction. Other signs of general paralysis well marked.

Inoculation.—Incubation period, nine days; number of rigors, eleven.

Present Condition.—No apparent alteration as the result of the treatment.

General Results.

In interpreting the results which have so far accrued it is of supreme importance to remember that time is of the essence of the experiment. The disease tends to run a course of something less than five years on the average, and its progress even when untreated is often interrupted by remissions of varying duration and completeness. Care is therefore necessary not to attribute to any given mode of treatment results which are possibly only incidents in the unfolding of the disease. Not until the diagnosis of general paralysis is placed on an unshakable foundation and the possibility of the "cure" being nothing more than a remission has been eliminated by the passage of time, can one be certain that this or that mode of treatment is a success. Quite recently, for example, a patient in Craig House, suffering from general paralysis, after an intensive course of antisyphilitic treatment had a remission lasting for fifteen months, during which he was able to resume the active management of a large legal business. In the end he relapsed and died of general paralysis. But of several others who had been similarly treated not one had the same experience—which goes to illustrate the old fallacy of arguing from *post hoc* to *propter hoc*. Similarly, from the very nature of the disease itself, it is obviously necessary at this stage to assay the results of the malarial experiment with equal caution.

Looking at the results as a whole, there is a complete absence of what, even when the term is generously interpreted, might be described as "cures." Such a result, keeping in mind the degenerative changes involved in general paralysis and the average duration of the disease in these cases, was hardly to be expected. Of the twelve cases originally inoculated two have since died, one of an intercurrent disorder and one of general paralysis. Another case has been transferred to a neighbouring hospital where the experiment is being continued. Of the remainder a well marked improvement has occurred in two cases. In one case (No. IX) the patient before inoculation showed

every sign that the malady was gaining the mastery. He appeared to be quite demented, and physically he was but a pitiable shadow of his former robust self. To-day he is to all outward appearance in excellent physical health. His habits are tidy; his speech movements, which were formerly almost wholly disorganized, are now well co-ordinated; and his vitality is not now drained by bouts of severe seizures as it previously was. Admitting, as one must do, that it is difficult owing to his taciturnity to assess the degree of mental enfeeblement which remains, yet one cannot but be struck by the general transformation. The other case is described above as No. IV. Here the conspicuous change is in the patient's mental state, though his physical health is also improved. To those who knew him in his former phase he now appears a new creature, a different personality altogether. In the remaining cases lesser, though often substantial, changes are common, but it is now generally recognized that many of these changes (for example, in the character of the pupillary reaction) may develop in the ordinary course of the disease. The average duration of the disease in the twelve cases was two years, and in every case the greatest care in the diagnosis was taken, all the usual serological tests being applied. At the moment these are again being investigated and so far as this has been done Wagner von Jauregg's conclusion that the condition of the blood serum and cerebro-spinal fluid is not materially altered by the malarial infection has been confirmed.

To the extent, at least, that none of the patients are any the worse for their experience, the experiment has been justified. Time alone will show whether any further justification will be forthcoming. Assuming that the results eventually turn out to be more favourable than they seem at the moment, how is the phenomenon to be explained? As long ago as 1883 Clouston described two cases in which mental disorders had been arrested by incidental sepsis, originating in one instance in the parotid gland and in the other in the hand. This led him to prophesy that "some day we shall hit upon a mode of producing a local inflammation or manageable septic blood poisoning, by which we shall cut short and cure attacks of mania"—the type of disorder from which his two patients suffered. The hypothesis underlying Wagner von Jauregg's work is virtually identical with that which Clouston here adumbrates, though it is applied to a very different form of mental disorder. Their common quest is for an infection which, while not of itself endangering the patient's life, will either stimulate the common bodily defences against the original disease or else will facilitate the operation of remedial agents. With this end in view some experimental work has been done with tuberculin and vaccines of different strains of staphylococcus. Apart from the risks involved in the use of these, the results from a therapeutic point of view have not been encouraging. Later still, attempts have been made to produce a more active bodily defence along some particular line without evoking the risks and discomfort of a general febrile disturbance. In this connexion some work has recently been done in Morningside with substances—for example, phlogetan—which produce a leucocytosis without the other accompaniments of fever. Here again, though a definite leucocytosis could be maintained for a prolonged period, the results of such treatment in cases of general paralysis were negligible. Whether the method of treatment with malaria will prove more efficacious time and a large field of experiment will be necessary to show. And even if the claims made for the treatment are in the long run substantiated there will remain to be answered many questions: Is the high temperature which can be produced incompatible with the well-being of the spirochaete? Has the infection with malaria any influence on the permeability to salvarsan of the choroid plexus? If the success of the method does not depend on such more or less mechanical effects, what subtle chemical changes occur? That these cannot be answered at the moment is enough to invest the further progress of the experiment with engrossing interest.

Conclusions.

1. Of the nine cases in whom the treatment was completed two are conspicuously improved; in one case the emphasis is on the mental, in the other on the physical improvement.

2. Besides these, four other cases show some improvement, although not so marked.

3. In the remaining three cases no distinct change has occurred. It is noteworthy, however, that in none of these cases has there been any progressive deterioration. This is specially true of the only early case—No. VII.

THE TREATMENT OF GENERAL PARALYSIS BY MALARIA.

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Wagner von Jauregg's[1] malaria treatment of general paresis, and the excellent results published by himself, Gertsmann,[2] Weygandt,[3] Kirschbaum, Delgado,[7] and others, first attracted our attention in the early months of 1922, and through the kindness of Professor Stephens of the Liverpool School of Tropical Medicine, who inoculated the first cases for us, we were able to commence this treatment in July, 1922.

Mosquitos are common at Whittingham, and recognizing the possibility of spreading malaria we had, prior to commencing treatment, examined many mosquitos caught within a mile of the hospital building, and felt satisfied that only varieties of Culex were present. In September of this year, however (fourteen months later), a further hunt for mosquitos revealed the presence of *Anopheles plumbeus*.

Whilst recognizing the impossibility of the restoration of degenerated cells and fibres we hoped for destruction of spirochaetes and complete and permanent arrest of degeneration. Authorities explain the influence of malaria upon the course of general paralysis in different ways. One is the destructive influence of high temperature as such on spirochaetes, as shown by Jahnel and Weichbrocht;[4] it is conceivable that waves of high temperature, as in malaria, may be more efficacious than continuous temperatures. Muehlens and Kirschbaum[5] believe that following inoculation there is a marked impoverishment of the blood, followed by a rapid regeneration of blood, which leads to a non-specific reactivation of the immunity processes. This theory would be supported by the views of Hauptmann. If these theories be correct, then high temperature and impoverishment of the blood should be aimed at.

It seems possible that different strains of *Plasmodium vivax* give different clinical types of malaria. Some authorities recognize only three species of malarial parasites, while others count double this number; it would appear that Muehlens and Kirschbaum were using a strain of *P. vivax* giving a different clinical type of malaria from ours, for in their experience of 76 cases of artificial malaria jaundice occurred in 12 cases, whilst in our 40 only one case of jaundice has been observed.

It was with these considerations before us that, after inoculating cases with quartan, malignant tertian, and two strains of benign tertian, we decided to allow all strains to die out except the second strain of benign tertian, which we named "W." This strain from the first gave a reasonably high temperature and a marked degree of anaemia. It has produced no untoward effects, no local disturbance at the seat of injection, and no very marked enlargement of the spleen. All cases have at once responded to quinine, and there have so far been no relapses. This strain has already passed through fifteen hosts and is at present in use in other hospitals. It seems advisable to name the strain so that it may be traced, for many points, such as increase or weakening of the virulence of the parasite, and various other questions which arise, will be more easily answered when the strain has passed through many more hosts than at present.