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THE RELATION OF SYPHILIS TO MENTAL DISORDER AND THE TREATMENT OF G.P.I. BY MALARIA*

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WHEN the Wassermann reaction was first employed as a routine investigation in mental hospitals, it was thought that syphilis was intimately related with the mental symptoms of the psychotic. As far as the disease of syphilis itself is concerned, obsessions and fixed ideas may occur in the primary stage or produce a condition of syphilophobia; many of these cases, though having exposed themselves to the risk of infection are actually uninfected and healthy. I have seen three such cases certified and sent to mental hospitals; they all improved and were finally discharged, but in two cases, the phobia reappeared with increasing anxiety and curiously enough both committed suicide by drowning. In the secondary stage of syphilis toxic infection sometimes produces a state of mental confusion, with delirium and hallucinations. Lastly, in the tertiary stage mental symptoms may occur concurrently with cerebral syphilis and indeed give rise to much difficulty in differentiating this condition from a very much more definite psychosis and one which is responsible for large numbers of mental hospital admissions, viz., general paralysis of the insane or dementia paralytica.

In mental hospital practice apart from general paralysis, syphilitic psychoses are practically non-existent and it cannot be stressed too often that in many cases of mental disorder, which do not present neurological signs of neurosyphilis, a positive reaction of the blood serum (and in a few cases even of the cerebrospinal fluid) is only evidence of old syphilis, in no way to be regarded as an ætiological factor. Many relatives have been led to believe, quite erroneously, that anti-syphilitic treatment

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will bring about a recovery, whereas the syphilitic infection has either preceded the onset of mental disease or has been contracted subsequent to the development of a psychosis. Syphilis in some cases may be regarded as a contributory cause, but excluding the cerebral syphilitic with mental symptoms and the general paralytic there does not appear to be any direct relation between syphilis and insanity.

It is interesting to record that the incidence of syphilis amongst the insane is on the decrease. In 1930 * Poynder reported the results of Wassermann tests in 946 male admissions to Long Grove Mental Hospital during a period of five years from June, 1924. All tests in the L.C.C. mental hospitals are carried out at the Central Pathological Laboratory and the Long Grove results are of interest, as they are comparable with earlier series investigated at Cane Hill, by Wootton in 1913, by McCowan in 1921, and at Hanwell by Lilly and Hopkins, 1923-25.

Wassermann Reactions

	Total Examined.	+ Wassermann.	G.P.I.	Non-Paralytics.
Cane Hill	284	89 or 31 per cent.	66 or 23 per cent.	23 or 12·5 per cent.
Wootton, 1913.				
Cane Hill	150	44 or 29·3 per cent.	32 or 21 per cent.	12 or 10 per cent.
McCowan, 1921.				
Hanwell	412	105 or 25·5 per cent.	50 or 12·1 per cent.	55 or 15 per cent.
Lilly and Hopkins, 1923-25.				
Long Grove	946	125 or 13·2 per cent.	87 or 9 per cent.	38 or 4·4 per cent.
Poynder, 1924-29.	males.			

In the accompanying table are set out the figures illustrating the evidence of past syphilis among new admissions, and these again are subdivided into general paralytics and non-paralytics. It can be seen that the incidence of syphilis has gradually decreased, being as high as 31 per cent. in 1913 and reaching the comparatively low figure of 13 per cent. in 1924-29. It is not wise, however, to draw any conclusions regarding the relative percentages of general paralytics, the years preceding malaria therapy show little variation, but the low figures for recent years do not necessarily mean that

* Poynder, *Journal of Mental Science*, LXXVI., p. 107, 1930.

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G.P.I. is a less common disease, because since the advent of malaria therapy, cases of G.P.I. have been concentrated at two or three mental hospitals in the L.C.C. service, where treatment is conducted. The greater incidence of non-paralytcs at Hanwell may be explained by the theory put forward by Mott, that syphilis is more prevalent in the West End of London, from which district the majority of Hanwell patients are drawn.

Yet with an indication of a decrease in the number of syphilitics amongst admissions for the insane, one might expect that the incidence of G.P.I. should be down also. Through the courtesy of the Board of Control I have had access to figures giving the total number of general paralytic admissions to mental hospitals in England and Wales between the years 1907-31. While stressing the fact that my views in no way represent those of the Board of Control, very great caution should be exercised before definitely concluding that G.P.I. is on the decrease. With female admissions (first attack) the ratio of general paralytcs to total admissions remains fairly constant. Though the total number of male G.P.I.s has gradually become smaller during the last ten years, it is impossible to draw any definite conclusions without being able to eliminate other factors. For instance, it has become the fashion in recent years to treat many cases in general hospitals instead of certifying them and sending them to mental hospitals.

Before the days of malaria therapy the early diagnosis of general paralysis was of little import ; sooner or later a doubtful case would become established by its clinical course and sooner or later, despite any effort at treatment by anti-syphilitic measures the case would die ; in fact, with few exceptions cases died within one to three years from onset of symptoms. In males the end might come with startling rapidity, a fatal issue supervening within a few months. Now that we have at our disposal a means of treating what hitherto was regarded as a fatal disease it is all important that G.P.I. should be diagnosed and confirmed as early as possible. The confirmation of a diagnosis demands a positive reaction of the cerebro-spinal fluid, yet here a word of warning is necessary, every case with a positive C.S.F. and superadded mental symptoms must not be labelled as a case of G.P.I. Last year when reviewing the results of malaria therapy in

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women over a period of seven years, it was found that 36 cases could not be included in the total, as they were not suffering from general paralysis, yet they presented positive sera and C.S.F. The syphilitic infection, except in the cases of meningovascular syphilis must be regarded as latent and not related to the psychosis. Six were tabetics with psychoses (3 delusional insanity, 2 melancholia, and 1 schizophrenia); amongst the others were old cases of epilepsy, manic depressives, confusional types of insanity, alcoholics, schizophrenics, a case of senile dementia, a Huntingdon's chorea, five showed varying degrees of dementia with gross brain lesions and seven from the history and neurological signs were cerebral syphilitics. With the exception of the cases of cerebral syphilis, gross brain lesion and the tabetics, these cases did not present any signs suggestive of neurosyphilis.

Psychoses somewhat resembling general paralysis are not uncommon in association with cerebral syphilis; the differentiation of this condition from the more serious one of general paralysis is often difficult. The symptoms of the cerebral syphilitic yield rapidly to energetic anti-specific treatment and indeed to malaria therapy itself, whereas the disease of general paralysis is progressive in character and uninfluenced by antispecific remedies. An important point in differentiation of these conditions is the length of duration of symptoms. The onset of G.P.I. is insidious, that of cerebral syphilis rapid. As Colonel Harrison says: "The patient glides into general paralysis while he jumps into ordinary cerebral syphilis." The length of time (if a reliable history is obtainable) that has elapsed between the primary attack and onset of later symptoms is seldom less than six years in G.P.I., whereas in cerebral syphilis it is the reverse.

Reliance should be placed on the physical signs; they are more definitely localised in cerebral syphilis; ocular paralysis is common. The cerebral syphilitic frequently gives a definite history of an attack of syphilis; the general paralytic often quite honestly denies ever having had an attack, or if he did the attack was very mild. Secondary reactions are the exceptions, not the rule. In mental hospitals, cases of cerebral syphilis are comparatively rare, only seven in seven years at Horton.

It might be convenient here to say a few words about the diagnosis of G.P.I. The mental symptoms are so

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protean in character, that in the early stages diagnosis presents considerable difficulty. There is an early stage in which the patient is often free from physical signs, but with the all-important fact of syphilitic changes in the C.S.F. Too often an alteration in character is the first symptom with loss of finer habits and without any obvious sign of insanity. Bunker* analysed 74 early cases and found the following symptoms in order of frequency: emotional irritability, restlessness, abnormal quietness and apathy, loss of weight, forgetfulness, increased tendency to sleep, defective judgment. All these symptoms are very vague. Much depends on the individual skill of the clinician. Anyone between the age of thirty to fifty who has indefinite neurasthenic symptoms should be examined for G.P.I., also anyone who suddenly develops fits in middle life. The practitioner is too often easily satisfied with a diagnosis of neurasthenia or epilepsy. In all these cases a Wassermann of the blood and C.S.F. should be done. It is not uncommon nowadays to come across cases with negative sera. The C.S.F. should always be examined in any doubtful case and if the case is one of general paralysis, the C.S.F. will be positive with an increased amount of globulin, which gives rise to the typical parietic colloidal gold curve. As the case progresses mental symptoms become more marked and it is possible to classify cases into different types—the grandiose exalted form, in which delusions of grandeur and wealth are the prominent features, the maniacal agitated form, in which restlessness and increased psychomotor activity predominate, the depressed form, characterised by the presence of delusions of persecution—often of a somatic nature, the affective state being the antithesis of that in the former group, and lastly the simple dementing form, in which general mental reduction is more obvious. By this time one or more of the physical signs may be present—Argyll Robertson pupils in some cases, tremors of tongue and lower part of face with a loss of expression, increased tendon reflexes (except in those cases accompanied by tabes), slurring of speech, an extremely valuable sign of it occurs early in the course of the disease, and in those cases not complicated by tabes a shuffling unsteady gait.

Before giving a brief account of the results of malaria

* *American Journal of Medical Science* 1926, p. 386.

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therapy at this hospital, I would point out that they deal with female general paralytics only. During the last eighteen months, facilities have been available for the treatment of male cases, but it would be premature to include the small number so far treated. Though sufficient evidence has not yet been adduced, one has gained an impression—perhaps erroneous—that G.P.I. in the male is a more serious disease, not only does the male case appear more physically ill than the female, but he does not withstand the course of malaria so well.

The results are based on a review of 200 female cases treated during the previous seven years.* It is not proposed to go into too much detail here, nor to burden you with unnecessary figures, but rather to point out some salient facts that have emerged from our experience and to say a little about the treatment itself.

On analysis of the cases, it was found that the grandiose maniacal and depressed cases were numerically smaller groups, compared with the total of the simple dementing type. All cases, with the exception of twenty-four, received malaria alone. The percentage of discharged cases was about 35 per cent., which compares favourably with the figures of other workers. The number of those remaining in hospital was high (40 per cent.), while the deaths which occurred during the seven years were low (25 per cent.).

There are three important factors which appear to influence the results: the duration of the disease before treatment, the clinical type of G.P.I., and the reaction to body weight. It was found that the highest percentage of remissions occurs in those cases where the disease is treated in the early stages, three-fifths of good remissions were confined to cases who received their treatment in the first six months. Disappointments occur and it is significant that while 45 per cent. of the cases of six months' duration recovered, 55 per cent. remained under certificate in hospital. Another feature of interest is the case who remits, when the disease has been established over two years. Treatment, then, should not be despaired of altogether. With regard to the clinical types the prognosis appears to be definitely better for the grandiose manic and depressed cases, 50 per cent. of these show

* A review of seven years' malaria therapy in general paralysis. W. D. NICOL. *Journal of Mental Science*, LXXVIII., Oct., 1932.

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remissions. In the simple dementing cases even in those of short duration not more than 25 per cent. recover and the remission rate rapidly falls with increased duration of disease. Some of the treated cases show rapid increase of weight and it was found that this abnormal weight increase was confined to the cases which showed no improvement. A very useful prognostic factor emerged from our results and that was, almost a constant limit could be assessed with regard to the time of recovery after treatment. Nearly all cases, if well enough to be discharged from certificate and to return to the outside world, were able to do so within seven to nine months following a course of malaria ; in fact, if a case is not mentally well by that time the prognosis should be very guarded. Only a very few cases received a supplementary course of anti-specific treatment or tryparsamide, but even with this small number and from the experience of other workers, supplementary treatment is indicated, the life of the patient is prolonged and the recovery rate in some series is higher.

Of those cases which do not improve sufficiently to leave hospital, in many the progress of the disease is arrested, while in others there is little change or gradual deterioration. In quite two-thirds of total numbers treated physical improvement is marked and the patient at least has a happier and cleaner existence than fell to the lot of the untreated cases of pre-malaria days. From the psychological point of view, it is of interest to see the changing form of psychosis in some cases—schizoid reactions and an acute hallucinatory psychosis, hitherto foreign to the original progressive deterioration of the disease. Malaria treatment undoubtedly prolongs life for the general paralytic. Out of 108 cases treated at Horton between 1925 and 1928, 70 per cent. are still alive. In the Board of Control series investigated by Meagher, of 624 untreated general paralytic admissions in 1923, 90 per cent. were dead by the end of 1927.

The mortality rate in induced malaria still remains high, varying from 10 to 15 per cent., and if death occurs within six to eight weeks, following the inoculation, malaria, if not the actual cause, is undoubtedly held to be indirectly responsible.

The risk of mortality would be reduced, if cases were sent for treatment in the very early stages, before the

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disease has progressed. In our series at Horton the mortality rate has become gradually lower ; in benign tertian over a period of seven years it was 5 per cent., in a series of over sixty cases treated by malignant tertian malaria the mortality rate was not more than 4 per cent. It should be mentioned that selection was aimed at with the M.T. cases, in those treated by B.T. no selection was made. Yet risks must be taken in treating a disease which, if left alone, will surely prove fatal. It is obviously courting disaster to treat an advanced semi-bedridden case, or a case in which there is some serious heart lesion (aortitis in G.P.I. however is extremely rare) ; marked obesity in a patient often causes considerable anxiety during treatment. It is surprising how many cases will pick up with ordinary hospital treatment after a few weeks ; the mere fact of being kept in bed and given a nourishing diet will restore a case to a condition sufficient to withstand malaria. The main secret of success lies in efficient nursing, such as one can obtain at a centre like this, coupled with expert laboratory control in examining blood films regularly. This, together with the interruption of fever when necessary, should prevent impending risks. We have found one dose of 5 grains of quinine sufficient for aborting an attack, it produces a remission of fever from ten to fifteen days, during which time the patient is regaining his strength, it has the advantage that the fever recurs, generally with less severity. What are the indications for temporarily interrupting the fever ? If all is not well with a patient, anxiety is generally felt about the fourth or fifth day—continued hyperpyrexia, a persistent high pulse rate after the temperature has fallen, faintness or collapse during the paroxysm, persistent vomiting, the occurrence of seizures, undue restlessness and the earliest signs of jaundice, also a change of the intermittent character of fever to a remittent type, are regarded as signals that the course should be interrupted. Digitalis as a prophylactic against cardiac complications and gentian and soda for vomiting are useful adjuncts, but the practice of giving a small dose of quinine during fever and knowing when to give it has in my opinion rendered malaria a safe procedure.

At Horton, on account of malaria research conducted in conjunction with the Ministry of Health, one has had

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the opportunity of trying different species of malaria—benign tertian, quartan, malignant tertian and *P. ovale* have all been employed. The therapeutic value of one particular species does not appear to be superior to another, but this cannot definitely be concluded until one has access to a much larger group of cases treated primarily by malignant tertian or quartan in order to compare them with the already big number treated by benign tertian malaria. Malignant tertian is too severe to use promiscuously ; it was given a trial on the hypothesis that the fever was more severe and the sporulating parasite had a predilection for the brain capillaries. Quartan is definitely useful for the case which is immune to benign tertian ; moreover, it can be given to a much older and more debilitated type of case with absolute safety. If the case runs true quartan, the length of time required for a course of treatment may be a drawback, on account of expense involved and time lost, which to the private case or the general hospital patient may be all-important. Benign tertian malaria, with the double tertian fever, which occurs in most primary cases of B.T. malaria, is much quicker, the whole course for an uncomplicated case being over in ten to fourteen days.

The employment of different species of malaria rendered it possible to give those cases of general paralysis whose mental condition did not respond to the first treatment a second course of fever. As one species of malaria does not confer immunity against another species, it was thus possible to give patients a second course of treatment, which was as severe as the first course. A patient who had B.T. could have M.T., quartan or ovale and so one could ring the changes and give a second or even a third treatment. Unless it improves their physical condition, the results are frankly disappointing, and I have failed to record any mental improvement except in those cases where the second course was applied in the first six months following the first. It seems almost certain that if a patient does not respond to the first treatment by malaria, he will not respond at all.

Now how does malaria act ? In our present state of knowledge this question appears unanswered and we must fall back on the idea that the treatment is mainly empirical. Yet we have been able to discover two important

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facts—the alteration in the serology of the treated patient and the appearance of the brain. Last year thirty-two fluids of unimproved cases were examined at the Central Laboratory at the Maudsley. Two years at least had elapsed since the primary attack of malaria. All cases had strongly positive findings before treatment; 17 returned a negative Wassermann and in 10 it was markedly reduced. These results are of interest, as the malaria alone must be responsible for this. None of these cases had any supplementary antispecific treatment, but there does not appear to be any correlation between the serological reactions and the clinical result. I have also had the opportunity of inducing malaria in two or three cases (not general paralytics) with an obstinately positive blood serum (in spite of ordinary antispecific means), and in each case the serum after a course of malaria has become negative.

Histologists are in agreement that the treated paralytic brain presents an altered picture. Geary,* who for many years has examined brains at the Maudsley and Claybury laboratories, writes that before the days of malaria therapy Mott found spirochætes in the brain in 66 per cent. of general paralytics. Forty-two brains of general paralytics treated at Horton have been examined and the results are tabulated in the accompanying table.

Forty-two General Paralytic Brains

	Total.	Spiro- chætes + +.	Total.	Histological Examinations.		
				Perivascular Changes.	Slight Changes.	No Change.
Treated .	31	2 (1 Cong.)	18	7 (2 Cong.)	2	9
Untreated .	11	3	10	6 (2 Cong.)	3	1

The absence of the characteristic perivascular changes in most of the treated cases is marked. In this series are included four congenital cases and it is noteworthy that treatment in these cases produced no pathological improvement. Spirochætes were present in only one

* Geary, "Histopathology of General Paralysis," Mott Memorial Volume, 1929.

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acquired case which had received treatment. The case was treated in 1925 and had a good remission, lasting four years; on her readmission she showed marked mental deterioration and her physical condition was too poor to withstand further treatment.

In view of the serological and histological findings one must admit that malaria has done more to produce these changes than any other mode of therapy.

In spite of education of the public to the dangers incurred in contracting venereal disease and the establishment of V.D. clinics, and in spite of energetic anti-specific treatment in the primary stages, there is no guarantee against the subsequent development of nervous and mental symptoms which necessitate certification. Ordinary antispecific measures are not prophylactic against the onset of G.P.I. In the application of malaria to medicine, have we got a prophylactic against syphilis of the nervous system? Surely the latent case with persistently positive changes in the cerebrospinal fluid is a potential G.P.I., and in these, as in other cases with obstinately positive sera, is not a course of malaria indicated? Malaria has been adopted by some workers as a therapeutic agent for primary syphilis in addition to routine arsenic treatment, and time alone can tell whether these cases will be protected from developing a disease, which even now, is responsible for many incurable insane.