Th. Sect.

M. D., 1926.

MALARIAL THERAPY

IN

GENERAL PARALYSIS

OF THE

INSANE.

BY

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ACKNOWLEDGEMENTS.

All the cases which are quoted herein have been under my care, except those who died before my appointment to this Hospital in September 1924, and these were treated by my predecessor.

I have acknowledged in the text any articles quoted, and the majority of private communications received.

The microphotographs of the untreated General Paralytic were prepared in this Laboratory, or in the Laboratory of Rainhill Mental Hospital, and I am indebted to Dr G. A. Watson for those of the Betz cells.

All the cerebro-spinal fluid tests were carried out here except in three cases quoted.

Joint articles are quoted from the Lancet, Journal of Tropical Medicine and Hygiene and L'Encephale: they appeared in the names of my colleague J.E.Nicole and myself, but the cases quoted were actually under my care the whole time, although they were in his Wards for some months.

The pathological slides of brains which I have used were sent to me by the Rainhill Laboratory.

THE HISTORY OF MALARIAL THERAPY.

Even so far away as the times of Hippocrates and of Galen, reports are found in medical literature of apparent remissions or "cures" of conditions evidently actually General Paralysis of the Insane, and as a rule these remissions are found to have taken place after a high fever.

More recently, similar cases have been reported in detail, and attempts have been made to stimulate the temperature to provoke an artificial high temperature: Dubuisson, in his "Traite de vesanie," published in 1816 reports a remission obtained by "suppuration produced with conscious intention", whilst in 1836 Esquirol remarked "There are few chronic illnesses (mental) which are not cured when a high fever develops", and he lamented the fact that physicians had not the wherewithal to provoke a pyrexia, although the Medicial Superintendent of the Tübingen Asylum in Württemberg had given muriate of mercury to his patients in repeated doses in order to provoke this pyrexia.

Frequent mention is found in medical annals of reported cures of General Paralytics, and in 1857 Baillarger demonstrated to the Paris Academy of Medicine certain cases of General Paralysis in remission consequent upon erysipelas, whilst 20 years later Meyer endeavoured to obtain such remissions by rubbing in a certain irritative ointment to the scalp.

Since that period a definite theory has been founded on the observations that such remissions can and do occur, and fixation abscesses brought about by turpentine, together with other means, have been extensively tried.

Wagner-Jauregg, however, seems to have been the first to actually use malaria therapeutically, and this only after he had had poor results with the usual anti-syphilitic remedies. He declares that the advance of General Paralysis could be checked by the use of salvarsan, but the remissions were rarely complete and never really lasting.

In 1887 he proposed that malaria should be used in

General Paralysis, basing his suggestion on the observations made that the chronic mental maladies often shewed improvement after sustained pyrexia, and possibly having in mind that Rosenblum, at Odessa had three years previously used the spirochoete of relapsing fever with some success.

Wagner-Jauregg, in 1887, did not use malaria but did some experimental work with the bacillus of tuberculosis in other conditions of insanity, and treated one case of General Paralysis, finally using Koch's tuberculin on a number, but never exceeding a dose of .1mgmx gram. He compared the life of these treated cases, in 1895, with a similar number of untreated cases, and found that a longer life and a greater number of remissions shewed in the treated cases.

Pilecz later confirmed this finding, and Wagner-Jauregg then began to make tuberculin his routine method of treatment of General Paralysis, but at this time he much increased the dose giving from .5 to 1 gram, and with this he combined a mercury salt intensively.

A lasting remission was found in many cases with a possibility of return to work, and cases reported in 1909 are said to have been at work in 1921.

Unfortunately, however, Wagner-Jauregg found that even after a remission a return of the disease in full force was found, and a necessity for treatment was again evidenced, which made him look for some agent which would give more effective and lasting remission. He finally commenced to use Besredka's typhus vaccine, which, given intra-venously, gave marked rigors.

To quote Wagner-Jauregg's own words:-

"In the course of experiments in treatment with tuberculin and vaccine extending through the years it has struck me that repeatedly just in those cases especially complete and lasting remissions occurred in which, in the course of the treatment, from any cause whatever, an infectious disease had set in, pneumonia, erysipelas, abscess, etc.

"The circumstance roused me to the thought that it might well be that treatment would be most effective if one directly produced an actual infectious disease in the parietic patients."

"Starting from this consideration I turned back to the proposal I had already made in 1887. In the summer of

"1917 I inoculated some general paretics from a soldier
"ill with malaria whose disease was established by clinical
"observation and microscopic findings as tertian malaria.
"From these patients I inoculated others. There
"were 9 cases in all, some advanced, some fresh cases.
"The effect of this treatment in all the cases not
"very far advanced, that was in six of the nine cases, was
"a plainly favourable one. Three of them today,
"four years after the treatment was concluded, are still
"actively and efficiently at work."

In September 1919 Wagner-Jauregg again commenced the treatment of General Paresis by malaria, using a benign tertian malaria, and since that date many other workers have commenced to use the method, the Mental Hospital at Whittingham being amongst the first British Hospitals to do so.

Other methods have been used: the nucleate of soda: the spirochoete of Dutton: fixation abscess: and tuberculin: but from the experience of Wagner-Jauregg, Scripture and the other real pioneers of the attempted treatment of the old standing disease, General Paralysis of the Insane, one feels confident that the ease with which malaria is transmitted, and the ease with which it is controlled, makes it at least the most suitable method of treatment at present known.

Wagner-Jauregg gives his opinion that the remissions are at least semi-permanent, and Marie has recently quoted many cases extending over four or five years who are still actively employed at their ordinary duties.

The treatment of General Paralysis of the Insane is of more recent origin in this country, and so one has largely to be guided by the extended experience of the Continental Schools, which are freely quoted, and freely given.

Desperate ills need desperate remedies, and one has to thank Wagner-Jauregg and his followers for the provision of a method of treatment which is rapidly becoming so stabilised as to be counted far from desperate, and which is bearing out, at least to some extent, the great results which he and his compeers claim for it.

Even taking a conservative British view of the treatment workers all agree that at least it promises more than other methods.

THEORIES UPON WHICH MALARIAL THERAPY IS BASED.

Although very definite clinical results are being obtained in the treatment of General Paralysis of the Insane by means of malarial therapy, it is really unknown why such improvements do take place, and quite a number of tentative theories have been advanced from time to time to explain the many artificial "remissions" which have been observed, and which one now expects almost confidently.

Such theories may be summarised:-

1. The high fever may cause the extermination of latent spirochoetes, and the increased metabolism may remove waste products.
2. The destruction of the erythrocytic elements may cause a rapid regeneration of the red blood elements, with the consequent creation of a non-specific antibody.
3. The relationship between the two protozoa may cause an antibody formation specific to protozoa.
4. The creation ~~of~~ the high temperature, of a leucocytosis and the formation of bacteriolysins.
5. A direct action by the malarial parasite on the nerve tissues and on the vessels.

Unfortunately, any one, or all, of these theories seems to fall short of a satisfactory explanation, although support can be given to each.

1. The action of the high fever in extermination of spirochoetes and the quickened metabolism and removal of waste products.

Experiments have been carried out by Weichbrodt, Jahnel and members of the Italian school, and they have proved to their critical satisfaction that high temperatures have a direct action on the spirochoete, and that syphilis infected animals develop no primary lesion if they are subjected to a high temperature (106 F.) for half an hour immediately after infection.

Jahnel points out that the spirochoete is difficult to obtain in the brain of General Paralytics who have had some high fever, but many British workers have demonstrated the spirochoete in brains of patients dying of intercurrent febrile disease whilst suffering from General Paralysis.

Although the high temperature does kill the spirillum yet in every Mental Hospital cases can be found giving a true laboratory and clinical picture of General Paralysis in which there is a definite history of malaria subsequent to the primary infection and antecedent to the noted onset of the dementia.

One of our cases here (H.H.B.) was infected by syphilis whilst serving in the Army in India in 1913, and he had an intensive course of arsenic. Within eight months of the primary sore, he was admitted to Hospital suffering from malaria, and during the remainder of his service he had recurrences.

He was treated with therapeutic malaria here in February, 1924, but with little or no effect and his dementia is progressive.

Another case (K.B.R.) admitted in October 1925 bore no signs of a primary scar: he had contracted syphilis eleven years ago, and had had three attacks of malaria in the intervening period, but his dementia increased very rapidly, in spite of twelve therapeutic rigors.

He died within three months of admission, and no spirochaetes could be demonstrated in his brain.

A third case, who has improved mentally, gives a history of "ague" nine years ago, and he is able to describe other attacks which he had whilst in the Army.

Indeed, his insight is such as to make him rather difficult to treat, as he frequently demanded quinine to terminate his induced malaria.

In spite of the three cases quoted, however, one feels bound to accept the experimental work of the Italian observers, and to agree that high temperature may have some retarding effect upon the activities of the spirochaete at the initial infection.

But when one is repeatedly confronted with cases giving definite history of malaria or other high-fever reaction in the incubation period of General Paralysis, one is compelled to come to the conclusion that where a definite trauma exists, as exist it does, in the higher centres of the brain, the high temperature has no effect upon such lesion.

That such a high temperature causes remission in many cases is an accepted fact, but such remissions are more nearly postponements than are the "remissions" obtained by malaria induced when the dementia is apparent. Wagner-Jauregg and Scripture quote cases in "remission" due to malaria and say observation has been complete for at least seven years.

In this connection it is perhaps worthy of note that no one has as yet brought forward pathological evidence of change in brain conditions due to say, pneumonia.

Such an incidental illness seems to have little or no effect upon the cerebro-spinal fluid condition, for the two cases one has examined before the exhibition of malaria but eight days after the crisis of a true pneumonia, gave no appreciable alteration.

The only change in the fluid to Lange's gold sol test was found in the first dilution, where the reading became "8" instead of "5". The glucose content was, however, increased from the 60mgm which one accepts as an indication of the usual. (Polonovski and Duhot, Presse Medicale, 1923, p.60, quote 45 to 85mgm per 100 c.c.)

That the high temperature alone is responsible for the "cure" obtained by malaria seems to presuppose that the existence of the spirochoete is responsible for the state of General Paralysis, which is far from the generally accepted view. It is true that the spirochoete does exist in a latent form, but the dementia arises rather from the after-effects of the protozoa.

The very fact that the arsenic preparations have little, if any, effect on the disease indicates that the actual presence of the spirochoete is not the true causal factor.

Recently, one has been much attracted to a treatment by the subcuticular introduction of milk and adrenaline ($\frac{1}{2}$ c.c. of each separately) and one obtained definite rigors, but of the three cases so treated, no good report can be given, although observation has been possible for a period of six months. One felt that with the high temperature, the delicate endothelial lining of the vessels would be 'shed' and that the arsenic given intravenously would have a rapid action on the brain and cerebro-spinal fluid. That such was not the case is seen by the two contrasted readings which follows:-

A case was admitted in May of last year and was treated by milk and adrenalin. The diagnostic reading of the

cerebro-spinal fluid was Lange 5555554322, with a positive globulin, and a cell count of 85. In all 4gm. of "914" was given, and a later reading taken six months after, gave Lange 555555443, with a weak globulin reaction and a cell count of 79.

Evidently, therefore, the high temperature action on the spirochoete, even coupled with the arsenic preparation, had had little or no effect on the condition. It may be said, in addition, that very little physical improvement had taken place and no mental progress was evidenced.

That the increased metabolism due to the rigor, with consequent increased elimination of toxins, plays quite an important part in the obtaining of a "malaria remission", few will question. Indeed, the globulin content of the cerebro-spinal fluid tends to remain constant, or even increase, in those cases where rigors are of poor character. One looks for a reduction, at least, in the globulin about twelve months after the termination of malaria, but in the few cases where it was felt advisable to permit only a moderate rigor, and where small doses of quinine were given to control the temperature, it is found the period of time is much lengthened. Unfortunately, however, one cannot quote figures in support of this, for the record of quinine administered in this case is no longer available

2. The destruction of the erythrocytic element, and creation of a non-specific anti-body.

One feels that the acceptance of this theory leads one to the conclusion that General Paralysis is entirely due to the actual presence of the spirochoete, many years after the original infection, and overlooks the microscopic changes which have very definitely been demonstrated.

It is quite true that towards the end of the malarial attacks, marked anaemia is found, with a rapid outpouring of red-cells from the bone marrow. Whether these conditions tends to produce an anti-body, one is hardly prepared to say, but the anti-body so produced would be infinitely more prone to be one antagonistic to the germ of malaria.

Actually, it would seem that the regeneration of the

red cells have some considerable bearing on the increased physical well-being so noticeable after malaria; little expression of opinion has been made on this point, although the supposition follows closely upon the lines of I.K. therapy.

It seems unlikely, however, that an anaemia alone would cause the remission: most of our patients suffering from General Paralysis of the Insane are admitted in somewhat poor health as the later tables will shew, and quite half of them shew a very poor blood picture, with haemoglobin less than 75%.

3. The relationship between the two protozoa may cause an antibody formation specific to protozoa.

Pilcz and Mattauschek (Fesse Medicale 10. 1924, Lancet , January, 1923.) have pointed out that the spirochoete of syphilis and of relapsing fever exist with difficulty in the same host. Dr Berwitz, in a letter of the American Medical Journal recently gives support to this view. He states that in Hainan, China, nearly all the nine million population harbour malarial parasites and that sixty per cent of the population are syphilitics. During his eight years residence he never saw a case of general paralysis, and only three of tabes dorsalis.

Other writers support this contention: one has, however, quoted three cases in a preceding page which shews a contrary experience, although in none of these cases was malaria co-existent in time with the primary syphilitic infection.

Whether such an antagonism extends to the after effects of the protozoal infection is unknown, but the general supposition is that the progressive dementia is stayed, if it is stayed at all, largely by the counter-action of the two opposing protozoa.

Padnier, quoting Bratz and Schultz (Presse Medicale 1925) contends that the malarial parasite has the tendency to lodge and rest in the small vessels of the brain, and to act on the delicate endothelium, facilitating the passage of any antibody in passage to the brain substance.

4. The creation of the high temperature of a leucocytosis and the formation of bacteriolysins.

Kirchbaum, in 1922, attempted to bring about the artificial "remission" in cases of General Paralysis by the production of a fixation abscess, using turpentine as the agent. Although he claimed one or two fair results, no real history thereof has been given, and the Continental workers, of whom Pilcz, Weygandt and A. Marie are the more prominent, all question his results.

Marie, indeed, states definitely that a leucocytosis alone has little or no effect on the condition and that without the hyperpyrexia no result is to be expected: and this verdict he gives where hyperpyrexia alone is obtained, with no concomitant leucocytosis, instancing typhoid fever in a patient.

Many observers point out that in a General Paralytic inoculated by malaria, the leucocytes become more mobile, and directed against the invading protozoa. This can very readily be demonstrated in the blood film which one examines daily, as one can frequently see the polymorph with the malarial germ ingested.

A series of blood counts on patients before, during and after each rigor, tends to make one sceptical of the theory of leucocytosis with high temperature, for the general average of the counts is:-

Before rigor.	4000 to 6000.
During rigor.	5500 to 8500.
After rigor.	4000 to 5500.

Graham, Belfast Mental Hospital, agrees with this in personal correspondence and in his paper in the Journal of Mental Science, July 1925.

One can, therefore, with safety say that a leucocytosis early in the rigor (possibly due to the "premalarial toxin of Stitt"), but towards the termination and especially in the interval a leucopenia, is usually found. One has formed this conclusion after some hundreds of counts have been made, and a relative increase in the polymorphous element is all ^{that is} to be expected.

One feels again, in considering the theory of the effect of bacteriolysins that one overlooks the main cause of the physical aspect of the disease, and the grave pathological findings which are undoubtedly due to the direct action of the spirochoete and its products upon the nervous elements. If the question of an antibody or anaphylaxis could "remit" the condition of General Paralysis, the disease would be much rarer than it is, and would react much better to the antisyphilitics.

5. A direct action by the malarial parasite on the nervous tissues and on the vessels.

Spillmeyer (Archives de Neurologie, February 1925), Bratz and Schultze (Journal of American Medical Association May, 1925) and others including Alzheimer, point out certain pathological conditions of General Paralysis modifiable by malarial therapy. Some of these alterable tissue changes are due to the spirochoetal toxin which has been so long existent in the host, and are chiefly of the chronic inflammatory type. They are the grosser signs of the disease such as meningeal infiltration and "peri-vascular" infiltration, and are amenable to treatment by other methods than malaria, for many of the pseudo-paretic readings one obtains by Lange's colloidal gold test shew evidences in the luetic and meningeal fields of tissue alteration, although in the true paretic field there is little suggestion of true General Paralysis. In this type of case a sustained course of mercury and potassium iodide in increasing doses yields a more rapid result than does malarial therapy alone. Such cases should, possibly, be regarded as tabetic, and not as true paretic.

Marie (Archives Internationales de Neurologie, November 1925) states he has pathological evidence of the damage to myelin sheaths of the nerves in Progressive Dementia and he contends that with the reforming of such supporting and nutritive structures, the true nerve elements will again be properly nourished and can then regain their functioning power.

CONCLUSIONS AS TO THE THEORIES GOVERNING MALARIAL THERAPY.

It is impossible to totally accept, and equally as difficult to completely reject, any or all of the theories which are advanced: the therapy is not of sufficiently long-standing duration to allow of definite conclusions being arrived at: nor does any one theory cover even the majority of cases.

The etiology of General Paralysis is only partially agreed upon, although all agree that the spirochoeta pallida forms the commencement of the train of events leading to the appearance of paresis: why, however, only some 5% of syphilitics should become either tabetic or paretic is contentious ground. Whether there is a tissue predilection, or whether there is a neurotrophic strain of the spirochoeta, seems to be a matter of opinion at the moment.

That General Paralysis of the Insane is the result of chronic inflammatory processes is quite agreed: whilst a definite pathological picture has been formed of the condition, although the pathology of cases in remission is by no means so definite.

One feels that possibly the train of events following upon the introduction of malaria into the system may comprise at least parts of each theory advanced, and that the "remissions" which are so definitely obtained are due in part to each of them.

The high-fever reaction has obviously a two-fold purpose to fulfil, the less essential being the role of spirochoetocide; the more essential is that of toxin-elimination, for there is good evidence that after malaria, the cerebro-spinal fluid becomes less toxic, with an obvious advantage to the brain; whether this will help the chronic inflammation already set up one doubts, but that the reduction in toxicity will partially prevent further meningeal and neuronal damage one is quite prepared to believe.

Evidence in favour of this supposition seems to be found in those cases who have had congestive seizures before malaria treatment, but who have had nothing of the kind afterwards.

That an antagonism exists between the attenuated spirochoete and the virile plasmodium, both of the protozoal group,

there seems to be little doubt, and it would appear quite natural that anti-body formation would take place to the malarial germ, which would be strong enough to finally destroy any lurking spirochoetes which were capable of doing damage by their toxins, or at least of forming a non-specific anti-body which would neutralise their toxins by raising the resistive power of the specialised tissues.

Consequent upon this there would be found a reduction of acute inflammatory re-action in the brain with a consequent prevention of the rapid spread of degenerative changes in the neuronie elements, whilst the increased metabolism would help in the elimination of the toxins. Whether any definite reduction in the chronic ~~infa~~ inflammatory reaction is to be expected one feels unable to say, but it may possibly be stabilised, unless there is a leucocytosis after malaria which has some depleting effect thereon.

That there is the regeneration of the myelin sheaths claimed by Marie one has no reason to doubt, but this would have but little effect upon the actual mental condition, although tabetics and tabo-paretics would undoubtedly benefit thereby.

Possibly the real reasons for the remissions which one obtains depend upon the permeability of the meninges and brain substance to the anti-body formed by the malaria, and also to the removal of toxic products by the increased metabolism caused by the malaria, whilst the regeneration of the blood elements and the supply of pure blood to the brain assists in the prevention of degeneration: the subsequent leucocytosis may have a real bearing on the reduction of the chronic inflammatory processes with an elimination of the pressure of the meninges: one always feels that if cases can be treated at a sufficiently early date the prognosis is much better, and where there is marked evidence of meningeal trouble one has grave doubts as to marked mental improvement taking place. In other words, one feels that if cell degeneration is only commencing it can be stayed with mental improvement, but if it is advanced, the most to be hoped for is real physical improvement.

THE CLINICAL DIAGNOSIS OF GENERAL PARALYSIS.

Two main types of cases are admitted to the Male side of this Hospital, the manic and the depressive. The former more frequently gives the clear cut picture of the condition one is led to expect by the text-book descriptions, but the latter is, or rather has been, frequently diagnosed provisionally as Melancholia.

Irrespective of type, various signs and symptoms are found in most of the cases admitted, and many have nearly all the classical signs.

On admission, the patient is carefully examined for scars, and here the primary sore scar may be detected. If there is any slurring speech, it is noted, as are the superficial reflexes. The mental condition is also investigated, and often some grandiose ideas are found to exist without any true reasoning power. At times, however, a patient is admitted with true grandiose notions which he very cleverly conceals.

One bases ones provisional diagnosis on:-

- The reaction of the eyes to accommodation and not to light.
- The regularity of the pupils.
- The centrality or otherwise of the pupils.
- The presence of labial and lingual tremors.
- The cordination shewn in voluntary and involuntary movements.
- The presence or absence of the Rhomberg sign.
- The response elicited to stimulation of the knee reflex.
- The presence or absence of a Babinski sign.

In addition to this classification, the mental condition has to be taken into account, and here considerable difficulty is experienced, as no reliable history is obtainable in the majority of cases, which will either substantiate or controvert the patient's statements.

The exaggeration or absence of knee-reflexes is perhaps the most obvious sign, and quite a number of our cases lead one to suspect a tabetic condition by the complete absence of these responses. One finds most frequently that this class of case has small, circular, and fixed pupils, and when the colloidal gold test is available, the tabetic field is seen to be markedly involved, a reading of 5555555551 being by no means uncommon.

The presence of an Argyll-Robertson pupil is by no means invariable, and quite a number of cases have been admitted with a reverse Argyll-Robertson sign, in which the pupils would react markedly to light and not at all to accommodation.

Where there is asymmetry of the pupils, one is quite prepared to find a parietic condition, and this holds good particularly if the pupils will not react to light.

Labial and lingual tremors are of no real diagnostic value alone, as so many of the debilitated cases one admits have these tremors, which clear up with nourishment.

An ataxic gait is not found in many of our patients, and where it is obvious one is more prepared to obtain a gold sol. reading corresponding to a tabetic condition, with the reduction spreading well into the meningeal field.

The melancholic type of patient usually presents many clinical difficulties, and, unless routine examination of the cerebro-spinal fluid is performed, quite a number of such cases may be months in Hospital, steadily going downhill, until they shew an advanced stage of the disease either by conduct or physical signs.

Case 120. J.C. was admitted to this Hospital from another County Mental Hospital (where he had been for six months) in April of last year. He was classified as of the Manic Depressive type of Insanity, and was so regarded until October. During that month he shewed some sort of mild grandiose delusions, with few, if any, clinical signs.

His cerebro-spinal fluid was tested, and gave a weak parietic reading of 2455433100, with merely a haze of globulin, and 25 cells to the c.mm.

He was retested again in November, and gave a really good positive reading of 455554330 with a haze of globulin, 45 cells to the c.mm. and a positive acetic-anhydride reaction.

He still continues to be of the melancholic type, and even after treatment shews only an irregularity of the pupils.

Such cases are of extreme difficulty in diagnosis, and may be missed for some time, until attention is called to their condition by the exhibition of slurred speech, or some of the other better-known clinical signs.

One case in particular is of extreme interest to me

as he bears out the need for care in diagnosis which is required when patients shew no real signs of the disease and who cause an instinctive feeling, possibly based on nothing more than a slight irregularity in gait.

He was admitted to this Hospital in June 1923, and was diagnosed as Melancholia, which diagnosis was accepted until a year later, when he was noticed to be somewhat ataxic in gait. No further clinical sign was seen but on repeated examination, a slight lingual and labial tremor was found after exertion. His habits had become somewhat faulty.

In March 1925 an effort was made to obtain his cerebro-spinal fluid for examination, but with no success. A fortnight afterwards, it was obtained, gave a mild parietic reaction, but a marked luetic one. Various subsequent readings gave no real alteration, but the patient was patently becoming more parietic, and slurred speech and irregular pupils were noticed. In August he gave a gold sol test of 2555554300, with positive globulin, and cells 75 per c.mm.

Treatment was at once given, but the patient died in October, and post-mortem evidence was found of quite well defined 'peri-vascular' infiltration, with granulations on the base of the 4th ventricle: marked dural thickening and a density of the bony skull.

One has been led to the conclusion, therefore, in view of the rapid deterioration so frequently found in General Paralytics that where the slightest suspicion is entertained, it is not only advisable but absolutely imperative to either prove or disprove the provisional diagnosis by the use of the laboratory tests. If the cerebro-spinal fluid is very definitely negative, no harm has been done: if, on the other hand, there is some evidence of cerebral involvement it is unfair to the patient to continue or start anti-syphilitic medication alone, and leave it at that. No definite diagnosis of tabes dorsalis, and tabes dorsalis alone, should be made until repeated examination, both clinical and serological, has definitely established the fact that General Paralysis of the Insane is ^{not} present. This is the more important because where a General Paralytic is treated early, the prognosis becomes much better for a "stabilisation" of the disease at the point of treatment, even if there is no definite improvement after treatment is finished. In other words, one expects to keep the patient in statu quo, if nothing better.

LUMBAR PUNCTURE.

In the last year some three hundred lumbar punctures have been made here, and the method is simple in the extreme, and is almost invariably without ill-effect, and has very little discomfort to the patient.

Each patient is kept in bed for the previous twelve hours, and for twelve hours at least after the puncture. Indeed, at the present time, lumbar puncture is performed on all suspicious cases before the certificate to the Board of Control is sent and as the practice in this Hospital is to keep patients in bed until this is done, it is usual to have the case in bed three days before and three days after the operation.

An aperient is given twenty-four hours before he is brought to the Hospital ward for attention, and a light meal is given three hours before.

The actual technique is simple in the extreme. Until recently the patient was asked to lie on a bed with his knees drawn up and his shoulders bent forward, his spine being just at the edge of the bed. This has now been abandoned as one found that the nervous patient felt suffocated by the fact that an Attendant held him in this position, whilst the excitable patient could easily fall off the bed.

Presently, one gets the case to sit upon an ordinary chair with his back towards one. This has a great advantage in that they cannot see any preparation, such as fitting the stilette into the needle etc. They are asked to put the elbows on the edge of the chair-back and the hands touching the opposite shoulders.

The highest point of each iliac crest is ascertained and a point selected half an inch below, just to the right of the middle line. The skin is carefully sterilised by the rubbing in of iodine, and then ethyl-chloride is sprayed around the site. One waits till the skin is frosted over, and inserts the needle slightly upwards and towards the

middle line, pressing firmly in and up until the posterior longitudinal ligament is pierced.

The chief care is that no septic matter should be introduced, and to this end one sterilises the canula with the stylette withdrawn, and endeavours to get the skin as sterile as possible.

It is usual to find the posterior longitudinal ligament rather toughened in those cases whose cerebro-spinal fluid will give a positive Lange's reading, but too much stress cannot be laid upon the fluid pressure as the slightest inhibition of breath, or the bending of the head with consequent slight constriction of the jugular veins will increase the pressure in the spinal canal.

The stylette should be slowly withdrawn from the needle, as the suction caused by its sharp removal is sufficient to make a nervous patient feel a slight pain.

N.K.Krabbe (Ugeskrift for Læger, October 1924) reports unpleasant and even alarming symptoms following the withdrawal of the fluid which he attributes to subsequent oozing. To avoid this he uses a very fine cannula.

No such ill-effect has been observed here, and the only trouble one has had has been a fainting attack, quickly recovered from, in an extremely nervous patient. It is seldom that even a trifling head-ache is complained of, and then one can usually account for it by the fact that the bone was "grated" at the anterior aspect of the cerebro-spinal canal.

This seems the more remarkable as quite frequently one has had a patient exclaim that he can feel a tingling sensation which extends to the foot at the moment of entry into the canal, suggesting that one or more nerve roots have been temporarily forced aside, if not actually pricked.

One has never encountered the repeated vomiting recorded by Krabbe. Possibly the system of complete rest obviates the unpleasant sequelae.

No oozing has been observed except in one case, and

one concludes that this is due to the fact that as soon as the needle has been withdrawn, the site of the puncture is well massaged with iodine, and collodion and cotton wool applied.

Sometimes one finds a case who will not submit to lumbar puncture, and no attempt is made without the patient's consent. If he is quite willing but appears too nervous, either Paraldehyde dr.2, or Morphia gr $\frac{1}{4}$ is given some two hours before the time, and, as a rule, little difficulty is experienced. The exhibition of either of these two hypnotics seems to have no effect on the spinal fluid.

After the puncture is completed, the patient goes back to bed, and no pillow is given him. Food is given about half an hour afterwards, but only a very light meal is allowed.

At times one finds a difficulty in obtaining fluid from the cerebro-spinal canal, and one comes to the conclusion that the meninges have been pushed aside by the needle point. In such an event, it is quite easily (and almost painless to the patient) to slightly withdraw the needle and to re-insert more towards the middle line.

If bone is encountered at any time, it is quite unjustifiable to attempt to force the needle through it, and if one does so, the fluid may not be obtained, as the spicule of bone will, in all probability, be drawn into the bore of the canula.

One has not felt it necessary to use a syringe to withdraw fluid: the stilette having been withdrawn the fluid is collected in a sterile test-tube as it comes from the needle, and the flow is immediately stopped by the insertion of the stilette into the barrel. About 25 c.c. is withdrawn, except in those cases giving a history of cerebral seizures where twice that quantity seems to give relief to the congestion, although such a relief is only temporary.

It has only once been found necessary to give aspirin to any patient, because of headache; no other complaints have been made.

LABORATORY DIAGNOSIS OF GENERAL PARALYSIS OF THE INSANE.

The differential diagnosis of this condition has been rendered more easy and more certain by the introduction of the Lange's colloidal gold test, and upon its result the chief reliance is placed.

Sometimes, however, either through the presence of blood in the fluid, or for other cause (chiefly a reading which more closely approximates a paretic curve than any other, say 223531100) it is necessary to re-test the fluid after a suitable interval has elapsed. The most difficult decision to make is as to whether there is a true paretic condition, or whether there is cerebro-spinal syphilitic meningitis present. In the latter case, however, the reactions given are usually temporary, whilst in cases of General Paralysis no improvement is found for months.

In no case, however, is a diagnosis of General Paralysis of the Insane, which is based on clinical signs, abandoned until three or four very definite contrary results have been obtained to all the feasible laboratory tests, and even then the patient is carefully watched and lumbar puncture performed at varying intervals. This has been very particularly impressed upon one recently as several cases have shewn but moderate luetic curves to Lange's test on three separate occasions, and yet at a fourth attempt, a very definite paretic result has been obtained, which has been consistent with the physical conditions on which the provisional diagnosis was primarily based.

In considering the cerebro-spinal fluid one is always advised to have regard to the pressure under which the fluid is found, and an increased tension has been claimed to give at least a warning of a paretic condition. However, in actual practice the pressure of the fluid can be largely disregarded: so many conditions give an increase, and even slight physical effort can cause a rise in this direction.

When one speaks of disregarding the pressure of the cerebro-spinal fluid one means in a relative fashion, for cerebral-haemorrhage, tabes dorsalis, encephalitis lethargica, meningitis, neuro-syphilis, and to a slight degree disseminated sclerosis, all cause this condition.

The cell count is of much greater importance, and it is usual to find a pleocytosis ranging from 50 to 500 per c.mm. The majority of the cases reviewed herein had a cell content of between 75 and 150. The prevailing type is the lymphocyte, but a varying number of the large mononuclear cell is found, and various authors give 5 to 20% as a common variation. Plasma cells form roughly 2% of the total.

Polymorphs are often found, and compound granular corpuscles are also almost invariably present.

Grant and Silverston, of the County Mental Hospital, Whittingham, have demonstrated spirochaetes in the fluid deposit after centrifuging. One has not here had that result, although quite a number of attempts have been made at varying times.

In almost every paretic fluid the globulin content is high, and raised above the 60 mgm. which is accepted as being the limit of the normal. In very few cases has any fibrin coagulum been found.

A true paretic reading to Lange's colloidal gold is always required before the case is definitely treated as being General Paralytic: only such readings as give a "5" or "4" consistently in the paretic field are finally diagnosed, and if any doubt is felt, a further diagnostic puncture is done at an interval of 10 days. The reading of the tube of first dilution is often found to be very low, from "1" to "3", but this accounted for by a protective quality of sero-albumin on the gold sol. Many cases shew this peculiarity, and readings of 1455554310 are by no means uncommon. Greenfield (National Hospital for the Paralysed and Epileptic) quotes a figure of 31% shewing this modified type.

The Wasserman reaction of the Cerebro-Spinal Fluid is not tested, as opportunity for such work is rather lacking, and one assumes it to be positive if all other tests are found to be positive.

Recently, the acetic-anhydride test has been used in addition and results follow closely those obtained by the use of the gold sol. The only alteration is to be found in patients treated by malaria, but this will be mentioned later.

Greenfield gives as his opinion that the diagnosis of General Paralysis of the Insane should rest upon the effect of anti-syphilitic treatment on the cerebro-spinal fluid, rather than upon the original reading, for he states that intra-theccal injections of various substances cause an increase in cells, a reduction of protein, and a diminution of the globulin content, but not its disappearance. The Lange reaction remains paretic, although sometimes only weakly so.

Whilst having little experience of treatment by intra-theccal medication, it does not seem practicable to defer a diagnosis of General Paralysis until various anti-syphilitic remedies have been attempted. Indeed, it does not seem wise, if malarial therapy is to be used, for all workers in this manner are agreed that the earlier the induction of pyrexia, the better the prospect of causing at least a "remission". If one has to wait for some weeks before diagnosing the case, much valuable time will be lost, and much increase in the dementia will be noticed, for many of the cases admitted go rapidly downhill both mentally and physically.

The diagnosis of General Paralysis is, therefore, based upon:-

- A paretic curve to Lange.
- A positive globulin content.
- An increased number of cells.
- A positive result to the acetic-anhydride test.

Given all of these tests answered in a positive manner there seems to be little room for an error in diagnosis.

CONTRA-INDICATIONS TO MALARIA TREATMENT.

The generally accepted view of the mortality of General Paralytics gives a key to the necessity for treatment. At no period in this Hospital has a patient so affected lived ^{UNTREATED} for more than two years after admission. It is quite obvious, therefore, that any factor in physical condition must be acutely grave before it can be recognised as a contra-indication to treatment. Actually, one feels inclined to inoculate with malaria if there seems to be the slightest chance that the patient will live through the incubation period and sustain even two rigors.

Age, within a limit say of 68 to 70, does not seem to contra-indicate malaria therapy, provided the patient is in a moderate state of health. One of our discharged patients was inoculated a fortnight after his 65th birthday, and has since been doing very well at home, and has resumed to some extent his occupation as a hawker.

Two patients shewed active signs of tuberculosis on admission, and were treated for this condition for four months before a definite diagnosis of General Paralysis was made. They were then treated with malaria: both are presently in Hospital: one has gained three stones in weight in 26 months, and the other has gained two and a half stones in 19 months. In neither case is there any sign of active tubercular lesion, and they are in infinitely better health than on admission.

Heart lesions are not necessarily a bar to treatment. Patients admitted as of the pauper class have frequent lesions either functional or organic, and they seem to stand the strain of the rapid pyrexia very well.

Two cases were admitted with an acute exacerbation of a chronic bronchitis: they were in poor health, but were very soon inoculated, and during the whole of the pyrexial period the bronchitis was in abeyance. Indeed one (J.B.) has such severe bronchitis prior to admission that a definite hernia of the left lung was found, a rib-resection having been performed at

some earlier date, and no ill-effect has been found: on the contrary, the patient says he is now less troubled with bronchitis than he has been for many years.

The chief contra-indication which one takes into account is the presence of a well-established lesion of the kidney, especially of the acuter forms. It has been noted that where epithelial or fatty casts are found in the urine, the additional strain thrown on the organs of elimination by the high temperature very often causes a complete breakdown. For this reason, no definite nephritic is treated by malaria unless the nephritis shews signs of responding to ordinary medicinal treatment.

If the patient shews any signs of jaundice, also, he is not inoculated. Jaundice is perhaps the most serious complication experienced in a malarial attack, and an intolerance to quinine medication is often found. This, obviously, is a serious matter in considering the termination of the pyrexia.

Summing up, one agrees almost entirely with Gerstmann (Die Malariabehandlung der Progressiven Paralyse, 1925) in concluding that malaria treatment should be instituted in nearly every case of General Paralysis, unless there is definite evidence of a grave breach in compensation in ~~either~~ the heart, or ~~some~~ well-founded reason to suspect that the excretory organs will give way under the strain of the rapidly occurring pyrexia. Gerstmann quotes cases of pernicious anaemia as being unsuitable for treatment, and from the blood films examined daily of every case, one can see that this disease is a very definite contra-indication, but an ordinary anaemia should not prevent treatment. Indeed, quite a number of our treated cases have suffered from an anaemia consequent upon focal sepsis, and have rapidly shewn ~~almost~~ a complete recovery of the normal blood picture after the malaria has been terminated by quinine, and before the focus of infection (teeth, nose etc.) have been completely treated.

PREPARATION OF THE PATIENT FOR MALARIAL TREATMENT.

Patients admitted to this Hospital are all of the pauper class, and as such are admitted from the various Unions in the County: they are not, as a rule, sent to us until some definite breach of conduct makes it undesirable to retain them at the Workhouse Hospital. For this reason we receive them either physically or mentally ill, and this causes us to investigate the cerebro-spinal fluid of all suspicious cases as soon after admission as possible.

This plan has been found to be very satisfactory, as the history supplied either by the patient or by his friends is often very vague, and gives but little idea of the duration of either mental or physical signs and symptoms indicating a definite onset. One patient was admitted from a Union in robust health, with slight slurring of speech. Combined with this there was some mildly grandiose psychosis, although the patient had been an Officer in the Army, and a Press Correspondent to a recent Royal tour.

In spite of this physical well-being, the patient became acutely maniacal within a month, was totally demented, became filthy in habit and would eat fecies. Treatment had to be postponed on account of certain Official difficulties apart from the Hospital, and the patient died at the end of two months, in spite of inoculation by malaria.

Such experiences as this incline one to treatment at the earliest possible moment, and to this end a definite diagnosis is attempted within the first week in hospital.

If the patient's condition is good, malaria is inoculated within a fortnight of admission: many of our cases, however, are in poor condition and their resistance has to be rapidly increased.

With this in view, every General Paralytic, on diagnosis, is given an acid tonic before meals, and cod liver oil in increasing doses after meals; liberal diet is given with plenty of greens, carbo-hydrates and fats, but the protein

element is slightly reduced.

This diet is continued from the time of diagnosis until the appearance of the first rigor, and only in two cases have we found any intolerance to the cod liver oil.

A strict watch is kept upon the heart, and upon the excretory system, and every method of eliminating toxins is encouraged.

The teeth receive particular attention, and any carious teeth are extracted when possible, as it has been seen that any focal infection renders the patient liable to have a somewhat acute malaria: whether the true periodicity of the benign tertian malaria inoculated is altered by the presence of toxins one is unable to say definitely, but one has repeatedly found that where focal infection exists, the liability to double tertian malaria seems to be greater.

In the endeavour to increase resistance and to obtain as good a bodily condition as possible before the advent of the pyrexial attacks, the amount of sleep obtained is carefully watched, and no sleepless night is allowed: paraldehyde, drachms 2, has been found to serve the purpose admirably.

It is quite usual to find that the first signs of the onset of malaria are early recognisable by the restlessness of the patient at night: if he is allowed to be without sleep for two or three nights at the end of the incubation period, and just before the rigors start, he is much more likely to shew signs of the acuter form of mania whilst in the pyrexia.

Paraldehyde, therefore, seems to be good treatment both as a hypnotic, and as a prophylaxis against the attacks of excitement in the true rigor which cause so much bodily wasting, and frequently compel the termination of the malaria before a reasonable number of rigors have been experienced. Morphia seems to be rather less effective in such cases than in the ordinary attacks of mania one has to deal with in patients who are not suffering from General Paralysis. It also seems to have a greater effect on the excretory organs, and so is seldom given.

CONSIDERATION OF THE STRAINS USED FOR INOCULATION.

The original infection was conveyed to patients in this Hospital towards the end of 1923 by infected mosquitoes, and for some three months no direct inoculations were made, but early in 1924 the intra-venous route was used, and blood was taken from a patient who had received mosquito infection.

This particular strain was used and kept in operation until May 1925, when patients from another Lancashire County Mental Hospital were inoculated from it, and, no General Paralytic being available here, it was left to the other Hospital to carry it on, and to have it available for us later.

The strain had proved very satisfactory, but had given rather a high proportion of double tertian results: it had been successful in causing pyrexia in every case of primary infection, but when used with the object of causing a second attack of therapeutic malaria on old cases (old in the sense of length of residence here, and in the period elapsing since the primary infection) results were extremely disappointing, for only two cases re-acted to it for a second inoculation.

Apparently, therefore, some immunity is obtained by a patient to a special strain, for our "repeat" inoculations had all harboured this particular strain at an early date, and the passage through other hosts had made no vital difference to the activity of the parasite.

When we again had General Paralytics to treat one obtained a renewal of this blood from Rainhill Mental Hospital, and used it on the new cases.

Rainhill had found the same difficulty with it that had been experienced here, for in the first half dozen cases it was found that double tertian pyrexia was the result: the strain then settled down to be a true benign tertian malaria, and the only reason which seems to give a feasible explanation of this change is that it was used to infect a patient who had had a previous sustained attack of tropical malaria, which had been treated by quinine.

The first host developed true tertian malaria, and

which continued for four rigors, and then a double tertian type set in.

Another patient, inoculated at the same time, with the same quantity of the same blood, developed the daily pyrexia, and to all appearances the resistance offered by both these patients should have been the same.

The next host, inoculated from the case who commenced with regularly timed rigors, (and who was inoculated six hours before the donor commenced to become irregular in time,) developed two-daily rigors, whilst another patient, receiving from the same syringe of blood, developed irregular rigors in point of time.

Such findings make it very difficult to give any indication as to the cause of the onset of double tertian malaria, as two cases inoculated at the same time and from the same 10 c.c. syringe, give a different type of pyrexia. Apparently, therefore, the question is one of resistance, and one would suggest that certain patients shew a resistance to the immature parasite and yet harbour the maturer form, and so go on to have true tertian malaria: other patients, apparently, are susceptible to any parasites and allow them to increase which will account for the out of periodicity rigors.

Unfortunately, this strain terminated at the end of November, and the opportunity arose, through the kindness of Col. S. P. James, of the Ministry of Health, of using mosquitoes once more, and one took advantage of this in an endeavour to prove or disprove a theory of immunity one had formed from the experience of resistance to the original strain on the part of certain patients referred to above.

This strain has been in use since that date, and is still being carried on, and is giving good results, but again one has to report that no reliance can be placed upon it to give a true tertian malaria in point of periodicity. It can be said, however, that where it is used for the primary attack of malaria, a rough average of 12 days can be regarded as the likely incubation period by the intra-muscular route.

Whichever strain has been used, one has found a well-

defined relationship in the height of rigors, patient to patient, allowing always some slight latitude.

One has never found an inexplicable hyper-pyrexia, although, of course, the actual physical condition of the case has to be taken into account in this connection.

The anaemia-picture of the blood follows a fairly regular sequence contrasting patient to patient, but here again the condition of the patient has to be largely considered, for the run-down patient shews consequent anaemia very rapidly indeed.

Apparently, therefore, the chief object in obtaining a strain of mosquito blood is to have some knowledge of the fever which it has previously produced in somewhat similar types of patients, and from this a working idea can be obtained of the results to be expected from it.

It has been repeatedly stated that to continue the use of any particular strain over long periods is liable to increase its virulence.

This has not been found to be the case here as in two and a half years only two strains have been used to inoculate 100 and more patients for the primary malaria.

As has been shewn, the incidence of double tertian rigors cannot be said to be due to an increased virulence, for our mosquito infection has, in the last instance, given double pyrexia.

In addition to this, it is by no means easy to renew a strain in most parts of the country, as mosquitoes infected with true benign tertian malaria are very difficult to obtain and are equally difficult to retain alive.

Attempts have been made to cultivate the parasite on most of the well-known media, but one has met with no success. As monkeys are the only well-authenticated sufferers from malaria in addition to the human, it has not been possible to keep a strain going by altering the host, or rather intermitting the host, as this Hospital does not possess a vivisection license. No report has been published of any work done in this direction, and one cannot, therefore, give any opinion on the value of the suggestion.

Mosquitoes.

Figures denote length of incubation period.
 * denotes that this case had previously been
 resistant to repeated attempts to infect
 with another well-known strain.

THE METHODS OF INOCULATION.

Since late in 1923, when the malarial treatment of General Paralytics was commenced in this Hospital, all the usual methods of infection have been utilised, and a careful record of the results has been kept, and a close comparison made.

The routes in question are by:-

- Direct Mosquito infection.
- Intra-venous inoculation.
- Intra-muscular inoculation.
- Subcuticular inoculation.

Direct Mosquito Infection.

Direct Mosquito Infection has been made to 25 cases for the primary attack: the original infection in this Hospital was conveyed by *Anopheles maculipennis*, infected with an Indian strain of *Plasmodium vivax*, and we have found the shortest incubation period to be 8 days, the longest 22 days, with an average for the 25 cases of 14 days.

Although mosquitoes are the natural infectors and would, possibly, be expected to be the most satisfactory method to employ, the experience one has had of this method of inducing malaria has been somewhat disappointing where the primary attack is required.

Apart altogether from the difficulty of obtaining and feeding the mosquitoes, there are numerous practical disadvantages which far outweigh the general certainty of the onset of pyrexia.

Chief amongst these is the fact that the incubation period varies very much indeed, even when two patients are "fed" at the same time and from similar mosquitoes. In addition to this, although the average incubation works out to be just above 14 days, this is accounted for by the fact that two developed pyrexia on the 8th day. The majority were from 13 to 17 days, and when pyrexia did develop, the first or first and second rigors were unsatisfactory, rarely reaching more than 102.F.

This is liable to try the resistance of the patient, as it compels one to withhold quinine until a reasonable number of high temperatures have been obtained, if possible, excluding the two minor rigors.

ANALYSIS OF THE INOCULATIONS AND THE RESULTS OBTAINED.

Route.	Total.	Rigors.		Relapses.	Died.	Discharged or removed.	In Hospital at date.
		Daily.	Two daily.				
Mosquito.	25.	3.	16.	8.	16.	4.	5.
Intra-venous.	25.	10.	15.	7.	7.	6.	12.
Intra-muscul.	50.	24.	19.	2.	20.	6.	24.

17%

43%

16%

41%

COMPARISON OF THE LENGTHS OF INCUBATION PERIODS, IN THE
PRIMARY INOCULATIONS.

Route.	Number of cases.	Longest time.	Shortest time.	Average time.
Mosquito bite.	25.	22.	8.	14.
Intra-venous.	25.	22.	4.	8.
Intra-muscular.	50.	25.	6.	12.

No marked difference has been noted in the actual height of the real rigors, and the blood films have shewn little alteration from those of patients infected in any other way. One finds, as a rule, that in the incubation period the onset of anaemia is slightly earlier, but no more severe. Possibly, also, in a differential count, there is a slight relative increase in the polymorphous element.

There has been a greater tendency to relapses of malaria after ^{mosquito infection} quinine treatment, and 8 cases out of the 25 so infected have at a later date shewn pyrexia with the presence of a few malaria elements in the blood. This contrasts with 7 out of 25 cases treated by intra-venous inoculation, and 2 out of the 50 cases treated by the intra-muscular route. In taking these figures, no allowance has been made for deaths before a relapse had reasonable time to occur. If this is done it is found that 8 cases relapsed out of twelve who lived three or more months after quinine was given to terminate the pyrexia: the relapses occurred at varying dates and some patients had two or more periods of renewed pyrexia.

Daily rigors, i.e. double tertian malaria, was found in only 3 out of the 20 cases who shewed a positive blood.

The advantages claimed for the direct inoculation by malaria seem to chiefly be that there is a greater certainty of infection, although this is not borne out at this Hospital: the question of blood injection has never been raised here by any patient or relative, and no ill-effect has been observed in any method.

One feels, therefore, that the additional care required to feed the mosquitoes, and to have them bite, together with the experienced liability to relapse, is a sufficient justification to disregard any of the advantages claimed.

For inoculation to induce a second therapeutic attack of malaria, certain other considerations arise, which will be dealt with later.

One feels disposed, therefore, to continue direct blood infection. X

Intra-venous inoculation.

Intra-venous inoculation has been performed on 25 cases for the primary attack. The shortest incubation period has been 4 days, the longest 22 days, and the average over the 25 primary infections, 8 days.

There is little advantage to be obtained by using the intra-venous method as compared with the intra-muscular, except where a short incubation period is desired, and there is very little difference to be found in the method of onset of the rigor. Contrasted with the direct mosquito infection one finds that the initial rigor is often found without the appearance of the parasite in the periphery, but the temperature is usually one to two degrees higher for the first one or two attacks of pyrexia.

Relapses seem more frequent in intra-venous infection than in intra-muscular, as out of 22 who lived for more than three months after quinine had been given and the blood brought to a consistently negative state, 7 patients relapsed.

Double tertian malaria was found in 10 patients.

No real ill-effect has been found after the intra-venous route has been used, but two or three patients have shown signs of slight leakage from the site of infection, and one had a slight but definite thrombosis of the vein which had to be carefully treated for over a week.

The technique of intra-venous inoculation is slightly more trying to the patient, and where the manic type are concerned it is sometimes almost impossible. One other disadvantage is found from the practical side: frequently a patient in malaria may act as donor two or three times and if an original entry has been made into a vein, it becomes more difficult to reach the median basilic with certainty when blood is required to be withdrawn to inoculate other patients.

With General Paralytics it is as well not to allow them to see too much of their treatment, and intra-venous injection certainly displays to their gaze quite sufficient to base other delusions upon.

Intra-muscular inoculation.

Intra-muscular inoculation has been used on 50 cases for the induction of the primary malarial therapy. The shortest incubation period has been 6 days, and the longest 25 days, whilst the average is 12 days.

By this route, the temperature rises as a rule to quite a good height, say 104 F. in the first rigor, and does not deviate much from this figure, although the third and fourth rigor sometimes are of 105 to 106 F.

One has found that relapses are less frequent by this than by any other route of infection, and only two of the 50 cases to be considered have shewn any relapse. In each of these two cases the temperature rose to 103 F. each second day, but no parasites were discernible in the peripheral blood.

Double tertian rigors were found in 24 cases, and true tertian in 17, and this seems to be chiefly due to the strain used. For a period of eleven weeks, using the same strain from host to host, one obtained a true tertian malaria, with an almost exact reproduction of temperature, rigor to rigor, and host to host.

No ill-effect has been found to occur in intra-muscular inoculation, and no trouble has experienced with any patient whatsoever. The slightly lengthened incubation period, as compared with the intra-venous route, has a distinct advantage in the preparation of the patient, and one finds that pyrexia can usually be looked for at any time between the 9th and 12th day after inoculation. Indeed, it is quite a common thing to find that where two or three patients are inoculated at the same time from the same donor, the onset of malaria is divided merely by hours for the three or more patients.

Intra-muscular infection is certain in primary cases, easy to bring about, and has few, if any disadvantages.

Comparison of the methods of inoculation.

Although intra-muscular inoculation is now the method of choice, one has had the opportunity of examining the blood of patients treated by all routes, and has had, also, the opportunity of seeing the pathological changes due to the introduction of malaria, in post-mortems performed on patients who died in the incubation periods.

Blood in the incubation period.

Daily films are taken, commencing after the inoculation and continuing until the slides are negative for a week after quinine has been given.

Little difference is found in the condition of the blood whichever method of inoculation or infection is used, except that where a mosquito bite is the originating cause, anaemia is found to be present some days earlier, and the advent of the parasite is usually noticed two or three days before a definite rigor is experienced.

With intra-venous and intra-muscular inoculation, it is usual to observe a very pronounced rise of temperature before any parasite is found. Indeed, by these routes it is not at all uncommon to have a patient who has two or even three high fever re-actions and yet who has no demonstrable parasitic infection of the blood.

The polymorphous element seems slight increased, in a relative fashion, when the mosquito is used, whereas the mononeuclear type of lymphocyte seems relatively increased by the other methods. In any case, the difference is very slight, and no explanation seems to be forthcoming, unless it be that the jars containing the mosquito act as a "congestive" bandage or perform the duty of "cupping". Usually, around the area of the mosquito bite there is a very slight local inflammatory re-action which persists for two or three days and may have some effect on the resistance of the blood.

No other differences in the blood picture are to be found.

Post-mortem differences in the incubation period.

Post-mortems have been performed on some 18 cases who died in the incubation period, and these are divided almost equally between the three types of infection used.

There is extremely little difference to be found, as one would expect, and in the four cases who died just before pyrexia seems imminent (2 mosquito, 1 each intra-venous and intra-muscular, infection) the only pathological difference was to be found in the relative size of the spleen.

In the cases treated by inoculation there was apparently no departure from the usual, but in the two cases suffering from the mosquito infection, some slight enlargement was found in each case. The substance of the organ seems to be somewhat congested, whilst the capsule was more translucent when stripped. No additional fibrosis was found, and no evidence of chronic stasis was obtained.

In the blood obtained within 8 hours of death from the spleen in each case, no trace of the malarial germ could be found, and no deviation from the usual condition was demonstrated.

None of the other organs shewed any alteration, and the brain presented the usual appearance of the General Paralytic of old standing. All the cases were in a poor state of general health before treatment, but none had any real organic lesion except in the heart, where a definite aortitis was to be seen in each.

The liver, in each case was found to be somewhat fibrosed, but no "hob-nailing" was present.

Apparently, therefore, from the few cases one is able to quote, the spleen does suffer somewhat under therapeutic malaria if induced by mosquito, but the effect thereon is very slight indeed.

INOCULATION TECHNIQUE.

The actual inoculation presents very few difficulties indeed, as the patients are usually able to be in the same ward and in beds close to each other.

It is, however, not always possible to have malaria blood available exactly at the time wanted, but blood has been sent both to and by this Hospital and has been injected some three hours after withdrawal and has been quite satisfactory.

R.M.Clark (British Medical Journal March 28th 1925) quotes a method whereby blood infected by malaria can be sent long distances. He defibrinates the malarial-blood by shaking it up in a sterile container, with glass beads therein. Then the defibrinated blood is placed in a sterile test tube, which is kept in an ice chest, or despatched in a Thermos flask surrounded with ice. He claims that the parasite has been obtainable by staining at the end of seven days, and that some successful inoculations have been made with blood sixty-five hours after withdrawal from the donor.

Such methods have not been forced upon us, as we have been fortunate enough to have in use a strain which was started more than a year ago and which has been passed back and forwards between this and another nearby Mental Hospital.

At one period it was considered necessary to withdraw blood from a patient actually in rigor, but this is not at all essential. One waits until the blood-film of the donor shews a sufficiency of parasites, and then withdraws blood from the median basilic vein, injecting it deeply into the muscles of the recipient, ~~deeply~~, in the area of the angle of the scapula.

For a long time only 2 c.c was used. Recently one has been using three or four c.c. and has the idea that by this means the incubation period is shortened, although in all probability this is not correct. Certainly, the last 24 cases inoculated with the larger quantity have given a shorter average incubation, in spite of the generally accepted theory that incubation is longer in winter than in summer.

In the inoculation one has to be certain that the sexual cycle of the mosquito is duly regarded, for if only gametocytic forms of parasites are introduced, no pyrexia will result. The sexual form gives the pyrexia, and it has been stated that for the renewal of the virility of the parasite it is necessary that it should pass through a mosquito at fairly frequent intervals. The experience here is that this is not necessary, for the one strain was in use for nearly a year, and for five months was a true, regular, tertian malaria of the benign type.

G. de M. Rudolf (Annals of Tropical Medicine and Parasitology, July 1925) quoting a series of cases reported from this Hospital mentions that when similar numbers of parasites were inoculated the incubation period tended to be the same in the various cases. He also states that where the number of parasites inoculated is great, the incubation tends to be short.

With his first conclusion we neither agree nor disagree for no attempt is made to measure the number of parasites. The inoculation is made direct from a known malarial patient, who has given clinical and microscopical evidence of harbouring the plasmodium: no further estimation or examination seems to be essential, and we have never found any difficulty in obtaining pyrexia even with the ordinary methods which we use.

Prior to the last 50 cases treated, four methods of infection were used, but now one prefers to use the intra-muscular route, as it is convenient, almost painless and certain, and has a distinct advantage in that the incubation period ranges round about 12 days, which allows good time to treat the patient for any focal sepsis, and also to get his excretory organs working in a satisfactory manner.

The Board of Control have recently recommended that mosquito infection be used, possibly because in certain private Mental Hospitals exception has been taken to the injection of blood from one General Paralytic patient into another. We, dealing entirely with patients admitted as of the pauper class,

have had no such objection raised by any friends of our patients, and have never found any ill result. After all, it is reasonable to suppose, in view of the etiology of the disease that no harm will come of the admixture of the blood of the two patients, and no attempt at mercurialising the blood has been made.

In view of the possibility of haemolysis being found ~~was~~ typed the blood of all the General Paralytics available at the time, and found that the blood grouping had no effect on the efficacy of the inoculation. Indeed, the majority of our donors happened to belong to Group 4, and they had, previously, acted as recipients.

One has never had any ill-effect directly attributable to the inoculation, and in no case has any inflammatory re-action been observed in the area of the inoculation.

Very little preparation is necessary for the patient, and all that is desirable is strict asepsis: if two or more patients are to be inoculated from the same syringe of blood from a donor, separate sterile needles should be used for each injection. This is one of the advantages of the intra-muscular route, for if the intra-venous method is chosen there is always the tendency, and sometimes the necessity, to make certain that the needle is in the vein of the recipient by withdrawing a little blood into the barrel of the syringe. By this means a dilution is obtained which is hardly satisfactory.

Intra-muscular infection is now looked upon here as the method of choice and, granted strict asepsis, is considered to be the most certain and painless for the patient.

If it is found necessary to carry the blood in the syringe from one ward to another, it is a simple matter to have the syringe wrapped in cotton wool which is dipped in water at about 100 F. and this has been found to be quite satisfactory.

After inoculation, the site of puncture is covered with iodine, gentle massage given for two or three minutes, and a sterile dressing applied, with collodion.

THE INCUBATION PERIOD.

Immediately the patient has been inoculated with malaria he is sent to his own Ward, and the amended diet is continued. He is also kept on the acid tonic before, and cod liver oil after, meals.

As a general rule there is very little physical evidence of the onset of malaria, but a blood-film is taken each day, and a careful watch kept for the advent of the parasite.

It has frequently been reported that the day after inoculation it is not unusual to observe a rise of temperature to 103 F.

Only one case has shewn this immediate rise in this Hospital, and this was due to a small abscess at the base of a tooth, combined with constipation.

During the incubation period, every effort is made to eliminate focal sepsis, and to encourage a full elimination of the toxic products of digestion, and one finds that for this reason the ten or twelve days allowed by the intra-muscular method is very satisfactory.

The blood film steadily becomes more anaemic, the central areas of the red blood corpuscles gradually failing to stain until they are almost "ring formed" when the pyrexia develops. For the first few days it is not unusual to find an actual increase of the white count to possibly 10,000, and there is an actual polymorph leucocytosis for the first day or two, and there may be from 85 to 95% of this class of cell, but with the near approach of the pyrexia it is quite usual to find that a fairly well marked anaemia is present with HbO of 60 to 70%, with a white count of 4500 to 6000, in which the large and small lymphocytes together make up 20 to 30% of the total, whilst the polymorphous elements are often seen to be in the transitional stage.

The red cells begin, possibly two or three days before the first rigor, to shew poikilocytosis and some anicytosis, and evidence is found of the drain upon the blood forming elements in the immature forms which are occasionally found.

Little change is to be noted in the condition of the organs of the body, and the spleen, which one is taught to expect to enlarge, shews no appreciable alteration in size. Only in two cases has one been able to demonstrate the enlargement in size, and in each mosquito infection had been used, with a very short incubation period, and with marked accompanying anaemia and a marked drop in the leucocyte count. Both cases came to autopsy almost immediately the fever was terminated after 3 and 4 rigors respectively, and both shewed a very definite enlargement of the spleen.

Gastric symptoms are sometimes complained of, and can be usually got rid of by a further reduction of the protein elements of the diet, together with the judicious administration of sod. bicarb.

Jaundice is, happily, very rarely seen, but if it does occur the patient has to be put on to milk diet and very carefully watched, as he will not stand the pyrexia at all well.

The most common complaint from the patient is that he has a cold in the head, which seems to get worse at stated intervals, usually every second day. No real discomfort, however, is complained of.

Bleeding from the nose occurs in a very few cases, but is quite easily treated.

In quite a number of cases the mental symptoms become very definitely worse during the incubation period, and facial twitchings, incoordination and slurring speech becomes more marked, and indeed continues to be so right through the period of malaria.

Retention of urine, though not frequent, has to be carefully guarded against, as has constipation.

The urine tends to become of high color, with a high specific gravity, a deposit of urates, and, at times, a definite re-action to sugar tests, but it seldom shews either acetone or diacetic acid in the incubation period.

Mentally, there usually seems to be an increase

of the symptoms under which one classifies the case as either manic or depressive, and the former need frequent sedative draughts to ensure both sleep and muscular rest. Paraldehyde in doses of 2 dr. has been found safe and also stimulating.

The temperature is taken fourhourly, and frequently, towards the time of the first rigor, a slight rise above the normal is found either daily or two-daily, and this gives, one thinks, an indication as to whether the resultant malaria will be simple, or double, tertian.

In many cases, especially those infected by mosquito bite, it is quite usual to find a rise of temperature to 102 F. before there is any evidence of the onset of a true rigor, and one is inclined to think that this is due to the liberation of toxins from the malaria which pass into the circulation and assist the existing parasites to flourish.

One has attempted to obtain this toxin, but without success, for it appears that in many cases malaria will not develop without this pre-malarial toxin. Possibly it is composed of haemoglobin ingested and excreted by the parasite whilst occupying a red blood corpuscle. Stitt considers that the incubation period lasts a certain period, which he puts at about two weeks until "a sufficient number of merocytes rupture simultaneously to produce sufficient toxins for ^{symptoms} incubation".

This statement bears out one's observations that a toxin usually causes the minor rigors before the parasite is found in the blood film

Towards the end of the incubation period it is usual for the patient to shew the anaemia which is existent, and he is usually rather restless at night. The onset of the actual rigor is generally rapid, and can hardly be mistaken. When it occurs the patient is at once transferred to a special ward fitted up in accordance with the regulations of the Board of Control, with wired windows and double doors, these precautions being enforced to prevent the spread of malaria by any mosquitoes which may happen to be about the Hospital.

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At no period, either before inoculation or during the incubation period, is any attempt made to ascertain the quinine tolerance of the patient. Usually, there is little chance before inoculation, as both clinical and laboratory diagnosis is made wherever possible within three days of admission, and then inoculation follows on or about the fourth day.

Experience has taught one that the exhibition of quinine even in very small doses during the incubation period brings the blood to a very negative condition, and no parasites can be found either then or later.

In one case, J.Y. who was inoculated almost on admission, a septic sore developed on the sixth day of the incubation period. Quinine was given for one day in 2grain doses until six grains had been given, with the object of keeping malaria at bay until the sore had cleared.

In spite of the fact that only gr.6 were given, no malaria developed at all, in spite of provocative injections of adrenalin, and the blood continued negative to the microscope for nearly two months, when the patient died of intercurrent broncho-pneumonia.

It is said (Col. S.P.James, Ministry of Health in a private communication) that malaria dies out naturally in many patients in winter, but this one cannot confirm as no case has been inoculated or infected for the primary attack who has not shewn malaria at the end of a varied incubation period. This of course does not include those patients who have had to have the incubation terminated for some other reason, or those patients who have died in the incubation period from intercurrent disease.

One has not found, either, that there is any real lengthening of the incubation period due to the climate in winter, nor does summer weather shorten the incubation appreciably.

Indeed, the length of incubation seems governed by no actual resistance on the part of the patient for weakly men often take longer to develop rigors than do the more healthy who are inoculated at the same time and with the same blood.

With intra-muscular infection, however, one looks for the appearance of the first rigor on or about the tenth day, and is rarely delayed after the fourteenth.

THE NURSING OF MALARIAL PATIENTS.

In this Hospital all malarial patients are kept in a ward which conforms to the regulations laid down by the Board of Control, and the same male nurses, therefore, are responsible all the time.

The ward is airy and plenty of bed space is given, which is essential for the comfort of the patient. Facilities for the disposal of excreta are good, and there is an adequate water supply for washing of patients.

Narrow beds are used, with a waterproof sheet below the cotton one on which the patient lies. He is not allowed to sleep between blankets as they would become unhealthy through the constant absorption of perspiration.

During the time of pyrexia the patient is not allowed to leave his bed for any purpose whatsoever, and if he is too restless a hypnotic is given. When the interval between the fever is present, he is allowed to get out of bed for necessary attention to himself.

His mouth and teeth are cleansed four times a day: and particular attention is paid to the state of his bowels and to the amount of urine he passes. A sample of urine is examined daily, and his diet regulated accordingly.

His temperature is taken half-hourly whilst he is in rigor, and any sustained pyrexia is at once reported to the Medical Officer. Any marked rise in pulse or respiration rate is also at once reported.

Frequent drinks are given during the rigor, and the patient is allowed as much milk as he wished to have: he is allowed to feed himself whenever possible, and during the intervals of rigors his diet is increased a little.

Considerable tact is required of a male nurse in dealing with the manic type of General Paralytic, and one has repeatedly observed that where this is displayed, the patient needs less in the way of sleeping draughts.

Bed-sores are to be avoided if possible, and to this end the skin is hardened with methylated spirits.

THE EARLY RIGORS.

In certain cases recently it has been noticed that there is a mild rise of temperature to between 100 and 101 F. for two or three days before the real pyrexia is developed, and before the parasite can be demonstrated in the periphery.

It has seemed possible that there may be an explanation of this in the fact that before a real high fever re-action can occur in malaria, there must be a large destruction of red blood corpuscles by the parasite, and that where these rigors do occur in such a mild form, there are parasites sufficiently numerous in the body to cause a mild rise, but not in large enough numbers to cause the true malarial high temperature.

Possibly this explanation is borne out by the blood examination in such cases, for the haemoglobin content of the erythrocytes usually varies from 80% to 65%, whereas, when the true fever is established the haemoglobin is somewhere in the neighbourhood of 60% and decreasing slowly with each succeeding pyrexia.

Stitt, however, as mentioned before, seems to consider that before the real malarial pyrexia can eventuate there must be a liberation of toxin, which occurs in these pre-malarial, or rather pre-massive, malarial attacks.

It is well known that before the parasite appears in the periphery it is well established in the organs of the body, especially in the malignant types, although the same conditions are known to occur in a lesser degree in the benign types of infection.

It seems, therefore, reasonable to consider that the incubation period terminates with the appearance of the first minor pyrexia, and this is the basis on which we regard our incubation period, although such small rises of temperature are not taken into account for statistical purposes in counting the number of rigors.

Where they have a very definite application is on the clinical side, for they take at least as much toll on the patient's resistance as do the higher temperatures.

THE MALARIAL PERIOD.

The ideal pyrexial period would conform closely to the text book description of benign tertian malaria, with a regular rigor every 48 hours, a short period of shivering, a rapid rise of temperature to about 104 F. and then a quick drop with the appearance of sweating.

If such could be regularly obtained, there would be little trouble in the malarial therapy.

Unfortunately, however, in very few patients is such a regular series of events obtained.

Wagner-Jauregg, in initiating the treatment, found that twelve rigors was nearly the maximum to be striven for, but this is not always possible owing to the condition of the patient.

At Whittingham Mental Hospital, Grant and Silverston say that six should be the minimum, and unless this number is possible, little good seems to result from the treatment. One has had cases who shewed marked improvement with less pyrexia than this number; indeed, two of our cases were discharged, one having had four and the other only five rigors.

Personally, one endeavours to continue the malarial infection until eight high fever re-actions are experienced, but in each case the physical condition of the patient has to be the only guide, and it seems better not to try resistance too far.

The actual rigor.

As a rule the patient is noticed to be rather pale, following a restless night, and then a very marked shivering is noticed with chattering teeth and increased labial and lingual tremors.

The patient is at once put to bed, and his temperature taken, and it is usually found to be well over 100 F.

Once pyrexia has commenced, the temperature is taken every half hour until it reaches normal again. One finds that the temperature at the close of the pyrexial period is usually sub-normal, taken in the axilla.

In many cases, particularly those infected by mosquito the first rigor has been found to be only about 102 F. and not until the malaria is well established does the temperature rise

to a malarial height.

A blood film is taken as soon as the patient is put to bed, but it is quite unusual to discover the parasite in any numbers until the third or fourth rigor. Indeed, some of our cases have shewn a completely negative slide for five or six days although the temperature has been as high as 105 F. in the axilla.

The diet during rigor.

In the first twenty cases treated, a full and liberal diet was allowed, but bilious vomiting was found to occur in more than half the cases, and now one has the patient fed on nothing but milk and lemon water during the pyrexia. If any bilious vomiting is found, soda bicarbonate is given, and this usually controls it, and prevents any onset of jaundice.

Medicinal treatment during rigor.

Although very few patients shew any signs of cardiac distress whilst suffering from the malaria, and the pulse as a rule seldom goes above 100, yet it has been noticed that in the later rigors some patients have a pulse of 120 or more if the heart is not nourished. To this end one gives as a routine precaution a cardiac stimulant every four hours whilst rigors are being experienced. Tr. strophanthus min. 2, with Tr. Nuc. Vom. min. 5, has been found very satisfactory, and where this is given it is very unusual to find any cardiac interference even in the later rigors of those patients whose condition allows the full 12 to be permitted.

The mental condition during malaria.

One has been taught to expect that the mental symptoms may become more marked in the actual pyrexia, but it is only in occasional patients that there is any marked alteration. Even then, the depressive type do not seem to change much. The manic type more frequently become noisy and talkative, and rather restless, but in such a case paraldehyde is at once given so as to obviate the additional strain put upon the bodily condition of the patient.

One case, who was of a mild manic

became acutely maniacal, and, avoiding the Attendants in some manner, was found plunging into a cold bath. Although he only got into the water up to his knees the result was a drop in temperature of three degrees, and the continuing of the rigor for 48 hours, at which point it had to be stopped by quinine.

One has found, however, that the mental condition seems to become more definitely grandiose towards the highest point of temperature, and the patient is much more inclined to give motor cars away, whilst the melancholic type usually begins to shew some signs of returning animation.

The physical condition during malaria.

Granted that the patient is in fair condition when the incubation period ends, little marked change is noticeable for the first three or four rigors, and until these have passed the anaemia which is undoubtedly present in the blood is not seen, except that there is the spread of generalised pallor.

There is a tendency to sleep much more than usual except in the manic type, and a general lassitude is noticeable.

Constipation is often rather troublesome, and has to be somewhat carefully treated. Under no circumstances does one give the mercurial purges as the kidneys are already under full strain. Aloin has been used with good results, but the dehydrating purges are to be avoided.

The urine becomes high coloured, with high specific gravity and usually a heavy deposit of urates towards the end of the rigor. It is by no means uncommon to find a trace of sugar in the urine, which seldom goes as far as either acetone or diacetic acid. Possibly the action of the temperature on the liver interferes in some slight way on the glycogen storing mechanism. Urea is diminished, but at times a faint trace of albumen is found, and where this is so it is an indication to reduce the amount of milk taken and to increase the fluid intake in other ways.

Very little alteration in the size of the spleen has

noted, and only in two or three cases has any real enlargement been found. These cases were those treated by mosquito infection.

In this connection, however, it must be said that two cases recently have shewn marked alteration in the spleen post-mortem.

Case 114, (B.S.) admitted in moderate health, was treated by intra-muscular inoculation. After an incubation period of 10 days he had 11 rigors, occurring daily. After the sixth which was of 105 F. the temperature never went above 103 F. and at the 11th $\frac{1}{2}$ c.c. adrenalin hydrochloride was given in an attempt to raise the temperature above this figure, without success. Quinine was given and the blood became negative after four doses of gr.X, and continued negative.

The patient died five days after the blood was negative, and on post-mortem examination the spleen was found to weigh 10 oz., and to be very congested and rather pulpy.

As, however, the other organs were markedly congested, and fatty, it does not seem that the splenic enlargement is entirely due to the malarial infection.

No parasites were recovered from the spleen.

Case 115, (G.C.) admitted in moderate health, was treated by intra-muscular infection at the same time and from the same donor as case 114 mentioned above. After an incubation period of 10 days he had a series of 12 rigors, the first four of which were of true tertian type and ranging from 104.6 F. to 106 F. Afterwards they became double tertian in type and until the 10th did not rise above 104.5 F. The 10th rigor was very severe indeed in length, lasting 14 hours, during which time the patient was tepid sponged twice, which procedure brought his temperature down to ~~102~~ 102 F. Quinine was given, but he had two other rigors and died after gr 60 had been given.

Post-mortem examination shewed marked fatty changes in all organs. Kidney disease of old standing was present, and the spleen was 12 oz. in weight, congested, and markedly pulpy. It was apparently not constricted by any capsule, and was absolutely shapeless.

The lungs shewed a commencing broncho-pneumonia of a deep seated type.

These two cases tend to give one the conviction that where pyrexia is allowed to continue unchecked for too long a time, some very definite damage is done to the spleen, due very largely to the persistent pyrexia, but possibly also due in some degree to the presence of the plasmodium.

One does not allow the temperature to remain high for more than four hours after the fourth rigor, and has the

patient tepid sponged until the temperature is found to be coming down at a reasonably rapid rate.

During the actual rigor, the lingual and labial tremors are noticed to be more pronounced, and the speech is found to be thickened to a noticeable degree.

Inco-ordination is also found, and sometimes to such a degree that the patient cannot feed himself, whilst headaches and mild "bilious" attacks are also sometimes found.

One of the patients who has since been discharged always gave warning of the onset of a rigor by projectile vomiting, although he could not remember having been troubled in this way before, and after the blood became negative to quinine he had no such difficulties.

The later rigors.

One has found that if a patient is able to retain a moderate bodily condition up to and including the fourth or fifth rigor, it is usually possible to allow him to have eight or nine. By the fourth rigor, the malaria has usually settled down to a more or less regular type, and one can often predict with a fair degree of certainty that the remainder will be either single or double tertian malaria, and can then base the diet on this supposition.

By the onset of the fourth rigor, the blood is nearly always markedly positive to the microscope, and parasites are found in large numbers. There is a marked anaemia of the simple type, and Schuffner's dots are very noticeable in the corpuscles. A relative increase in the polymorphous elements is found, although it is only slight: and the transitional stage is that chiefly noticed. The staining properties of the red cells commence to be marked impaired.

The mental condition in the later rigors.

It is by no means uncommon to be able to make some slight provisional diagnosis of the ultimate improvement or otherwise of the patient's mental condition from the amount of coherent thought he can display towards the termination of his pyrexia. Quite a

number commence to settle down, either from the manic or the depressive condition in which they commenced, and one is not in the least surprised to find that the grandiose patient loses many of his grandiose ideas, and becomes somewhat despondent about his continued stay in Hospital, as it will have serious effects on the income of his household. About this time many of our patients shew returning insight in some degree and can explain perfectly well their actions just before admission.

Case 102. (H.M.) admitted in a state of complete dementia with filthy habits, and with no interests and only two words "I cannot", at the end of his 7th rigor commenced to be clean in habit, to pass urine freely instead of being catheterised three times a day, and began to write quite reasonable letters home.

Since that time he has steadily improved in both mental and physical condition, and will shortly be sent home.

The physical condition in the later rigors.

As is to be expected, the continual strain upon the system tends to cause a marked loss in weight, and some of our patients lose 16 to 25lbs in weight during the pyrexial period.

Unless, however, other complications are found, the loss in weight and the consequent anaemia seem to be the only matters which call for attention, and these can easily be remedied once the patient has been cured of malaria.

The complications found in the malarial period.

Unfortunately, complications arise in nearly every case of therapeutic malaria, and some are very serious and call for immediate cessation of the pyrexia.

Dealing with the simple complications first, one has found that nearly every patient shews a herpetic form of rash on the upper lip and face, but very little treatment is required for this condition unless the patient scratches his face and causes a mild septic condition. One usually has the face smeared with Ung. Hydrarg. Ammon. 1% as soon as the rash appears, and this is found to be very soothing, and also a mild antiseptic. One has never seen a case go beyond a mild local septic infection, and expects to find herpes usually.

Restlessness and lack of sleep is occasionally met with, and such a difficulty tries the patient's resistance rather highly, but is very easily overcome by giving paraldehyde. One makes a practice of not allowing any patient sustaining the actual malarial infection to pass a sleepless night. Morphia is very seldom necessary, and is avoided where possible as the action on the respiratory centre would seem to favour the onset of broncho-pneumonia if there is such a tendency.

Occasionally one finds that a patient has attacks of bilious vomiting at the height of the rigor, and that he can not retain any milk. In such a case peptonised milk is given, and frequent drinks of lemon-water combined with soda-bicarbonate allowed. As a rule the condition clears up quite quickly, but if it does not, the patient's condition is prone to become very weak indeed, and quinine has to be given.

Persistent hiccough is found in a small number of cases, and one has taken this to be due to reflex irritation of the diaphragm due to the high temperature. It is very difficult to overcome, and one case had the difficulty for 36 hours in spite of morphia gr. $\frac{1}{2}$ repeated twice in that time, each time one hundredth of hyoscine being combined.

When such a complication is found, the patient is also found to be in very bad condition, and it is regarded as a signal to terminate the malaria by quinine, unless the hiccough responds rapidly to treatment.

Intermittent hiccough is not so serious, especially if it does not interfere with the patient's rest, and this sort can often be remedied by paraldehyde or a small injection of morphia (gr $\frac{1}{4}$).

Retention of urine has to be carefully watched, for and the fullness of the patient's bladder should be frequently tested. One has often had to pass a catheter on patients who are said to have passed urine freely, but who are found to have a dribbling incontinence which disguises an atonic bladder, or a stricture which prevents the free voiding of urine.

Abnormal constituents are often found in the urine, but a trace of albumen does not seem to have any serious significance, and is not found frequently here, because the diet in rigor is chiefly milk, whilst in the apyrexial period the protein element is somewhat reduced.

Sugar is sometimes found, but is usually transient: if, however, acetone and diacetic acid persist in spite of alkaline treatment it is evidence that the patient's liver is being too heavily taxed, and the termination of the pyrexia must be seriously considered.

Seizures of a cerebral type have occurred in three cases, and in no instance was morphia or any other hypnotic successful in preventing them. Two of the cases had had seizures before treatment, and continued to have them after, but the third gave no history at all of such an incidence.

In all three cases, quinine was at once administered, and in the one case referred to no further trouble was experienced, nor has he had any such convulsive attack although he has been under observation for nine months since.

Hyperpyrexia very frequently occurs, and any axillary temperature of 105.5 F. is regarded as serious, and the patient is at once tepid sponged to 102 F. As a rule there is a slight rise after, but the temperature should never reach the summit point after sponging. At present, one concludes that a temperature of 105 F. for more than half an hour is dangerous, and when this figure is reached the temperature in the mouth is found to be slightly over 106 F. If hyperpyrexia will not respond to treatment the malaria must at once be terminated by the administration of quinine in gr X doses, and the patient must be sponged until the temperature is lowered by two degrees at least and until it commences to drop from that point.

Sustained pyrexia over 36 hours is also regarded with grave suspicion, and if there is no other physical condition to account for is (e.g. pneumonia) one feels compelled to stop the infection. One has tried, by small doses of quinine,

to reduce the temperature in order to produce a period of apyrexia for 24 hours, but has only been successful in reducing the blood to a malaria-negative condition:-

Case 118, admitted in very poor condition, was infected by the intra-muscular route, and developed a temperature of 103 F at the end of 6 days. This temperature was maintained for 48 hours, at the end of which time a gr $2\frac{1}{2}$ of quinine sulphate was given and repeated in 6 hours.

The temperature fell to 98.4 F. in twelve hours, and no further rigor was found to occur.

Prior to the quinine being given the blood was scantily positive, but on the day following the administration it was negative to prolonged examination.

Other workers use quinine in small doses, one hears, to control the height of rigor in female cases, but wherever one has given it in small doses (chiefly where double tertian malaria is taking toll of a patient's resistance too rapidly) the pyrexia has not recurred, and for this reason one now gives the ordinary grX dose repeated if sustained pyrexia is found.

Jaundice in any degree is alarming. If the diet of the patient has meat or much protein in during the pyrexial period it is possible that the elimination of this will allow the malaria to be carried on, but if there is the slightest indication of persistence or increase, it is indefensible to wait, as, unless quinine is given very soon, the patient will seldom recover.

At this Hospital, with the carefully regulated diet and constant observation of the urine and stools, if jaundice appears and persists more than six hours, quinine is given in large doses, for it seems better to keep the patient alive and hope to be able to give inoculation of malaria at a subsequent date, rather than to risk his death.

The general condition of the patient, and his power of resistance to the fever, and his recuperative powers in the apyrexial period, must be carefully and fully considered, and he must only be allowed to continue with the infection so long as his general health is undamaged from a permanent point of view.

A devitalised patient may last the whole twelve

rigors with little benefit to himself if he dies soon after of inter-current disease, and one always feels somewhat culpable if a patient, having had a large number of rigors, dies soon after of say broncho-pneumonia, which is markedly easy to contract after malaria.

For these complications, then, one has to be on the outlook, and each must be decided on its merits as to whether it will endanger the life of the patient. This attitude of terminating malaria a little before the absolute limit is, one thinks, perfectly justifiable because the whole treatment of General Paralytics is based on such indefinite lines that one cannot point to any fixed number of high fever re-actions below which one cannot expect improvement.

THE METHOD OF TERMINATION OF THE MALARIAL ATTACK.

Two drugs have been tried in this Hospital: one experimental and the other with preconceived ideas which have been always substantiated.

Arsenic in various forms has been administered to cause a cessation of the pyrexia and clear the blood of the infecting parasite. It has frequently fulfilled the former duty, but has no real effect on the continuance of the parasite.

For some time one felt bound, in dealing with a disease resultant upon the action of the spirochoete, to use a spirochoet-icidal preparation which would prevent further fever. To this end "914" was given at the height of the rigor purposed to be the final, and it was found that the temperature came down to normal and as a rule stayed at or below normal. This was felt to be quite satisfactory, but when the blood came to be repeatedly examined microscopically, parasites were still found to be present some four or five days after the last pyrexia, although in apparently diminished numbers.

Therefore, it was determined that quinine was the specific which would give the best result, and quinine is now a matter of routine, without any aid from arsenic whatsoever.

Spontaneous remissions, or cures, of the malaria have occurred in twelve of our patients suffering from the fever for the primary infection. In none of these cases was quinine given during the period of pyrexia, although in three, a quinine tolerance has been tested for before the inoculation of parasites.

Of the twelve cases shewing this spontaneous cure, seven had been infected by mosquito-bite, whilst three were infected intra-venously and two intra-muscularly. In no case did the patient have more than seven rigors, and in no case was any medicinal treatment given to cause the reduction of the blood to a microscopic negative result.

Three of these cases suffered relapses of double tertian malaria at a later date, but in no case was the relapse within four months of the original fever.

It is possible that this figure for spontaneous cures would be larger, were it not for the practice of always endeavouring to terminate the malaria well within the limits of tolerance of the patient, and perhaps this also accounts for the comparative fewness of the relapses. When quinine is given with the parasites abundant and shewing freely in the blood, one can at least be sure of attacking the parasite when it is circulating, rather than when it is lurking in the interstices of the spleen and other organs.

Examination of the blood films in these cases of natural disappearance of the parasite gave but little indication of such a result, except that the numbers found on the film, either thick or thin, tended to diminish somewhat progressively. In this event, no quinine was given until the blood had been definitely negative for five days, and until a provocative injection of adrenalin and milk, or adrenalin alone, had been given on two successive days.

No special immunity was found afterwards in the cases shewing this spontaneous cure, when they came to be treated for the second time, although it is ~~only~~ true that only three were so treated.

THE CAUSATION OF DOUBLE TERTIAN MALARIA.

In thirty-seven out of the hundred cases quoted, one has found that rigors occurred daily, instead of two-daily, although the strain being used for inoculation is known to be of true tertian type, and it has been of considerable interest to examine carefully the daily blood films under the microscope.

In those cases where double tertian rigors are to be found, there is no uniformity of development of the parasites, and with little trouble one can find the ring form trophozoite co-existent with the mature schizont, and also the schizont segmenting, and setting free the merozoites.

It is thus easy to explain the actual appearance of double tertian malaria, but it is much more difficult to give any adequate reason why an inoculation from one patient having true tertian malaria should produce a double tertian pyrexia in the patient receiving blood.

Possibly, each patient has a definite resistance index to the parasite, and by this means retards the development of more than a "sufficient" quantity of the more immature forms of the plasmodium.

It is of interest to note that when mosquito infection is used, there appears to be a greater certainty of obtaining an outbreak of pyrexia more true to type, for only three cases developed the double tertian fever, whilst sixteen were of the two daily variety, and this fact leads one to think that the life circle in the mosquito has the effect to bringing the parasite to a regular state of maturity,

Examination of the blood early in pyrexia is said to shew parasites in all stages of development even in the case of mosquito bite (Muir and Ritchie), and if this is so it would further point to a doctrine of survival of the fittest, for except in inoculated malaria, atypical rigors in point of time are somewhat rare. From this point, also, one is inclined to believe that the development of double tertian is due to some inherent lack in the host, unless a mass infection has taken place.

THE EFFECT OF QUININE UPON THE PARASITE.

One usually gives the quinine mixture at or about the apex of the determined rigor, and it has been the usual experience to find that no further pyrexia develops, although in one or two cases a mild fever has been found on the following day.

Where "914" was given in conjunction with quinine no such post-quinine rigor has been found.

Where mosquito infection was used it was by no means uncommon to find that the blood took five or six days to become absolutely negative to the microscope, but for the last two days the parasites were shewing marked quinine affected forms.

On the other hand, however, where inoculation infection was used, it has been the almost invariable rule to find that parasites are almost entirely absent from the blood at the end of 60gr. of quinine.

Although attempts have been made to provoke further rigors by the injection of adrenalin, after quinine has been given for two days, no case has shewn a further rigor.

A possible explanation of the tractability of the inoculated malaria is that ~~the~~ when the plasmodia reproduce themselves only in an asexual way, as they do in the human subject, their quinine resisting power is much diminished: even when there is an abundance of plasmodia, gametocytic forms are markedly few.

Other workers have reported that where a quinine tolerance test has been applied to the strain in a rigoring patient, and that patient's blood used for subsequent inoculation the following hosts require more quinine to effectually clear the blood of the parasite.

In double tertian malaria, which seems to be the commonest type at present in use here, no difference in the time taken for quinine to affect the parasites has been found, and the "growing" parasite seems to suffer as speedily and as completely as does the more mature form, both being found in almost equal numbers.

Quinine sulphate is always used now, although other salts have been tried intra-muscularly and intra-venously.

One gives gr.X, three times a day, and dissolves gr 90. for nine doses.

The sulphate is put into water, and then some two drachms of dilute sulphuric acid is added, and a tablespoonful dose three times a day ordered from the mixture which is made up to four and a half ounces with water.

Two cases alone have shewn parasites resistant to this amount of quinine, and they were treated with gr.V doses for the remainder of the week and then cleared up.

The blood film taken on the morning of the second day after the exhibition of the quinine mixture is frequently quite, or almost, negative to the microscope. Where parasites are found they are seen to be markedly quinine affected: by the end of the third day, i.e. when the gr.90 of quinine have been taken it is the almost invariable rule to find that parasites have gone from the blood.

Although films are examined every day for a week after the termination of the quinine, only in the two cases before mentioned has any persistence of malaria been found.

The blood film after quinine soon begins to shew a renewal of the haemoglobin in the red cells, with a slight leucocytosis, an actual increase in the polymorphs, and a slight diminution in the large and small mononeuclear leucocytes.

In this connection it is possibly of interest to mention a case which was treated away from this Hospital by quinine alone, until benign tertian malaria could be obtained. He received gr.2 of the sulphate four times a day for two months, and from being bed-ridden he became able to get up and go to a Hospital for inoculation.

Although one concludes that the improved physical well-being was chiefly due to the onset of a mild remission; for no real benefit was obtained from 7 rigors which were permitted when the malarial blood could be obtained and used.

No cases appear in available records of entire treatment of quinine alone.

THE AFTER TREATMENT OF MALARIA.

As a rule the blood picture becomes negative to malaria about the third or fourth days of quinine exhibition, and one endeavours to get the patient up a little on the fifth day, increasing the time allowed up gradually until he is resuming the normal ward routine about the end of a fortnight.

The diet is increased fairly rapidly immediately the blood has been negative twenty-four hours, and no sickness or jaundice has been observed on this account. Cod Liver Oil is continued for some weeks after, unless the patient shews a marked dislike thereto. After Cod Liver Oil has been withdrawn, an iron and quinine tonic is given for a month, and very good results have been obtained thereby, for the haemoglobin index rapidly approaches the 100%.

Anti-syphilitics have been tried at various times, on the lines of reasoning that there may be latent spirochaetes in the brain and that the endothelial destruction in the small vessels of the brain will favour the rapid penetration of the arsenic. It has been found that such medication has little or no effect upon the contents of the cerebro-spinal fluid, and except for the tonic properties of the arsenic, one does not feel it useful given in an intra-venous manner.

There is also the draw-back to the "914" group, which one is warned against. So many General Paralytics shew very definite evidence of arterio-sclerosis that one feels dubious of the wisdom of giving intra-venous medication.

A large number of our patients have received mercury and potassium iodide over long periods, and the results obtained from these drugs seem to be rather good. Whether they have any definite action on the spinal fluid is doubtful, but where there is a good result indicating marked tabetic field damage it would appear wise to give iodides.

Monrad-Krohn, writing in the Journal of Mental Science in January 1922, gives several suggestions as to why the anti-syphilitic remedies are of little avail, and considers that

possibly the spirochoetes have developed an immunity to the anti-syphilitic remedies, or else that the spirochoetal infection of the cortex has started a vicious circle, which will continue in spite of the spirochoete.

Whatever the explanation may be, it would seem that most workers have at one time or another used the arsenical preparations in an endeavour to hasten the advent of "stabilisation" and have been disappointed.

Personally, in view of three collapses, two mild and one of rather a severe nature, consequent upon the use of very small doses of "914", one hesitates to use it, and has not done so for some time.

One would rather, then, give a general tonic to the system of the patient, chiefly comprising iron and quinine, and the scale preparation "Ferri et Quin Cit" is used over a long period, with excellent results both to the general condition and to the blood picture.

Fresh air, and a good deal of mild exercise, is always insisted upon, and the patient is not allowed to do any ward work for ten days after he has shewn a negative blood film for three days.

Whenever possible, the patient is got out of doors for a large part of the day, and receives a special diet with gradual increase of the protein element in an endeavour to compensate for the tissue waste which was caused by the repeated malarial attacks.

No attempt has been made here to assist the malarial treatment by the intra-theccal use of salvarsanised serum: one feels that the results obtained by malaria alone are sufficiently promising to trust, and that additional interference of an uncertain kind will not tend to raise the resistance to the bodily illness which is found in practically every case of General Paralysis when admitted to the Hospital. Indeed, the after care may be summed up in few words. One should see that the blood is clear of the parasite, and that every step possible is taken to increase the general health.

MALARIAL RELAPSES.

Relapses are not at all common, and we have only had 17 cases out of ~~50~~ a total of 100 treated who shewed renewed fever after quinine had been given and the blood brought to a negative condition.

It is of some interest to find that the mosquito infection seems to give a greater proportion of relapsed cases than either of the other routes: 66% have had further rigors compared with 33% where intra-venous infection was used, and 8% where intra-muscular inoculation was the method chosen.

The parasite can not always be demonstrated in the blood of cases relapsing, but the clinical signs are such that it is obvious malaria is still to be reckoned with.

S.D.A. who had eight daily rigors in December 1925, had a consistently negative blood after three days of quinine. Three weeks after the termination of malaria he developed a confluent broncho-pneumonia, which was of 15 days duration. A pleurisy was then found, and a needle inserted, some 38 ounces of fluid being drawn off.

At the end of March he developed a double tertian malaria, and had four high fever re-actions, each day shewing a temperature of 104.5 F. The parasite was only found on the fourth day.

Whether the body creates a greater degree of anti-body formation when the unnatural methods of infection are used i.e. intra-venous or intra-muscular, one cannot say, but there is no doubt that relapses are found more frequently where a direct mosquito bite in the source of infection.

TREATMENT OF RELAPSES.

Quinine is given in ten grain doses three times a day for three days, and afterwards for four days or rather longer, in doses of gr.V three times a day.

The blood does not seem to suffer to such an extent in the relapse period, whilst the temperature is, as a rule, from half to one degree lower than an original rigor. Otherwise the relapse pyrexia goes through identically the same physical conditions, but it is, sometimes, slightly less amenable to the quinine treatment.

The incidence of relapses and double tertian malaria in cases.

Route.	Total.	Number living 3 months after Quinine.	Relapsed.	Rigors.		Relapsed	
				Daily.	Two daily.	After daily rigors.	After two daily rigors.
Mosquito.	25.	12.	8.	3.	16.	2.	6.
Intra-venous.	25.	22.	7.	10.	15.	1.	6.
Intra-muscular.	50.	x 26.	2.	24.	17.	1.	1.

x. In addition to these 26 there are 8 cases in Hospital who have been treated within the last three months, and only one of these has relapsed, and is shewn in the total of relapses, and as having relapsed after having daily rigors.

THE CAUSATION OF RELAPSES.

Seventeen cases out of our series of 100 cases have at one period or another relapsed, although in every case quinine is administered until the blood has been negative to repeated examination over two or three days.

Two or three cases have been treated with adrenalin intra-muscularly when the blood was brought to a negative state, and just before quinine was terminated, in the hope that any latent parasites would be brought to the periphery, but in none of these experiments was any result obtained.

It is quite likely that relapses are due to the persistence of parasites in the organs, and possibly in the deeper vessels of the brain and in the bone marrow, although slides taken in one case from the spleen, bone marrow, and brain showed no parasites. (The post-mortem in this case was done 8 hours after death.)

Even granting this, it is difficult to explain why a patient should go nearly two years with no relapse, and then have a series of three or four rigors, with a spontaneous cure.

Scaudinn found that the macrogametocyte of tertian malaria may give rise to a merozoites by a process of parthenogenesis, and these in their turn infect the red blood corpuscles and start the life cycle of the parasite again in the human.

He claims that the chromatin of the macrogametocyte divides first into two portions, one smaller than the other, and the smaller portion divided, and the protoplasm becomes segmented as is ordinary schizogony, and a young brood of parasites results.

The larger and more faintly-staining chromatin along with part of the protoplasm breaks up and disappears.

In our cases which have relapsed, no seasonal incidence has been observed, nor has any particular bodily weakness tended to precipitate the relapse.

No further infection by mosquito has been possible as the malaria-carrying mosquito is unknown in this area so far as one can say.

THE PHYSICAL RESULT OF MALARIAL TREATMENT.

When the patient recovers from the malarial pyrexia, it is usual to find a very rapid improvement in his physical condition to at least the point at which the rigors commenced.

As a rule, however, one finds that as soon the patient gets about the ward there is a steady increase in well-being and he quickly recovers the weight he has lost through the strain consequent upon the fever. His appetite is much improved, and he gains strength, and soon begins to take an active part in the ward work and the ward games.

Within a month of the termination of malaria one confidently expects that the patient will be in much better health than he was before he was inoculated.

Of the 41 cases remaining in Hospital at the present time only four can be said to have suffered permanently in health owing to the malarial treatment, but, as will be seen from the particulars attached 27 have improved, and three retain their previous good health. In explanation, it should be said that bad health includes those patients bed-ridden or almost so: poor health includes those who were confined to bed for more than half a day owing to some definite physical debility consequent upon the disease: moderate health includes those who were unable to take an active part in the ward work: fair health includes those who were able to get about quite well, and to take ordinary diet and ordinary exercise.

Of the fifteen cases discharged, one was admitted in bad health, five in poor health, and nine in fair health. All were discharged in good condition.

It is usual to find a marked increase in weight in patients within two months of their treatment and this is as a rule progressive, the increase being a general one, and not confined to "abdominal" fatness. Indeed, the remarkable thing is the frequency with which patients require larger suits to accommodate them.

Old standing diseases such as bronchitis usually share in the general systemic improvement.

THE RESULT OF MALARIAL THERAPY ON THE HEALTH OF PATIENTS AS SHOWN BY
THE 41 PATIENTS PRESENTLY IN HOSPITAL.

Admitted in	At present in				
	Bad health.	Poor health.	Moderate health.	Fair health.	Good health.
Bad health.	6.	1.			5.
Poor health.	13.	4.			9.
Moderate health.	6.			2.	4.
Fair health.	10.		1.	2.	7.
Good health.	6.	1.	1.		3.

Of the 6 admitted in good health, three are or have just been under treatment and their health is classified as they are at present.
Of the 13 admitted in poor health, two have just been treated and are classified as still poor.

ANALYSIS OF PHYSICAL CONDITION OF DISCHARGED AND REMAINING
PATIENTS.

Remaining 41.
Discharged 15.

	Admitted to this Hospital.			At 31st March 1925.		
	Health		Fair.	Health		Fair.
	Bad.	Moderate.		Bad.	Moderate.	
Remaining.	10.	19.	12.	5.	6.	28.
Discharged.	2.	4.	9.			15.

It is fair to point out that two of the "remaining" cases shewn as in "bad" health were admitted in "fair" condition.

From the summary which is given, it will be seen that in nearly every case some physical improvement has resulted from the treatment, and the improvement is usually well maintained.

Of the patients admitted in bad health four out of six have been in Hospital for more than eighteen months, and have been under observation for that period. All are now well and going about in an ordinary manner. Of the thirteen admitted in poor health, the nine who are now in good health have been under observation for a similar period of time. The six admitted in good health have been treated more recently, but one has definitely suffered through the malaria, and is almost bed-ridden.

THE RESULTS OF MALARIAL TREATMENT ON THE REFLEXES .

Many of our cases have been admitted with slight alteration to the knee-jerk reflexes, and the greater part of the number remaining in Hospital now have had fixed pupils, mainly contracted. Practically every case has shewn some lingual and labial tremor, and many have shewn marked inco-ordination. Slurred speech has also been found in some degree in most of the cases.

In no case, either remaining or discharged, has any alteration been found in an absent reflex. Where the knee-jerks were absent on admission, they have continued to be absent. Where they were excessive, very little diminution has been found after treatment.

In no case has any alteration been found in the eye reflexes, and where the pupils were either acentral, acircular, fixed and contracted or fixed and dilated, they have continued in ~~the~~ that state.

On the other hand, the labial tremor is found to disappear in the majority of cases fairly soon after quinine has terminated the malaria, and especially is this so in those cases who are going to improve mentally as well as physically.

The lingual tremor persists longer, and is never really cured: but it is often found that the marked slurring of speech is to some extent relieved, and becomes much less noticeable.

One has to record, however, two cases shewing a real mental and physical improvement after treatment, but with a slur in the speech which has become much worse since the pyrexia and which is almost a definite impediment.

No actual reason can be given for this, as in neither case is there any physical disability: both developed the increased slurring in a second attack of malaria, and in one it has persisted for six months, whilst in the other it has been found to improve slightly about the end of the third month, but it is still markedly present. Graham of Belfast reports a similar case, but can give no explanation.

One has found that co-ordination undergoes a really definite improvement, and this is well exemplified in the gait. Prior to treatment many of our patients have been ataxic and of a "slack" method of walking. After treatment they become much more brisk, and their movements are all purposeful.

The handwriting too, in patients sufficiently well educated to write a legible hand, seems to undergo a marked improvement, due no doubt to the better co-ordination found.

Intention tremors disappear very soon after malaria, and continue to improve as the physical health is improved.

THE RESULT OF MALARIAL TREATMENT ON RE-ACTION TIMES.

One has found, by varied tests, that after the acute weakness of pyrexia is passing off, some slight improvement is to be found in re-action times in certain patients, and these are those whom one expects eventually to do well mentally. The re-action times do not appreciably improve, however, until the sluggishness of malaria has passed off, although a quite definite quickening of interest is to be found frequently even towards the end of the pyrexial period: "coarse" interests in such matters as food seem to return much more quickly, and then the interests which tend to keep a patient clean in habit are next observed to be returning. The "home-instinct" is also early found in the period of euphoria following malaria.

THE RESULT OF MALARIAL THERAPY UPON HABITS.

Of the 41 patients presently in hospital, 25 were admitted unclean in personal habits, and some were particularly degraded, which made the nursing extremely unpleasant, and was also liable to cause considerable inter-current sepsis.

Of these 41, however, 17 have become clean in habit, and now need no supervision ~~whatsoever~~, as they attend to the calls of nature in the ordinary manner, and are able to sleep in dormitories without special attention.

Two patients who were admitted with clean habits have become faulty, but both these cases are in extremely bad ~~in~~ physical condition and are completely bed-ridden.

Eight cases were admitted with faulty habits and are still faulty, but three are somewhat better than they were on admission, and with a little care can be kept clean.

Fourteen were admitted with clean habits, and have not altered, whilst of the fifteen patients discharged with complete control of their habits, three were admitted who were not able to look after themselves.

For some little time one was disappointed with the results obtained in the regaining of the control of the sphincters, but as soon as a mercury and potassium iodide mixture was either reduced in quantity or withdrawn altogether, the habits of the patients shewed a very marked improvement.

Not only do the foregoing remarks apply to the intimate habits of the patient, but they apply with equal force to their general tidiness, for one finds that with the improvement a general tendency to tidiness in person and in work returns. This is particularly borne out in the hand-writing, and also in the method of expression in letters, which seems to become much less involved as the improvement progresses.

One has found General Paralytics treated with malaria very much easier to deal with than those untreated, especially with regard to the retention of urine. It is a rare thing to have to pass a catheter on a malaria treated patient, and

an acute retention has not occurred in a treated patient in the last four months.

It should be said, however, that during the time of pyrexia it is quite common to have to catheterise patients.

H.M. who was admitted in July 1925, had double tertian rigors, and was filthy in habit. He had to be catheterised twice daily during the whole period of the infection and for four days ~~sin~~ after quinine was given.

Hexamine had to be given in large doses because of a pyelitis, and this was continued for a fortnight after quinine was discontinued.

After that, however, he regained control of his bladder, and he has not required any such attention since.

He will, in all probability be discharged within the next six weeks or two months.

On the other hand, where malaria has been withheld for some reason, one has continually to be on the watch for urinary difficulties, and it has been no uncommon thing to find an acutely distended bladder with a dribbling incontinence.

The improvement noticed in respect of habits, apart from any other consideration, seems to make the malaria treatment of a very definite value in a Hospital, for not only is the ward kept much sweeter, but the patient's general health is markedly improved, whilst the time of Attendants is utilised in more useful and more congenial work.

In addition, the economic consideration of the saving in laundry is considerable.

Where a bed-ridden patient is clean of habit, one has found it of rare occurrence to find a bed-sore develop, and of recent months such a sore in a treated General Paralytic is a rarity, and a matter for very stringent enquiry, with always the feeling that someone else is to blame, rather than the patient.

No post-malarial case has given rise to any bladder complication, of those remaining in Hospital although three of those who died after treatment shewed pus cells in the urine. All three were bed-ridden cases and two had definite urethral strictures, and needed to be catheterised occasionally for this reason alone.

One therefore feels that malarial therapy is worth while if only from the point of view of cleanliness.

THE RESULT OF MALARIAL THERAPY ON THE HABITS OF PATIENTS AS SHOWN BY
THE 41 PATIENTS PRESENTLY IN HOSPITAL.

Admitted.		At present.		
Faulty in habit.	Clean in habit.	Admitted faulty now clean.	Admitted clean & still clean.	Admitted faulty & now faulty.
25.	16.	17.	14.	8.
				2.

In addition to these figures it must be borne in mind that of our 15 discharged patients, three were admitted with faulty habits, but all were discharged with clean habits.

THE LABORATORY RESULTS OF MALARIAL TREATMENT.

One has been fortunate in this Hospital in having cases still here who were admitted more than three years ago, and it is, therefore, possible to give an opinion of any change found in the cerebro-spinal fluid, and to instance repeated observations.

Until recently, most workers considered that there was little, if any, change in the serological findings after malarial treatment. Houston and Armstrong (Journal of Mental Science, October 1924), McAlister (Journal of Mental Science April 1925) and Claude and Targola (Bulletin et Memoirs des Hopitaux de Paris, June 1925) all state that no important changes are found in the cerebro-spinal fluid.

Gerstmann, however, states that the findings are modified gradually, and this is borne out by Graham (Belfast), Grant and Silverston (Whittingham), whilst one endeavoured to prove this by instancing cases in the Lancet (October 1925 in conjunction with J.E.Nicole.) Since that date one has contributed further evidence of a definite change observed.

On the attached table will be found the evidence one based one's results and conclusions upon.

One has found that quite half of the cases shew a negative globulin re-action at varying intervals after the termination of the malaria, and that the gold sol. reading corresponds somewhat closely, in that with the conversion of a positive globulin to a negative reading there has been a diminution of the reducing power of the fluid. The change has not only been the "displacement to the left, and upwards" quoted by Pappenheim, but is also of the nature of a conversion of a true paretic reading to that more closely associated with a diagnosis of cerebro-spinal syphilis.

This was the conclusion one arrived at in considering cases examined at periods varying from four to twenty-two months after the termination of pyrexia.

The period which has intervened has allowed the opportunit

of examining the same cases again, and also to compare them with further results obtained on more recent cases, and one has come to the conclusion that any changes found in the cerebro-spinal fluid tend to onset about twelve months after the malaria has been terminated. With further lapse of time after this period the change in the gold sol reading becomes frequently like a weak tabetic condition, although in the first instance it may have been strongly positive in the paretic and tabetic fields. In some of the cases so investigated, no higher reduction than a "2" has been obtained, in either the paretic, tabetic or meningeal fields.

One would emphasize the fact that such diminution in the content of the cerebro-spinal fluid cannot be taken as a sign that the mental condition is improved, and in support of this would quote No. 15 of the tabulated results:-

E.W. aged 31, admitted 21:12:23, with a gold sol reading 5555543100, cells 49 per cmm, and a double plus globulin, was treated with malaria, and had a series of rigors. Ten months after malaria his fluid shewed a reading of 0112332100, with a negative globulin. Sixteen months after pyrexia Lange's test gave 0112221000, with a negative globulin re-action. Cells are only 8 per cmm, but the acetic anhydride test is positively paretic.

In spite of this marked improvement in the laboratory tests he remains a very typical example of the grandiose General Paralytic.

In contrast to this case of improvement in the laboratory findings, with no clinical improvement, case 25 may be instanced:-

J.C.C. aged 42, admitted 28:12:24, with a gold sol reading of 5555553100, cells 68 per cmm, and a positive globulin, was treated with malaria, and had a series of rigors.

Nine months after treatment his Lange's reading was 2455421001, cells 18 per cmm. and a negative globulin.

His mental condition, however, had so much improved that he was discharged on trial and continues to do well at his ordinary work.

From these two cases, it will be seen that one is not inclined to accept the fact that actual conversion of the gold sol reading as having any real bearing on the mental condition.

Possibly, however, on the physical side one is more able to give a general opinion that with the disappearance of globulin, and with a reduction in the reducing power of the cerebro-spinal fluid, combined with a diminution in the number

of cells, one may expect some improvement in health.

In support of this, perhaps two cases may be instanced. Case 5 tends to prove that the improvement of the cerebro-spinal fluid may have some bearing on the general health:-

M.P. admitted in November 1923 was in extremely poor health, and was almost bed-ridden. He shewed a positive globulin, cells 97 to the cmm. and a reading of 555555432 to the gold sol test.

At present, some two years and a half after the malarial treatment, he is in good health, working in the grounds, and is scrupulously neat and tidy in person.

His cerebro-spinal fluid shews a negative globulin reaction, a cell count of 19 per cmm. and a gold sol reading of 0032110000. He has also recently commenced to improve markedly from a mental standpoint.

Case 27, however, shews little alteration in the fluid, but marked deterioration in physical state:-

R.N. admitted 12:1:25 in very bad condition, but could get about the ward. He shewed a positive globulin reaction, cells 77 per cmm, and a gold sol result of 5555554300.

Presently, fourteen months after termination of malaria, he is absolutely bed-ridden: extremely faulty in habit, with signs of impending complete collapse. He now gives a double positive globulin reaction, 48 cells per cmm. and a reading of 5555555552.

The last mentioned case has only been under observation for a little over a year, but he has steadily gone downhill, and his cerebro-spinal fluid has evidently not received any benefit from the malarial treatment.

In the alteration in readings it has been repeatedly noticed that the change commences at the paretic end of the curve, and this is more noteworthy as so frequently the reduction of the first or first and second tubes is held up by the presence of sero-albumen, whilst, when a change is found in the reading it is frequently coincident with the disappearance of the demonstrable globulin.

Apparently, therefore, when the reading is so little altered in the Lange's gold sol in spite of a negative globulin reaction, the balance between the precipitating action of the globulin and the protective action of the albumen on the gold sol has been disturbed.

One has not found that the induction of a second attack of malaria has any marked quickening effect on the alterations

taking place in the fluid, and one feels that where a change is evidenced in a reading taken after a second attack, it is due to the interval of time which has elapsed since the first malaria.

This seems the more justifiable aspect, as so many of the cases shew a change about twelve months after the malarial pyrexia, and as a rule it has been the practice to allow at least a year to intervene between the original pyrexia and further inoculations, although Wagner-Jauregg recommends that an interval of six months should be the time.

One has administered arsenic in various forms, but little evidence has been obtained of any benefit obtained thereby. No quickening of the clearing of the cerebro-spinal fluid has been found when "914" has been given, for case 33, H.M. has received 4gm. intra-venously, and no appreciable difference has been found in the fluid within six months.

The numbers of rigors permitted do not seem to have any bearing on the condition of the cerebro-spinal fluid, because cases 15 and 23, shewing an approximately equal change, had 10 and 2 rigors respectively.

As one has already pointed out, the alteration in the spinal fluid has little direct bearing on the clinical diagnosis, for cases shewing a weak paretic condition of the fluid after malarial treatment frequently shew a strong clinical picture of the grandiose general paralytic.

The acetic anhydride test, which has recently been used in every case, has given extremely interesting information, for a positive paretic reaction has frequently been obtained by this test on a known General Paralytic whose cerebro-spinal fluid has "cleared" after malaria.

The chemistry of this test is as yet unknown, but it is of some value when taken in conjunction with the gold sol., globulin reaction, and cell-count, whilst for treated cases with altered reading it may, when definitely recognised chemically, shew an intermediate form of cerebral and neuro syphilis.

COMPARATIVE RESULTS OF THE CEREBRO-SPINAL FLUID.
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Case.	Original reading.			Second reading.			Third reading.		
	Range.	Glob.	Period since malaria.	Range.	Glob.	Period since malaria.	Range.	Period since malaria.	Glob.
1.	5555554321	Pos.	15 months.	4555554433.	Weak.	22 months.			
2.	4555554321.	Pos.	23 months.	0034321100.	Neg.		1334552100.		Neg.
3.	5555554322.	Pos.	16 months.	3455543100.	Neg.				
4.	5555555543.	Pos.	19 months.	2345554300.	Neg.	24 months.	0032110000.		Neg.
5.	5555555542.	Pos.	18 months.	1155553100.	Pos.	26 months.	0234322100.		Neg.
6.	5555554321.	Pos.	20 months.	0234331000.	Neg.				
7.	5555543210.	Pos.	10 months.	1333211000.	Neg.				
8.	4555543300.	Neg.	15 months.	0245544321.	Pos.	26 months.	0112221000.		Neg.
9.	5555532000.	Pos.	11 months.	5555554430.	Pos.	15 months.	0123432200.		Neg.
10.	5555533100.	Pos.	12 months.	0123322200.	Neg.				
11.	5555420000.	Pos.	17 months.	0123322100.	Neg.				
12.	5555542100.	Pos.	15 months.	0133332100.	Neg.	21 months.	00111100000.		Neg.
13.	45555521000.	Pos.	21 months.	3555554000.	Neg.				
14.	5555541000.	Pos.	8 months.	0354432000.	Pos.	13 months.	4555531000.		Neg.
15.	5555431000.	Pos.	10 months.	0112332100.	Neg.	16 months.	0112221000.		Neg.
16.	5555555410.	Pos.	14 months.	0155432000.	Neg.				
17.	5555551100.	Pos.	13 months.	0023321100.	Neg.	19 months.	0003320000.		Neg.
18.	5555542100.	Pos.	16 months.	0244322000.	Neg.				
19.	5555541000.	Pos.	14 months.	0123443210.	Neg.	21 months.	0013320000.		Neg.
20.	5555554100.	Pos.	14 months.	4555553311.	Pos.	20 months.	5555553320.		Neg.
21.	5555555543.	Pos.	14 months.	1255433000.	Neg.				
22.	5555531000.	Pos.	12 months.	0344433000.	Pos.	17 months.	1233332100.		Neg.
23.	1155555510.	Pos.	13 months.	5555544300.	Weak.				
24.	5555431000.	Pos.	12 months.	4555544320.	Weak.	18 months.	4555543200.		Neg.
25.	5555553100.	Pos.	9 months.	2455421000.	Neg.				
26.	5555554210.	Pos.	9 months.	5555552110.	Weak.				
27.	5555555430.	Pos.	3 months.	5555555432.	Pos.	10 months.	5555555552.		Pos.
28.	5555554200.	Pos.	4 months.	4555554420.	Weak.	10 months.	5555554320.		Neg.

COMPARATIVE RESULTS OF THE CEREBRO-SPINAL FLUID.

.....

Case.	Original reading.		Second reading.		Third reading.		
	Range.	Glob.	Period since malaria.	Range.	Glob.	Period since malaria.	Range.
29.	5555553200.	Pos.	2 months.	4555553320.	Weak.	10 months.	5555554320.
30.	4555555320.	Pos.	2 months.	4555554321.	Pos.	8 months.	55555543210.
31.	5555554310.	Pos.	2 months.	4555555543.	Pos.	7 months.	5555555543.
32.	4555553200.	Pos.	3 months.	1345542200.	Weak.	6 months.	0233344321.
33.	5555554322.	Pos.	2 months.	5555552210.	Weak.	6 months.	55555555443.
34.	4555553200.	Pos.	4 months.	5555553220.	Neg.		
35.	5555554310.	Pos.	14 months.	3555544220.	WPos.	18 months.	3445543100.
36.	5555555432.	Pos.	3 months.	5555554320.	Neg.	8 months.	5555554320.
37.	2555543000.	Pos.	9 months.	2555555300.	Pos.		
38.	5555431000.	Pos.	7 months.	2444433211.	Weak.		
39.	55555421000.	Pos.	18 months.	5555554420.	Weak.	22 months.	5555554420.
40.	5555322100.	Pos.	15 months.	33355444300.	Pos.		

THE RESULTS OF MALARIAL THERAPY AS SHEWN BY THE ACETIC ANHYDRIDE REACTION.

One has only had the opportunity of using the acetic-anhydride test on the cerebro-spinal fluids of the 41 cases presently in Hospital, and upon two of the discharged cases, although it is now being used as a routine on every case whose cerebro-spinal fluid is being tested.

The results, in primary tests, follow very closely the colloidal gold curve, and sometimes in cases where the gold sol shews a weak paretic condition, the acetic anhydride result is strongly positive.

Where, however, cases have been treated and shew a marked diminution in the gold sol reduction power of the cerebro-spinal fluid, together with a negative globulin content, and a reduction in the cell count, one has found that the acetic-anhydride test continues to be positive.

Only in one case of a known General Paralytic who had been treated elsewhere (and admitted to this Hospital in a relapsed condition) has the acetic anhydride test shewn a negative result at a period after malaria. In this case it was a second attack of malaria, for when he was originally treated here it was unknown that he had been previously treated elsewhere.

Actually, this patient shews but a very modified type of alteration in the cerebro-spinal fluid when tested by Lange's method, although his cell count is much diminished, and no globulin is to be demonstrated.

Clinically, he presents no mental signs of General Paralysis of the Insane although the altered reflexes are still noticeable.

The chemistry of the acetic-anhydride test is at present quite unknown, and it is found to have a percentage error of about 8%, so that one uses it for confirmation rather than for actual diagnosis. Only in conjunction with a true paretic reading and the presence of globulin with increased cells does one place any reliance upon it. It is quite interesting to have it at hand, and to compare its results, but one cannot as yet rely on it.

THE INDICATIONS FOR SUBSEQUENT MALARIAL THERAPY.

As will have been observed from the tables previously included, a definite remission cannot always be traced after the first attack of malaria, on both the mental and physical side, but one can often find that a definite physical improvement has taken place, with a corresponding improvement in the habits and self-control of the patient.

It is much more rare to find a patient shewing marked mental "remission" without physical benefit, and one has felt that where a patient's health has become better owing to the malaria, it is quite possible that the progressive deterioration is, at any rate, arrested. Under such circumstances one has evidence of the efficacy of the malarial treatment on the physical side to that particular patient, and one can align the mental benefit shewn by other sufferers: for this reason, and granted the condition of the patient is such as to allow it, a further attack of malaria seems hopeful from the mental aspect.

In addition to this factor, one has sometimes felt compelled to terminate malaria in a weakly patient before it has really taken hold of him: that is to say, he has only be able to withstand two or three pyrexias. If, subsequently, his health improves, it is deemed advisable to provoke further rigors so that further "stabilisation" may have the opportunity of shewing itself.

Therefore, one bases ~~on~~ one's diagnosis of the need for further treatment on the factor of adequate resistance and fair physical health, combined with the obvious lack of good response to the previous attack.

The further results of repeated malaria will be discussed, but one feels that some further benefit is found, for of our cases discharged two have shewn marked benefit, which was not so evident, from the second attack.

Whether the results of subsequent malaria are uniformly as hopeful as those obtained by the primary attack, in continuing the improvement seen, one can hardly form an opinion as sufficient time has not elapsed on which to base an opinion of value.

REPETITION OF MALARIAL TREATMENT.

Wagner Jauregg as a routine treated patients who had not shewn a sufficient improvement under the first malarial therapy by a renewed infection, and as quite a number of our cases shewed real bodily improvement with but small mental improvement, or at least an amelioration by no means sufficient to warrant their discharge, one decided a year ago to follow the lines laid down by the originator of the treatment.

One was led to believe that the second attack was as easily provoked as was the first, but this was found to be very far from the fact. A paper published in the Journal of Tropical Medicine and Hygiene, December 1st 1925 sums up the results and may, perhaps, be quoted:-

"Fourteen cases were subjected to re-inoculation some three times or more, and shewed no clinical signs of malaria.

"To remove any doubt as to the technique of the inoculation we would say that we are aware that if only gametocytic forms of parasite were introduced, no pyrexia could result. Proof that asexual forms were injected is to be found in the last column of the accompanying table, for in every case except one we can point to other patients who were inoculated from the same syringe of the blood of the donor, and who, later, developed true malaria, these patients being infected for the first time.

"Having been confronted with such a definite immunity we had, perforce, to search for some factor peculiar to these immune cases which might be correlated with this resistance to subsequent infection, especially as we had found only one case to be resistant to a first infection.

"In so far as naturally occurring malaria is terminated as speedily as possible by the exhibition of quinine, and whereas, in contrast, therapeutic malaria is allowed to continue to the limit of tolerance, we thought perhaps the number of rigors in the primary attack was responsible for the subsequent immunity and that relapses might also be a factor.

"Our figures show that such is not the case. Reference to our table will also prove that the inoculation methods of neither the primary infections nor the subsequent attempted infections had any bearing on the matter.

"It should be added that all the primary pyrexias have been terminated in the usual way by means of quinine, which was administered until the blood was definitely negative to Microscopic examination.

"Further, our reinoculations have been performed at widely varying intervals of from six to twenty months.

"In view of the theory advanced in support of the I.K. treatment of tuberculosis, viz:- 'that the more important protective substances of an immunised blood exist chiefly, though potentially, in the erythrocytes', we thought for a time that the relationship between the blood-groups to which the various donors belonged, and those of the recipients, might form a fruitful field for research. It seemed possible that the haemolysis consequent upon the mixing of different bloods might thereby liberate certain antibodies capable of having been produced by the first malarial attack.

"The inoculation would necessarily account for an
"extreme dilution of such liberated antibodies, as is laid
"stress upon by those who support the I.K. theory.

"Although having no practical experience of I.K. therapy
"and no real knowledge thereof, it seemed worth while to
"investigate and type the blood of the cases under review.
"We were again disappointed to find that no conclusion as to
"the significance of blood grouping could be drawn, especially
"as all our donors except one happened to belong to group 4.

"Owing to the difficulty hitherto experienced in obtaining
"infected mosquitoes we can, at present, point to but one case
(No.51) where a subsequent infection has been attempted by all
"three routes, inclusive of mosquito bite. Colonel S. P.
"James, of the Ministry of Health, has recently arranged to
"help us in this matter, so we hope it will be possible at a
"later date to report further on this point.

"Whether the serum of an "immune" patient will abort
"or prevent the development of a rigor, we are not in a
"position to say, nor have we the opportunity to ascertain,
"as the results obtained from the malarial treatment of
"general paralysis of the insane appear to be so beneficial,
"in our experience, to prevent our terminating the pyrexia
"before we are compelled to by the condition of the patient."

The Ministry of Health, through the kindness of Col.
James, provided infected mosquitoes on November 21st 1925, and three
of the cases who had shewn this "immunity to infection" were
submitted to mosquito bite.

The results obtained were communicated to the Journal
of Tropical Medicine and Hygiene and were published on February
1st:-

"On November 21st 1925 three cases, which had previously
"proved refractory to repeated inoculations with malarial
"blood were bitten by infected mosquitoes. The following
"is a brief summary of the results and the previous inoculation
"history:-

"Case 43. Inoculated intravenously 27/7/24. Nine rigors
"resulted, terminated by quinine. Subsequently has
"relapses of malaria.

"Unsuccessfully reinoculated:-

I.M.	February 11th 1925.
I.V.	May 30th 1925.
I.V.	July 27th 1925.
I.M.	August 5th 1925.

"Was subjected to mosquito infection on 21/11/25, and
"after 21 days incubation period he developed true malarial
"pyrexia, with parasites in the peripheral blood.
"He had six rigors, occurring daily, and terminating
"spontaneously, the blood becoming negative to the microscope
"before the exhibition of quinine.

Case 62. Inoculated intravenously 29/4/24. Ten rigors
"resulted, terminated by quinine. No subsequent relapses.

"Unsuccessfully reinoculated:-

I.M.	August 5th 1925.
I.M.	August 31st 1925.

"Was subjected to mosquito infection on 21/11/25 and after
"19 days incubation period he developed true malarial pyrexia
"with parasites in the peripheral blood.
"He had five rigors, occurring daily, and terminating
"spontaneously, the blood becoming negative to the microscope
"before the exhibition of quinine.

"Case 51. This case was treated by mosquito infection before admission to this Hospital (15/12/23) and had a number of malarial rigors, details of which are unknown, although he acted as donor of infected blood to many other hospitals.

"Unsuccessfully reinoculated:-

Mosquito	January 7th 1924.
I.M.	April 30th 1925.
I.V.	July 17th 1925.

Was subjected to mosquito infection on 21/11/25. No pyrexia developed, but on several occasions from the 23rd to the 31st day after infection, malarial parasites were found to be present very scantily in his blood."

"The last case, No. 51, presents features of interest, as he was successfully infected by mosquitoes originally. Since then he has been subjected to malarial infection by all three usual routes, and has not shewn pyrexia. Blood examinations have been made daily, since December 1st 1925, and the results have been:-

December 1st to 13th	Negative.
December 14th	One parasite found.
December 15th	One parasite found.
December 16th to 19th	Negative.
December 20th	One parasite found.
December 21st	Negative.
December 22nd	One parasite found.
December 23rd to January 13th	Negative.

"No constitutional symptoms of malaria have been observed and since December 22nd 1925, despite injections of milk and adrenalin, the patient has shewn a persistently negative blood picture."

Further reference to cases was made in this publication, but they will be referred to in the text later.

It may be of interest to note that the last instanced case died on January 13th 1926, and a very complete autopsy was made, but no trace of splenic enlargement was remarked, whilst blood was taken from the choroid plexus, from the spleen, from the heart, liver and a scraping from the marrow cavity of the femur.

Thick and thin films were made but in none of the stained preparations could one demonstrate the parasite.

No explanation could be given of this immunity which was evidenced in so many cases, and not until some two months later was one able to give any reason for it.

Once one had the two mosquito infected patients well under way with pyrexia, one was enabled to re-infect the previously "immune" patients, and one has found that no such immunity has been found to the new strain.

The table which is attached will shew that many of the cases had had repeated attempts made with the original Hospital

Case.	Blood group.	Age,	First Inoculatn.	Blood from Case.	Group.	Route.	No. of Rigors.	Relapses.	Subsegt. change in C.S.F.	Subsegt. Inoculns.	Blood from Case.	Group.	Route.	Same blood successful in cases Nos.
3.	/	41.	10. 1.24.	15.		I.V.	7.	Yes.		29. 4.25.	S.T.M.		I.M.	94
8.	X	38.	3.12.23. 11. 4.24.	40. 40.	1.	Mos. I.V.	11.	No.	No.	27. 7.25.	97.	4.	I.V.	100, 101, 102.
17.	X	36.	11. 2.24.	Mosquito.			5.	Yes.	Yes.	27. 7.25.	97.	4.	I.V.	do.
18.		36.	3.10.23.	Mosquito.			4.	Yes.	Yes.	30. 5.25. 17. 7.25.	96. RS.		I.V. I.M.	97. 98. 99.
29.	X	40.	23.11.23.	Mosquito.			10.	No.	Yes.	31. 7.25. 31. 8.25.	97. 102.	4. 4.	I.M. I.M.	100. 101. 102. 28. 77.
40.	X	32.	31. 3.24.	Mosquito.			9.	Yes.	Yes.	17. 7.25.	RS.		I.M.	97. 98. 99.
43.	X	36.	27. 7.24.	20.	2.	I.V.	9.	Yes.	Yes.	11. 2.25. 30. 5.25. 27. 7.25. 5. 8.25.	88. 96. 97. 97.	4. 4. 4. 4.	I.M. I.V. I.V. I.M.	53. 100. 101. 102. do.
51.	/	31.	Infected successfully before admission.							7. 1.24. 30. 4.25. 17. 7.25.	Mosquito. 78. RS.	4.	I.M. I.V.	79. 22. 97. 98. 99.
53.	X	30.	9. 9.24.	43.	4.	I.V.	10.	Yes.	Yes.	9. 2.25. 3. 5.25. 17. 7.25.	88. 78. RS.	4. 4.	I.V. I.V. I.M.	79. 22. 97. 98. 99.
54.	X	35.	28. 5.24.	75.	4.	I.V.	7.	Yes.	Yes.	5. 8.25.	97.	4.	I.M.	100. 101. 102.
62.	X	48.	29. 4.24.	8.	2.	I.V.	10.	No.	Yes.	5. 8.25. 31. 8.25.	97. 102.	4. 4.	I.M.	28. 77.
63.	/	43.	29.4.24.	8.	2.	I.V.	3.	Yes.	Yes.	31. 7.25.	97.	4.	I.V.	100. 101. 102.
71.	X	38.	6. 5.24.	62.	4.	I.V.	6.	No.	Yes.	24. 5.25. 17. 7.25.	94. RS.	3.	I.M. I.V.	100. 101. 102.
79.	X	32.	24. 8.24.	78.	4.	I.M.	2.	no.	yes.	11. 2. 25.	88.	4.	I.M.	53

X: successfully inoculated by either chain or a later date.

Dead.

strain with no result, yet, when inoculation was made with the new strain, not very far removed from the mosquito, the "immunity" came to an end.

One feels justified, therefore, in concluding that where a patient has been host to a strain he will, or may, form some specific antibody to that particular strain which will confer an artificial immunity to that strain alone at a subsequent date, but that the "immunity" does not extend to any other strain, either direct from a mosquito infection or a few stages removed.

It may, possibly, be feasible to test the correctness of this theory about the middle of the present year, for several patients who were inoculated with the "recent mosquito strain" may need further malaria, and it will be very interesting to note whether there is again an artificial "immunity" to a previously harboured strain.

Attempts were repeatedly made to culture the "immune" blood to try to find some other reason for the resistance, and also to endeavour to obtain parasites by culture if they were at all present in the blood, but no success was obtained: indeed, one would have been somewhat surprised if any parasites had been later found, for both thick and thin films gave negative results to the most careful microscopic examination, and shewed no obvious infection, except that there seemed to be, even two days after the inoculation, a mild anaemia which grew apace, but which appeared, all the time of examination, to be of a very simple type, with little or no upset in the white count. For this reason, therefore, one felt that possibly the anaemia was due to a mild toxic reaction, and not to the presence of parasites, for when a successful inoculation had been made the picture of the blood became very rapidly anaemic in the ~~true~~ malarial fashion.

That an increased resistance to malaria is acquired by a primary attack not cut short by quinine, seems to be borne out by the fact that every case except one where one has been able to allow the second attack to progress without interference, a spontaneous cure has been found with the disappearance of parasites.

INOCULATION AND INCUBATION FOR THE SECOND MALARIA.

All three routes of infection have been utilised in varying degree, mosquito infection being used in a successful endeavour to overcome the "resistance" shewn to our own strain, whilst intra-muscular inoculation has been the route of personal preference.

In all, nineteen cases have been successfully infected, and a summary of the routes, and incubation periods is given herein.

Although one's experience of successful inoculation for a second attack of malaria has not been extensive, the results of the incubation periods are interesting as contrasted with the larger series of the first infection.

It will be seen that the length of time intervening between inoculation and rigor is slightly lengthened at the second malarial attack, although it does not seem fair to base such a conclusion on so few results. One has felt that when a greater number of figures are to be quoted, it will be found that the intra-muscular route will yield somewhat the same result as in the primary inoculations.

No difficulty has been experienced in any of the routes, and the only case worthy of note in this connection is No. 51, referred to in the communication to the Journal of Tropical Medicine, who shewed a definitely negative clinical picture and an almost negative picture to the microscope. Unfortunately, the patient died nearly two months after infection which one feels gave ample time for the development of malaria.

The conclusion of an immunity to a strain previously harboured seems justified, and it would, evidently, be as well to have two strains running in the Hospital at the same time when one finds the necessity to re-inoculate patients who have previously had pyrexia, and who have not improved.

This immunity to a harboured strain may, to some extent, account for the fact so frequently noted that a partial immunity is found in parts of Asia where malarial is universal, and where children harbour the parasite.

ANALYSIS OF SUCESSFUL SUBSEQUENT INOCULATIONS.

Route.	Number.	Average incubation.	Daily rigors.	Average rigors.	Spontaneous cure.
Mosquito,	2.	20 days.	2.	5.	2.
Intra-venous.	1.	10 days.	1.	5.	1.
Intra-muscular.	16.	13 days.	13.	5.	14.

COMPARISON OF THE LENGTHS OF INCUBATION PERIODS FOR THE PRIMARY
AND SUBSEQUENT SUCCESSFUL INFECTIONS.

Route.	<u>Primary infection.</u>				<u>Subsequent infection.</u>			
	Number of cases.	Longest.	Shortest.	Average.	Number of cases.	Longest.	Shortest.	Average.
Mosquito bite.	25.	22.	8.	14.	2.	21.	19.	20.
Intra-venous.	25.	22.	4.	8.	1.			10.
Intra-muscular.	50.	25.	6.	12.	16.	22.	9.	13.

During the incubation period the blood seems to take on a more rapid anaemia, but the haemoglobin does not go below about 60% until the pyrexia is well established, and the disturbance in the leucocyte count is little, if any, different to that found in primary malarial pyrexia. One has seldom found any nucleated reds in the blood, which is good evidence that the anaemia consequent upon the original attack is rapidly recovered from, as one draws these conclusions from patients who have been re-infected within seven months.

There is very little constitutional disturbance, and in almost every way the occurrences of the primary incubation period are repeated.

One does not, however, find that jaundice is so liable to affect the patient, nor is there the same liability to vomiting which has been previously found.

Constipation is, however, somewhat more marked, and reacts on the patient's health unless it is carefully corrected. No case has shown retention of urine, and only one has had any inter-current disease. The latter fact is not to be wondered at in view of the improvement which has taken place in the health of the patient and on which the second infection advisability has been based.

The same thorough preparation of the patient is carried out for the second malaria as is put in operation for the primary.

One has noticed in some three or four cases who are almost due to rigor that a return of the labial and lingual tremor is noticed, although it may have been much in abeyance since the first pyrexia: in two cases at least this has been found to persist for two months after malaria has been terminated, in spite of the fact that both patients have shown some real improvement in their mental condition and are considered to have benefited from the further treatment. No reason can be given for this, and it may, possibly, disappear as time goes on.

THE MALARIAL PERIOD OF THE SECOND INFECTION.

There is a marked tendency to obtain double tertian pyrexia, even contrasted with the somewhat unfavourable figures obtained in this direction in the primary attack. It is, one finds, the exception for a patient to shew true two-daily fever, and the class of malaria he has already had seems to have no bearing whatsoever upon the subsequent periodicity.

In fact, one has to come to expect a daily rigor, and if it does not appear, one feels somewhat dubious of the onset and is inclined to give a provocative injection of $\frac{1}{2}$ c.c. of adrenaline to hasten the fever.

There is, in contrast to the original malaria, less of a tendency for small rises of temperature to occur before a real rigor is experienced, and in the 19 cases one has treated, only in three cases has this "pre-malarial" rise been found, and each case had a temperature of 100.8 F. the night previous to the definite rigor.

Parasites appear in the periphery sooner than is the case with first pyrexia, and it is somewhat unusual to find more than one rise in temperature without demonstrable parasites.

The onset of the rigor follows closely the text book, description, and approximates the ideal, in that the temperature rises very quickly, stays up near the summit for perhaps an hour an a half, (our patients have their temperatures taken half hourly whilst in rigor, unless they are asleep) and then as rapidly drops.

No deaths have occurred from the second malarial attack, so no post-mortem pathology can be quoted, but it is rather rare to find any enlargement of the spleen.

Patients seems to stand the subsequent malaria to a better degree than they did the first attack, and the actual complications of the malarial period are very much lessened. They, of course, are given the same diet, and the same cardiac stimulation as they received previously.

The average number of rigors sustained is just over 5 as contrasted with 7 for the first attack.

It has been repeatedly noticed that patients are much more liable to become noisy, and difficult to deal with in this period, and one has found that in the actual malarial period the habits are inclined to deteriorate temporarily, whilst the mental condition seems, for the moment, to become definitely worse.

During the first attack one has not found the onset of maniacal symptoms to be so frequent as one is led to believe, but during the second attack, five of our patients have become almost acutely maniacal, of whom three shewed no such disposition when being treated previously.

Possibly this may be due to the fact that patients stand the second infection better, and so have the bodily strength to express their sufferings, both mental and physical, in a manner which is very distinctly noticeable. Happily, Paraldehyde is still efficacious, and is freely used

The urine in one case shewed sugar, and diacetic acid, but apart from this, nothing has been noticed in the excretory system. The deposit of urates in the urine is markedly less than is found in the previous treatment. Albumen has only once been found, and the urea content is slightly diminished.

From the foregoing description of the rigor, it will be concluded that hyper-pyrexia is of rare occurrence, and this is correct, for though the rigors reach 106 F at times, the temperature rapidly becomes normal, and we have had no case of sustained pyrexia such as is occasionally found in the earlier fever.

Seizures, which cause such trouble, have never been experienced in any of the 19 cases, although two had to have their first malaria cut short on this account.

The mental condition does not seem to make the very marked strides towards the end of the pyrexia that one would expect, but the improvement which has been noted in our re-inoculated cases has come on gradually, the semi-demented case becoming very slowly more interested, and more able to express himself, whilst the melancholic becomes slightly more rapidly cheerful and interested.

TERMINATION OF THE SECOND MALARIAL PERIOD.

In this connection is found the greatest difference between the first and second attacks of malaria, for, whereas quinine has to be given in almost every case of primary malaria before the blood becomes negative to the microscope, in 16 out of the 19 re-inoculations who have shewn pyrexia, the blood has become devoid of demonstrable parasites before quinine has been exhibited, and has remained so in spite of injections of adrenaline spread over a period of three, four, or five days, according to circumstances.

In fact, in every one of these 16 cases, one has felt that the blood has been definitely negative, and in only one case was anything approaching a relapse found, but even in this man, it was impossible to demonstrate the parasite, and he only had one pseudo-rigor, some seventeen days after the exhibition of quinine, and this temperature cleared up without any medication whatsoever except a purge.

Of the three cases who required quinine, two were treated at the close of their second and third rigor respectively. It was felt advisable to terminate the pyrexia because of existent asthma in one case, and of a mild nephritis in the other, both of which diseases were pre-existent.

The spontaneous cure found in this comparatively large number of cases presents features of interest, and makes one feel that a previous attack of malaria does provide some resistant body to a subsequent attack, but that the resistant body is not of a sufficiently strong nature to altogether impose an immunity.

Whether this "resistant body" requires the presence of the malaria toxin in order to form an antibody, is a question one cannot answer through lack of knowledge.

One finds, however, that the second attack of artificial or therapeutic malaria in General Paralytics is a much less severe and a much less drawn out condition than it is in the first attack, and under such conditions one feels that there may be a partial immunity conferred by different strains, as contrasted with the

almost total immunity to the same strain, as is previously reported in this paper.

One does not now expect to find that the second attack, however, induced, will go on sufficiently long to require the administration of quinine to terminate it. Indeed, after the third or fourth rigor one examines the blood films with the certainty of finding that the parasites are not so numerous, and not to "healthy-looking", and if one wishes to use as a donor a patient suffering from a second attack of malaria, one endeavours to withdraw blood about the second or third rigor, for one has found on occasion that blood withdrawn later and inoculated into a primary case entails a somewhat lengthened incubation period.

Where a spontaneous cure is found, however, the blood remains in the same anaemic picture even though parasites are markedly few, and the haemoglobin continues at the same poor level until quinine is finally given.

Although the blood picture is negative to malaria in these cases, one is not content to leave the patient without any quinine medication: rather one waits in the hope of having further rigors develop, and endeavours to provoke them with adrenalin: sometimes a patient will have five daily rigors, and then two mild true tertian malaria fevers before he finally shews a level temperature chart. Apparently, therefore, the weaker parasite suffers destruction by tissue changes before the more developed.

As has been pointed out, quinine is always given, and it is given in the form of the Sulphate, ten grain doses being given three times a day for three days, and in none of the 19 cases quoted has the parasite been found after that dosage. In the three shewing no spontaneous cure, the blood became negative on the morning of the second day, and remained consistently so for the remaining period during which it was examined, in one case seven, and in the other eight, more days.

The spontaneous cure seems to have no real bearing upon the malady for which the patient has been treated, and has, one thinks, no significance from that point of view.

THE RESULTS OF THE SECOND MALARIAL THERAPY.

2

It will be readily understood that it is a very difficult matter indeed to allocate an improvement noticed in a General Paralytic to either the first or second attack of pyrexia, for everyone working on the subject has found a marked variation in the time of onset of any improvement which has been sustained.

Perhaps, therefore, it is as well to merely tabulate the cases treated, and to advance a few reasons for the view that at least the second malaria carried on the improvement commenced by the first series of rigors.

In the first place, therapeutic malaria has only been used in this Hospital where the first attack seemed to have had some definite, if only transient, influence of the progress of the disease, and for this reason one has not had to overcome the same grave physical disabilities as exist in the poorly nourished and devitalised patients admitted. All our cases retreated have had at least the benefit of six months Hospital treatment, with the food and care which they receive, and their physical health has been well looked after.

No death has taken place of any of the 19 cases so treated, but one has been discharged, and will be quoted later.

A very definite improvement has been found in 10 other patients, three of whom have amended their habits and are now no longer a distress to the ward in general, although they are mentally little, if any, improved.

Four patients, all of whom were in but moderate health and who were occasionally confined to bed with minor ailments or because of slight feebleness, have become sufficiently well to be able to take some part in the work of the wards and the grounds, and no longer need the same care and attention which was previously essential.

Two of them are, in addition, now able to write home, and to shew some signs of returning insight into their position, but are not sufficiently mentally altered to be counted improved.

One has always here to take a very conservative view

of what constitutes an "improvement", as heretofore it has been the almost invariable practice to keep a General Paralytic under Hospital ward observation for a period of nearly a year.

However, of the 19 cases re-inoculated with success, four at least can be said to have definitely improved, and they are able to read, write home, take an intelligent interest in the daily papers and the surrounding affairs of the Hospital.

Two of the four write letters home asking for information as to their small businesses, and reply in a rational manner, whilst another has improved in memory, habit, conduct, and in insight to such an extent that he will be discharged to his home within the next month or two.

The last named, prior to his second attack of malaria, was of the acute melancholic type with delusions of unworthiness, combined with well hidden grandiose ideas. He is now well on the way to recover from his melancholic tendency, and is able to realise the reason therefor, whilst his memory for recent and past events is infinitely better. He, indeed, gets some considerable amusement from the grandiose ideas which he realised he has had, and explains that one should be thankful he only offered thousands of millions of pounds.

A case which has become definitely worse has to be reported. He was admitted in poor health, and in a state of acute confusion with marked grandiose idea. The first attack of malaria lasted for six rigors before quinine was given, and he improved physically and in habits, and became more able to converse in a simple fashion. He was re-inoculated, and has four daily rigors with spontaneous cure. Since then he has relapsed into the condition in which he was admitted, and is, if possible more confused, and more filthy in his habits.

Six cases are too recent to correctly assess, but two have had malaria three months ago, and are doing a little work, and are better in health. Mentally they seem to be a trifle brighter. The other four are just about as they were before treatment two months ago.

ANALYSIS OF THE PATIENTS WHO HAVE BEEN INFECTED
FOR THE SECOND TIME.

Total.	Remaining.	Discharged.	Improved.			Worse.	Too recent to assess.
			Habits.	Health.	Mentally.		
19.	18.	1.	3.	4.	3.	1.	6.

Of those shewn as mentally improved, all now do work about the wards and buildings, whilst one has made such marked mental improvement that he will, in all probability be discharged on trial within the next month or two.

THE PROGNOSIS IN CASES IN REMISSION.

In a disease giving the chronic pathological findings of General Paralysis of the Insane, one must be very chary in speaking of a "cure". Although Wagner-Jauregg quoted cases still in remission after seven years observation, yet it is said that untreated cases of the disease have shewed this length of "stabilisation".

Unfortunately, however, one has not the experience here of extended observation, but one can at least say that no case discharged to his home has been admitted to this, or any other Mental Hospital, and that all continue at work. As, however, this statement only covers a period of months instead of years, it cannot be accepted as any very definite evidence.

Although one realised to the full that any opinion given as to the value of the remission must be tentative, and even then of little weight, it is a source of satisfaction that 15 cases, admitted in the conditions heretofore described, have responded sufficiently to the malarial treatment to be able to return to the ordinary duties of the world, shewing no mental symptoms of the disease. All shewed, on close investigation some physical signs, but not in sufficient manner to disqualify them in their normal occupation.

Whether this "stabilisation" will remain constant at the level it had reached at the time of discharge, time alone will tell, but after discharge the patient has always been examined by independent Medical men, who have in each case certified that the discharged patient is perfectly fit for the outside world.

From personal visits paid to one by the patients, one is able to say that they keep well, shew no signs of the physical onset of disability, and retain their insight into their affairs.

No discharged case has reported a recrudescence of the pyrexia, and no Medical Officer of Health for the district to which they were discharged has made any report of such occurrence.

As to whether the remission will continue, one is only able to hope that it will: unfortunately, at the present

one has definite evidence in the Hospital of a case who relapsed after having been treated with malaria:-

J.W. case 107, was diagnosed and treated at Rainhill Mental Hospital by malarial therapy. He was admitted to that Hospital on 4:7:24 in a condition of grandiose melancholia, and was inoculated with benign tertian malaria early in August 1924. He had 11 rigors, and was considered well-enough to be sent home on trial in February 1925, finally being discharged on 24:4:25.

He had been treated with quinine and with the arsenic preparations.

On 18:9:25 he was admitted to this Hospital, in a mild maniacal condition, with grandiose ideas as to the wealth he had obtained by betting.

He shewed slurring speech, irregular and fixed pupils, with marked variation in his knee-jerks. His cerebro-spinal fluid was tested after admission and was found to give a reading to Lange of 3555442200, with a positive globulin.

He is presently in Hospital, and is now becoming of the melancholic type, with considerable insight and a good memory, for he told of many details of the treatment at Rainhill.

This case presents much to interest one, for he was diagnosed here as ~~an~~ General Paralytic, and at the time one had no knowledge that he had been in a previous Mental Hospital. When, however, one commenced to give him arsenical preparations after his malaria was checked, he commenced, slowly at first, but much more fluently later, to remember details of his previous malaria, and previous arsenical treatment. His memory was correct in almost every detail, as one had the opportunity to prove.

He has again improved in his stay of 7 months in this Hospital, and seems to have lost all his grandiose ideas. Indeed he simulates a melancholia very closely.

His cerebro-spinal reading is now but little altered, being 34455431000, with negative globulin (in place of the positive result obtained at the original reading in this Hospital) and the acetic-anhydride test gives a negative result.

Of additional interest is the fact that he, in common with the majority of our cases treated with malaria for a second time, shewed a spontaneous disappearance of the parasites before quinine medication was commenced.

This case, of a renewal of the mental symptoms of General Paralysis, is disturbing to contemplate, in an endeavour

to estimate the probability of a complete, or life long, remission consequent upon malarial therapy. One has been unable to find a definite report of any such case elsewhere, and would wish to hear if such a repetition of the condition is known, before taking the case as an indication that relapses on the mental side are probable.

Perhaps, in this case, the very poor class of livelihood, with the consequent worry over unemployment, and the actual lack of food, which the patient suffered between his discharge from one Hospital and the admission into another may have had something to do with his relapse.

From publications of other workers, no report seems to have been made of any case being re-admitted to a Hospital with true and typical signs of General Paralysis, and one may, perhaps, take this as an indication that the majority of the cases who are discharged live a life which calls for no real supervision, and who finally die of inter-current disease.

Marie and Kohen, one should point out, report that out of their three hundred cases of neuro-syphilis, tabes dorsalis, and General Paralysis of the Insane, some do return to Hospital in so advanced a state of their particular condition that no further inoculation is deemed advisable.

Unfortunately, no classification is made of such readmissions in regard to disease, and none as regards the inoculations: they use malaria, tuberculin, recurrent fever, and also milk or nuclein. Bismuth is also given, so that without a definite classification and details it is impossible to say from their paper published in the transactions of the "Societe Medicale Des Practiciens, October 1925, how many, if any, of the relapses referred to are General Paralytics treated by infection with malaria.

One has, therefore, to give only a guarded opinion, ~~and~~ and has to say that in the series of 100 cases treated, only one is known to have had a recurrence of the mental symptoms of General Paralysis of the Insane up to date.

FACTS UPON WHICH A PROGNOSIS OF REMISSION CAN BE BASED.

Malarial therapy is, unfortunately, an unknown quantity and is sanctioned by results rather than by definite chemical or serological knowledge, whilst the pathology of malaria-remissions is almost unknown. Therefore, only a generalisation is possible in endeavouring to give factors governing prognosis.

A further difficulty is experience in dealing with this matter, in that cases admitted to a Mental Hospital are usually well-defined: in other words, somewhat far advanced, for they are not usually certified as General Paralytics until the condition has so far affected their behaviour as to make it desirable for their detention in a Mental Hospital.

One knows that the generally accepted view is that malaria in the "incubation period" of General Paralysis tends to prevent the disease. Whether this is so or not is too large a question to be decided, but one has been able to quote cases herein where the disease developed in spite of malaria in the incubation period. From this one feels that until there is a very definite organic lesion in the brain, malaria has but little effect upon the disease; and one is inclined to believe that when such a lesion commences, disposition also commences to change. If one could diagnose and treat the condition by malaria at that stage, one would expect infinitely better results. At present one is treating cases not diagnosed until they are sent from the Unions in a comparatively advanced stage, and the physical condition is often such that it seems hopeless from the very commencement. Even so, the results are rather encouraging, and one feels compelled to treat even the cases who seem to have but little prospect of any recovery.

It is difficult to give any prognosis in regard to age, for one of our cases was treated at the age of 65 and has since been discharged, whilst another, admitted in approximately a similar bodily and mental state is rapidly going down hill, although he is a year younger.

The actual physical condition, given a reasonable possibility of recovering from the malaria, does not seem to have any direct bearing upon the prognosis, nor does the cleanliness or otherwise of the habits before or during treatment.

On the mental side, one has formed the opinion that those patients who before or after the malarial period display a marked manic type of General Paralysis respond worse to treatment than do the pure confusional type: those patients who are melancholic seem to give a better result than either of the other types. During the actual pyrexial period one often finds an inversion of type, the manic becoming of the acutely depressive order, and vice versa, but one does not give a prognosis on the malarial phenomena as they are so diffuse and widely varying, according to bodily resistance.

Whether cases shewing a mildly paretic type of reaction in the cerebro-spinal fluid shew a better response to treatment, one hardly dares to venture an opinion for, unless the case is actually one of General Paralysis it is unfair to confuse results by quoting: there seems, at present, to be no true dividing line between tabo-paresis and paresis proper from the serological point of view, and Lange's test, though very accurate for ordinary working, is hardly delicate enough to base such a diagnosis upon. The acetic anhydride test, also, has a fallacy in connection with neuro-syphilis which is quoted at about 8%, and this alone is sufficient to prevent any worker diagnosis true paresis thereon invariably.

If one approaches the question from the point of view of mental improvement being comparative only with the improvement in the cerebro-spinal fluid, one is utterly unable to say that as the fluid improves in content so the mental state improves. Possibly two contrasting cases will prove this point:-

R.B. admitted 7:5:25, Discharged 6:3:26.
First reading 555554300, Glob. pos.
Last reading 555543210, Glob. neg.

E.A. admitted 29:5:25, presently in Hospital but little improved.
First reading 455554321, Glob. pos.
Last reading 3455432111, Glob. neg.

These two cases of about the same age, admitted about the same time, and receiving treatment within a week of each other, shew comparatively the same changes in the cerebro-spinal fluid, yet one is sufficiently improved to have resumed his work as a Clerk, whilst the other is still in Hospital and only slightly improved mentally.

One can only draw a very vague conclusion in regard to prognosis from observation of the cerebro-spinal fluid content, and that is that where there are larger numbers of cells, with a very high globulin content, and marked affection of the meningeal field, the outlook cannot be considered too favourable.

Where one can obtain a General Paralytic shewing the true parietic curve, but of a mild order, which does not spread strongly through the luetic field, and which does not implicate the meningeal field, one feels that the prognosis is somewhat better than where these conditions are not fulfilled.

A prognosis is never attempted here, until after the termination of malaria, and even then one requires a few weeks to decide how the patient is settling down mentally. Where one finds the malaria well tolerated, with no real diminution of the body tone, and where the patient commences to have some return of insight into his condition, together with alteration in habits and the desire for occupation, one feels justified in saying that it is possible a remission will occur.

The prognosis is usually bad, where seizures of a cerebral type are experienced frequently before treatment, for in such a case there is evidence of congestive damage to the brain, which cannot be made good by malarial therapy, although the high fever reactions may be sufficiently useful in terminating the incidence of such attacks.

The incidence of one or two seizures before treatment does not, however, make ones prognosis despondent, for quite a few of our patients have had a recorded seizure before malaria, and have yet done quite well, one being on the point of discharge.

DETAILS OF THE 15 CASES DISCHARGED FROM HOSPITAL.

Number.	Initials.	Admitted.	Pyrexia commenced.	Rigors.		Cerebral seizures.	Alteration in C.S.F.	Discharged.	Length of time in Hospital after malarial
				Number.	Type.				
25.	J. J.	3. 7.23.	15.11.23.	7.	True.	No.	No.	6. 5.25.	13 months.
32.	H. K.	26. 7.23.	29.11.23.	8.	True.	Yes.		8. 5.24.	6 months.
33.	J.J.T.	28. 7.23.	27. 9.23.	11.	Double.	Yes.	Yes.	9. 1.26.	27 months.
50.	H.J.H.	15.12.23.	7. 1.24.	11.	Double.	No.	No.	9. 1.26.	23 months.
55.	J.W.R.	2. 1.24.	20. 2.24.	9.	True.	No.		13.11.24.	9 months.
56.	J.C.S.	7. 1.24.	14. 4.24.	10.	Double.	No.		1. 8.25.	16 months.
69.	M.N.	14. 3.24.	14. 4.24.	6.	Double.	No.		22. 2.25.	10 months.
72.	G. B.	1. 4.24.	9. 6.24.	11.	Double.	No.		14. 2.25.	8 months.
77.	A. G.	11. 6.24.	2. 7.24.	8.	Double.	No.	Slight.	9. 1.26.	13 months.
81.	T.A.G.	20. 6.24.	15. 7.24.	8.	Double.	No.	Slight.	8. 3.26.	20 months.
82.	G. B.	20. 6.24.	27. 6.24.	5.	Double.	No.		4.11.24.	5 months.
88.	J.C.C.	7.1.25.	14. 1.25.	8.	True.	No.	Slight.	8.11.25.	10 months.
89.	F. W.	7. 1.25.	14. 1.25.	7.	True.	No.	No.	19. 1.26.	12 months.
94.	W.H.C.	24. 2.25.	29.4. 25.	5.	True.	No.		13.11.25.	7 months.
97.	R. B.	7. 5.25.	17. 7.25.	11.	Double.	No.	Slight.	7. 3.26.	8 months.

THE RESULTS OF MALARIA THERAPY ON THE MENTAL CONDITION.

Whilst many tabulated statements have been published in the last few years shewing varying degrees to improvement consequent upon treatment of General Paralytics by malaria, one is, as a rule, unable to definitely assess just what improvement has actually been shewn, for terms used by other workers may not correspond to those in one's own use. Discharges, too, have to be studied closely, for a pauper patient cannot be discharged if his remission is largely partial, whereas a more wealthy patient has not the same need for active wage-earning, and from this point of view alone, the statistics will be found to be markedly different.

Before discussing the actual figures one has available it is better to say that a very conservative policy is adopted in this Hospital in regard to discharges of General Paralytics, and except in very exceptional circumstances discharge is hardly considered until 9 months have elapsed since the malarial attack has been terminated.

In addition to this, most General Paralytics are sent out "on trial" for a period of one or two months, and their certificate is in abeyance until they are certified as being suitable for actual discharge by an outside, and independent, practitioner, usually their family Doctor.

During the period of absence "on trial" a monetary allowance is made to them, and this has the additional advantage of keeping the patient in touch with the Hospital authorities, which gives one the chance of observing their mental and physical state for a little while at least.

Turning now to the actual figures, it is necessary to say that although more than 100 cases have been treated in the period under review, some are too recent to consider, and the first 100 admitted are being considered, without regard to the condition in which they were admitted, and there has been no selection of the better cases.

In an endeavour to make more plain exactly what is meant by terms of improvement used, cases will be quoted as shortly as possible. It is always confusing, in reading the reports published from time to time by other Hospital regarding their results to align their findings with one's own, for the terminology is largely a matter of personal preference.

Of the 41 cases remaining in Hospital of whom a fair opinion can be given by reason of their length of residence five can be classified as much improved, and by this one means that they are, to all intents and purposes almost fit for return to their homes. They shew no signs of grandiose ideas, are able to converse in a reasonable and intelligent manner, are well behaved, and can take part in the ordinary work of the Hospital. All have a real understanding of the causal factor of their Mental trouble, and give an account of its onset: they are all able to realise that they have been mentally extremely ill, and speak with veiled disgust of their previous grandiose condition. All are scrupulously clean in habit and personal appearance, and take in pride in their neatness.

They are, for the most part, granted parole in the grounds and come and go without supervision. They write to their friends regularly, and their letters are uniformly sensible and shew real insight into their past and present condition, and though expressing the wish for early discharge, they realise that it is difficult to obtain work, and so do not wish to leave until either their particular trade gets better, or until there is a prospect of other work being found for them.

Case 8, N.B. admitted in January 1923, in a confusional condition, with rapid grandiose ideas, facile and easily aroused temper, presented the picture of an incipient dement, with depraved and faulty habits. He could not write a sensible letter: such letters as he did write spoke of buying the Hospital for millions of money, paid to Lord Derby, and describing it as dirt cheap. He had had seizures of a cerebral type before admission, and had one before, one during, and one after treatment.

Presently, he is writing pleasant letters home, discussing the possibilities of obtaining work as an Engineer (his previous occupation) and his home affairs in an intelligent fashion. He works well and is able to assist materially in the Ward.

He takes a keen, but quiet, interest in all Labour topics.

Case 102, H.M. admitted in July 1925, is a brick-layer. He was admitted under certificate as a case of dementia, with little power of coherent thought, and less power of self control. His habits were absolutely filthy, and he was content to lie in bed all day, with no attempt at interesting himself, or helping himself.

Presently, he is working about the grounds, with little or no supervision, and can give a rational account of all his actions. He suffers from no physical disability which is noticeable, except a slightly slurred speech and fixed pupils. He is scrupulously neat and clean in person, helps the older patients to write letters home, and is now asking if his discharge can be arranged at or about the beginning of May as his brother, for whom he works has secured a building contract. He can give a very good account of himself, and laughs at his former condition, saying that he was "mad".

From these two quoted cases it will be observed that one classifies a "good" result as a remission which allows the patient to resume a normal life, with no mental disability in the way of hallucinations, delusions or real impairment of intellect.

The first case quoted has improved to his present condition gradually, and has been treated with malaria a second time, but the other patient commenced to improve extremely rapidly after the termination of the pyrexia. Both were of the confusional melancholic type in the first instance.

Nine other cases may safely be classified as being much better in mental condition, but hardly in the same category as those considered "good". Of these, at least six, were admitted in an apparently advanced stage of the disease, and were of the true "dementia" type, with little knowledge of time or place, no insight, grandiose and unreasoning ideas, lack of all reasoning power, and with habits markedly poor.

They are now able to look after themselves, to converse fairly freely with the officials, to make friends with other patients who are not General Paralytics, to get about in the ordinary way, and to take an interest in life outside as seen in the newspapers. In varying degree they shew an awakened interest in their home life, and two at least write reasonable business letters to their wives about the conducting of business.

There is, however, some slight trace of either marked dullness, or liability to fits of unreasoning bad temper which prevents their being classified good, although in two of the

nine, except for the usual physical signs of General Paralysis of the Insane, the sole mental trouble seems to be an acute depression, whilst one exhibits a psychosis of the true delusional type, with no grandiose ideas whatsoever.

Case 45, S.W.F. admitted in November 1923 had already been in this Hospital the previous year and had been diagnosed as Delusional Insanity, and finally discharged. On subsequent admission he was in fair health, but was grandiose, excitable and violent, with habits that were faulty. The physical signs of General Paralysis were fairly well advanced, but there was little slurring of speech, or alteration to the eye reflexes.

He was treated in May 1924, and now presents no apparent sign of the disease, except that he is still somewhat bad tempered, and has a delusion concerning his wife's conduct.

Physically, he is in excellent health, and during last summer he played cricket fairly regularly. In this connection, one discovered that he was, to say the least of it, self-satisfied.

This patient is of but moderate type of intellect, and has, therefore, to be assessed in accordance. If he could overcome the one delusion he seems to be at present suffering from, no doubt his discharge could be considered in the near future.

Case 99, E.A. admitted in May 1925, is of a poor type of mind, and was in a markedly grandiose condition when he was admitted, claiming to be King of Bury and to have millions of pounds to give away. He shewed marked physical evidence of the disease. His habits were faulty, and he was prone to break into weeping without the slightest reason.

After pyrexia he lost all these grandiose ideas, and is now able to discuss his monetary affairs with insight, and to laugh at his ridiculous ideas. He has made great strides physically, and mentally seems more settled, although he is much inclined to melancholia. He is being treated again with malaria, in the hopes that he will regain more activity of mind. At present he is sluggish in ideation, although markedly better than on admission.

Eleven of the 41 cases remaining shew an improvement which is more safely classified as slight: this chiefly takes the form of the departure of the grandiose condition of mind, with a return of insight in that direction, but they have either adopted other delusions, or are of the melancholic type, and of an apathetic mental nature. All these cases are able to write home, letters usually being somewhat of a depressed nature, but shewing no attempt at a return to the grandiose condition. One has, dealing with these cases, to realise that in all probability some of the depression has a very real basis as they all seem quite able to realise the struggle their immediate relatives are having to exist upon the allowance made by the Guardians.

Case 54. A.S. Admitted to Hospital in November 1923, and treated in May 1924. He was grandiose, impulsive, but had not progressed sufficiently far towards dementia as to be very faulty in habits. He would seldom converse rationally, desired to be first considered in the giving out of meals as he felt he was of more importance to the world than other people, and was generally self-centred in a grandiose way. Physically he was in fair condition, but had marked signs of General Paralysis except that the eye reflexes were but sluggish. He gave a typical laboratory picture of the General Paretic.

Presently, after his second attack of malaria, he is able to converse rationally, to interest himself in the work of the place and to do quite a fair share without any supervision. He is rather dull, but quite interested. Recently, his insight into his condition has commenced to return rapidly, and shortly, one feels, he will be able to be classified as almost well enough for discharge.

He shews, however, since his second attack of malaria, a marked increase in the speech slurring, although facial tremors are non-existent.

Case 40, A.M.B. Admitted November 1923, in an advanced state of dementia, with great ideas of his personal prowess, his wealth, and his capabilities. He was liable to attacks of acute depression, in which he felt persecuted because of his exalted condition, and in which he was subject to fits of weeping. He had slurred speech, marked facial tremors, and was of extremely faulty habit.

He was treated by malaria in March 1924, and at once commenced to become more level in mood and temper, and to improve in health. His habits improved, but he still was extremely grandiose. He became a very good ward worker, and this continued for some six months during which time he evinced considerable pride in his work, and also never expressed any grandiose ideas unless questioned.

Quite suddenly in October 1925, he declined to do any more work, and began to become a little irritable. During the fits of irritability it was obvious that there was a return of his grandiose state of mind, and his letters to his wife were full of ridiculous nonsense of his racing winnings.

He was treated again with malaria, after being long resistant to infection, and as soon as he was permitted to get up he went back to the condition of mild "remission" which had occurred after his first pyrexia. At present he is an extremely useful man about the place, but is still "simple".

Four of our cases shew no mental change whatsoever, and remain the same type of incipient dement as when admitted, with the exception, and a most important exception it is, that in three of the four cases a marked improvement has taken place in their bodily habits. All these cases, both by clinical and laboratory investigate, were in an advanced state of the disease when admitted, and except for some slight physical benefit, one is unable to notice any improvement. Of the four cases, three had cerebral seizures of a very severe type before admission.

Four cases have become definitely worse during the post-malarial period, and have shewn either a marked increase in the grandiose condition, or have become absolute demented with little mind, and less initiative. Unfortunately, one has to record that of these four cases, two were admitted in quite fair bodily health, and they are now bed-ridden. No reason can be given for this retrogression in health and in mental condition, for all made some slight improvement as the immediate result of the malarial treatment.

March

Case 18. H.H.B. admitted in ~~October~~ 1923 was treated in ~~March~~ October of that year, and was a typical example of the advanced General Paralytic, with slurring speech, grandiose ideas, all physical signs, combined with faulty habits. He had had malaria abroad within eight months of the original syphilitic infection.

Since his treatment he has steadily gone downhill, and is at present unable to articulate, can only express himself by grunting, is acutely emotional and is still faulty in habit. Except that he has lived for over three years the malarial treatment has done him no good at all.

Case 90, R.N. admitted in January 1925, and treated at once, shews a definite deterioration. When admitted, at the age of 62, he was able to walk a little, and could talk fairly well, and told many tales of his life as a cab-man in London. His speech was slurred, and he was, from all investigations, an advanced General Paralytic with faulty habits.

Now, 15 months after treatment, he is liable to cerebral seizures, is acutely faulty in habit, cannot articulate, has to be moved in bed, and lies in a state approaching coma. His cerebro-spinal fluid has gone from bad to worse, and shews increased globulin and an almost complete reduction of the colloidal gold, the first 9 tubes being decolorised completely.

The remaining cases (8) have been treated within the last three months, and one hesitates, therefore, to put them into a definite class of improvement or otherwise as yet. It is, however, possible to point to three cases who have made, so far, a definite improvement and are able to get about completely unaided, to write letters home, to receive their visitors pleasantly, and to take an interest in the outside world. In each case the near relative say the patient is almost "normal", but a real opinion cannot be given for some months yet.

Two other cases of the eight under consideration have become much more active and are no longer confined to bed: their habits have also improved.

THE COMPARATIVE PATHOLOGY OF MALARIAL THERAPY.

Gerstmann, quoting his experience of many cases of autopsy on General Paralytics treated with malaria, states that marked differences have been found contrasting the treated case with the ordinary pathology of the untreated case: he says that in some cases the treated case shews little sign of the paralytic condition.

He has, evidently, had extended opportunity of examining cases dying at varying intervals, but one has not had that opportunity, and none of our discharged cases have, happily, come to the post-mortem table.

Post-mortems have not been readily granted in this Hospital for some time past, and by an unfortunate coincidence they have been especially difficult to obtain where a treated General Paralytic was concerned.

It is, therefore, obvious that the expression of any opinion can be of little value at the moment, and will only be really definite when many more cases have been examined microscopically.

It may be said at once that very little alteration has been found in the brains of those cases examined who have been treated by malarial therapy, contrasted with the ordinary accepted findings of the brain of an untreated General Paralytic.

THE PATHOLOGICAL FINDINGS IN THE BRAIN OF AN UNTREATED CASE.

To the naked eye there is an obvious oedema of the brain substance, found especially in the Frontal area, and the membranes are patently thickened: the convolutions often shew some flattening, whilst the membranes strip very badly. Pacchionian bodies are present in large numbers over the surface of the membranes granulation changes are found on the floor of the Fourth ventricle and also universally throughout the ventricle.

There is generally an excess of cerebro-spinal fluid in the Lateral Ventricles, whilst the excess of such fluid is marked. The spinal meninges may shew a diffuse thickening, and they may instance pressure on the anterior part of the cord.

Microscopically, of course, the changes depend upon the chronicity of the disease, but in a well-marked case there is found a universal granulation of the Fourth ventricle, due in part of the toxicity of the cerebro-spinal fluid. This, however, is by no means diagnostic of General Paralysis of the Insane, as it is found in chronic hydrocephalus of non-specific origin; in cerebral syphilis, and sometimes in chronic Bright's disease.

A chronic thickening of the pia-arachnoid is found, with usually some more active recent changes, the former being possibly due to the original spirochaetal infection, and the latter to the condition of the cerebro-spinal fluid.

A wrongly-named "peri-vascular" infiltration exists: on examination, however, this infiltration is found to be actually in the vessel wall between the media and adventitia, the small round celled infiltration being chiefly of lymphocytoid and plasma cells which are proliferated and not extravasated.

The endothelial lining of the vessels is frequently seen to be shed, or in an unhealthy state, and do not take the stain at all well.

The neuronie changes consist of a variable amount of destruction of nerve cells, either of an acute or chronic nature, or both, according to the stage of the disease, the smaller pyramidal cells being especially and markedly affected: a degeneration of nerve fibres is found especially of the tangential layer, but the radial and other cross fibres suffer to some extent, in the line of Baillarger.

Secondary, or accompanying reactions are found, various types of glia being laid down due to the toxin of the spirochaete possibly. Irritation or replacement processes, either or both, are in evidence, and may be consequent upon the neuronie destruction.

The pre-frontal cortex suffers most, usually, with some marked affection of the central cortex, whilst the occipital area is least affected. Wherever nerve cells are found to be damaged, it is always noticed that the smaller cells of the

pyramidal type are chiefly affected, the larger pyramidal elements being little changed, whilst the Betz cells shew no change at all, this latter fact being in marked contra-distinction to the Betz cells in Pellagra, where they shew a marked lack of Nissl bodies, or staining granules, and where the nucleus is displaced to the side of the cell and the concavity of the limiting membrane to the cytoplasm is lost, a "fuzziness" of the cell outline being in evidence. Such a lack of definition of outline is found in the smaller pyramidal cells in the condition of General Paralysis.

In the spinal cord of paretics there is an alteration in the shape and staining power of the Betz cells, with a consequent change in the Pyramidal tracts.

THE PATHOLOGICAL FINDINGS IN THE BRAINS OF TREATED CASES.

The cases one has been able to examine after treatment have, as has been said, presented but little microscopic change, but to the naked eye there has been, possibly, a slightly less oedematous condition of the brain substance, although in every case a sensation of "water-logging" has been present. The membranes have shewn the typical translucent appearance, and no diminution of granularity has been found. Details of the microscopic findings are given hereafter.

E.B. C.S.F. 5555421000, on 23:6:24. Treated by malaria September 1924: died July 1925, having improved a little mentally. Certified cause of death, General Paralysis of the Insane, and Broncho-pneumonia.

Microscopic findings.

Pre-frontal area. Membranes thickened with acute and chronic changes. Smaller pyramidal cells markedly affected. Deeper layers not so degenerated. Vessels shew infiltration with plasma and lymphocytoid cells. Endothelium lining very poor in quality, and staining badly. Numerous rod cells (stäbschen zellen).

Other areas shew somewhat similar changes, but not to such a degree.

Apparently, in spite of treatment, a very typical microscopic picture of a well marked General Paralytic.

W.P. C.S.F. 5555555400, on 31:3:24. Treated by malaria October 1924: died June 1925, having made but little change. Certified cause of death, General Paralysis of the Insane.

Microscopic findings.

Pre-frontal area. Marked parenchymatous thickening with smaller pyramidal cell degeneration. Betz cells

Granulations on base of 4th Ventricle, in three cases of untreated General Paralytics.

Medium power 1x6

Low power, 3x4.

Plasma cell, Alzheimer's
method.
1x12, oil immersion

High power.
1x12 oil immersion

The cells in the Cerebro-Spinal fluid of an untreated
General Paralytic.

Betz cells.

From case of
Melancholia.

From untreated
case of S.P.I.

From case of
Pellagra.

The formation of glia in
an untreated case of
S.P.I.

shew no alteration. Vessels shew some degree of infiltration with plasma and lymphocytoid cells between the adventitious and muscular coats.

Central area.

Marked meningeal thickening with evidence of both acute and chronic inflammatory changes. Larger pyramidal cells but little changed. Gliomatous proliferation in the tangential layers well marked.

Occipital area.

Little departure from usual.

Again, this case some 11 months after treatment, shews a fairly typical microscopic appearance, and only in the occipital region could one say that there was any slight improvement, and this would be exaggerating the point, as so many untreated paretics shew little, or no, degeneration therein.

E.P. C.S.F. not examined. Died whilst under malarial treatment. Certified cause of death, General Paralysis of the Insane. Smear made from spleen substance shewed presence of Malarial parasite.

Microscopic findings.

Pre-frontal area.

Meninges not thickened. Vessels shew marked small round celled infiltration. Plasma cells very marked in amount. Nerve cells shew degeneration, the smaller pyramidal cells shewing especially, whilst the large pyramidal cells are more markedly affected in this than in other areas.

Central area.

Changes corresponding to those found in the pre-frontal cortex, but to a less marked degree. In this region there was an unusually large amount of glia proliferation, and the young amoeboid fibro-glia cells were seen in abundance.

Occipital area.

Very few changes to be found.

This case is not one of those belonging to this Hospital, and is of interest, apart from the brain pathology, as the parasite of benign tertian malaria was recovered from smears taken from the spleen, a result which one has been quite unable to obtain here.

A senior colleague, at Rainhill, (Dr G.A. Watson) has been good enough to supply me with these details, and agrees that in the many brains they have examined, no appreciable change has been found after the malarial treatment. He points out that the very typical "stäbschen zellen" are found in equal abundance in both the treated and untreated cases which he has examined, and agrees that the changes in the cells as described above are found in both classes of cases.

It is to be regretted that more opportunities have not arisen to contrast the findings of the pathological anatomy of the treated and untreated cases, but one is always faced with the difficulty of refusal of post-mortems by the relatives.

Added to this, there is also a great drawback in the formation of a definite opinion as to whether the malarial treatment has any real effect on the pathology of the condition, in that when our cases leave the Hospital apparently "cured" it is impossible to keep in touch with them until they die. Indeed, none of the cases "cured" have as yet died, and when they do it will not be possible to perform a post-mortem on them, and it is in these cases that one would expect, possibly, to find the greater microscopic changes to correspond at least in part to their increased mental well-fare.

The only conclusion one feels justified in drawing is that there has been little alteration in the brain structure of those cases examined, and none of these were really "improving cases".

Whether, in later years, the well-marked changes noted heretofore in the condition of the cerebro-spinal fluid will be found to have been precursory to pathological improvement in the brain cells, one hesitates to hazard an opinion. It would seem quite a reasonable supposition, however, to conclude that where the toxicity of the cerebro-spinal fluid is reduced, as it is evidently has been in the cases one has quoted previously, some benefit may accrue to the more delicate structures of the brain and spinal cord from the purer nutriment they are obtaining. Whether the meningeal inflammation will ever be recovered from is a very different matter, and one would imagine that there will always be found a thickening in the meninges, especially in the pia-arachnoid area, which may have a far reaching effect upon the structure of the brain.

One cannot, therefore, attempt to give an adequate prognosis from the pathological standpoint as to the ultimate or even temporary benefit obtained, nor can one say how this will correspond to the physical or mental "stabilisation".

CONSIDERATION OF THE DISCHARGED PATIENTS.

Although our discharge percentage is only 15 up to the present time there is satisfaction in having that number of sufferers from what has until recent years been regarded as a fatal disease: there is a further satisfaction in the knowledge that all these patients have, since their leaving Hospital, been able to take their place again at their ordinary occupation.

For twenty years one will not be able to speak of any of these patients as having been "cured" of General Paralysis of the Insane, and even now one has to meet the argument that "remissions" are of occasional occurrence in the condition. One has to admit this fact also, but it is a source of pleasure to be able to point to the records of 56 cases who have been diagnosed as General Paralytics and who are still alive, whilst the other ⁴⁴~~54~~ treated are dead. It seems reasonable, therefore to conclude that some benefit has accrued from the treatment for there is not the slightest doubt that had not these 100 cases been treated, the majority would have been dead, and of the minority, ~~many~~ would have been dying.

Our discharges are very carefully considered: and no case is discharged under at least six months close observation from the termination of malaria: many of our cases have been watched for more than a year, and if there is the slightest sign of a relapse in the mental state immediate notice is taken thereof.

The suitability of discharge is carefully weighed up over three or four months, before action is taken, and the main basis of consideration is "Can the patient return to his ordinary everyday work, and every day life?" Not until an affirmative answer to these questions can be given is the patient considered well enough to go home.

These grounds may appear rather too stringent, on the surface, but one has to remember the class of patients, and has to realise that where one is dealing with the monied class, the discharged person is not necessarily compelled to earn his own living, and can often be under fairly constant supervision.

Patients admitted to this Hospital, however, all come under the designation of the "Pauper class", and by far the larger number are those who depend for their livelihood on a weekly wage. To such, a matter of a day or two off work is a serious matter, sometimes causing actual bodily privation, and some real mental stress: for these reasons, shiefly, one has to be very cautious in discharge, and has to be convinced that the patient is well enough both mentally and physically to return to his former occupation with little or no disability.

Even with these difficult conditions to fulfil, we have seen sufficient benefit to send 15 of our patients home to their work, and from fairly frequent news of them we can say that they continue in their state of remission.

Details of some of these patients may be of interest to record.

Case 25. J.J. Admitted July 1923. Clerk. Aged 43.

History of heavy drinking for 8 years.

Admitted with grandiose ideas, slurring speech, marked tremors of tongue and lips. Argyll-Robertson pupil.

Weight 9st 12lbs.

C.S.F. 3455553321, with positive globulin.

Treated with malaria in October 1923, and in January 1924 he was beginning to shew both mental and physical improvement. In February 1924 he was allowed to work in the grounds, and his improvement continued steadily. At first he was rather facile in speech and conduct, but in May 1924 he was noted as having good insight. He put on weight and the marked tremors of lips and tongue improved.

He was discharged on trial on April 6th 1925, and the following month he was definitely discharged on a Medical Certificate of fitness to continue at his clerical work.

Since that date several communications have been received from and concerning him, and he appears to be doing well. His weight on discharge was 10st 12lb.

Case 32. H.K. Admitted July 1923. Labourer. Aged 36.

History of accident in March 1923, and subsequent pneumonia.

Admitted with grandiose ideas, slurring speech, marked lingual and labial tremors, slurring speech and Argyll-Robertson pupil. Weight 9st 11lb.

C.S.F. 4433221100, with globulin positive.

Treated with malaria in November 1923, and had two cerebral seizures during treatment: in March 1924 he was working about the grounds, but was rather childish. In April definite improvement was noted, and he had a good memory with good insight into his condition and surroundings.

He was discharged on trial in May, and had improved in health and mental condition, going back to his work after being certified by an outside Medical man as being fit. His weight on discharge was 10st. 8lbs.

Case 33. J.J.T. Admitted July 1923. Engineer. Aged 33. History of syphilis is 1911, and dysentery in 1915. He was admitted as a case of confusional Insanity, with a mildly grandiose demeanour. He had Argyll-Robertson pupils, and slurring speech. Weight 11st 3lbs.

C.S.F. 5555543210. Globulin positive. Treated with malaria in September 1923, and in January 1924 he was shewing considerable insight into his condition, and became somewhat of a nuisance in his constant demand for and intensification of the anti-syphilitic treatment he was receiving. Tremors of the lips and tongue were first observed at this time.

In March 1924 he was noted to be improving slowly, but was very reserved and hypochondriacal.

His improvement was slow and very gradual, but he began to be allowed about the grounds in December 1924, and worked quite well. Early in January of this year he was discharged, and finally passed by a Doctor Examining for a Public Service, as being quite fit to return to his duties.

His C.S.F. had undergone a marked change and read 133321000, with a negative globulin, and a decreased number of cells.

This patient has since been heard of two or three times in the short space of time elapsing, and he is earning £4:10:0 a week as a Craneman at the Docks. He is also being shewn to various Clinical Post-graduate classes by a neighbouring University as a result of their treatment of General Paralysis of the Insane!!

Case 50. H.J.H. Admitted December 1923. Labourer. Aged 44. No history given.

Admitted in an exalted condition, with marked self-satisfaction and mildly grandiose. He had Argyll-Robertson pupils, accentuated knee jerks, lingual and labial tremors, and slurring speech.

Weight 10st 2lbs.

C.S.F. 4555552110. Globulin positive and increased cells. Treated with malaria almost immediately on admission.

In April 1924 he was noted to be shewing some improvement in bodily health, and a returning interest in every day affairs. An inguinal hernia kept him from hard work,

but he became very useful in the Hospital in May 1924, and was allowed "parole" the early part of 1925.

He continued to do well, making slow but steady improvement, and the tremors of tongue and lips were not noticeable unless patient became excited. His memory returned and his letters rapidly became rational and pleasant.

He was discharged finally in December 1925, and considered fit for his work by independent opinion.

His C.S.F. had undergone little alteration, and read 3555554000, with a negative globulin, and a decreased cell count.

He has since been heard of, and is able to do a full days work, and occasionally writes to his friends who are still in Hospital. His hernia troubles him, so he intends to have it operated on.

Case 55. J.W.R. Admitted January 1924. Fireman. Aged 34. Had been in Police Force, and has a family history of insanity.

Admitted in a rambling, grandiose condition, making extravagant claims of his prowess. He had few of the more marked clinical signs of General Paralysis but had a slight lingual tremor, with sluggish eye reaction to light.

Weight 11st 10lbs.

C.S.F. 5555542000. Globulin positive.

Treated with malaria in February 1924, and had two injections of "914". In April he settled down and commenced to take a more reasonable view of his own powers. In May his letters were found to be very sensible, and the improvement continued until October, during which period he endeavoured to do as much physical work as is available in this Hospital. He was discharged in October 1924, weighing 14st 5lbs, and was passed for duty elsewhere a month later.

Since then this patient, who lives within two miles of the Hospital, has been repeatedly seen, and has not had any further mental trouble. The amount of weight he gained would seem abnormal were it not pointed out that he was of fine physique, and was 6ft 3½ in. in height.

He obtained work tending boilers, an arduous task, and has remained well in spite of the physical exertion required.

Other similar cases could be quoted, all shewing the same gradual improvement, which commenced soon after the malarial period had been terminated. A point of interest arises in considering these cases: it will be seen that the last quoted was almost of a manic type, and one has noticed that where such a tendency is exhibited, and where either during or soon after the end of pyrexia, an improvement in the "noisiness" of the patient is found, one comes to expect a marked improvement generally. It is found, however, that such a type of case may turn out, at the end of the first pyrexia, to be more of the incipient dement, and from this point of view the next case quoted is of interest.

Case 77. A.G. Admitted June 1924. Motor driver. Aged 46. Father became insane at 65 years of age.

He was admitted in a mildly maniacal condition, boastful and grandiose. He had lingual and labial tremors, with exaggerated knee-jerks, and slightly slurring speech. Weight 10st 13lbs.

C.S.F. 555555543. Globulin positive.

Treated with malaria in July 1924, and in the period of pyrexia he suddenly became apathetic and listless, with little attempt to help himself. His bodily health increased, but he was childish and quite of a simple type of mind.

In August 1925 he was re-inoculated with malaria, and during the pyrexia became markedly discontented and

querulous, and at times noisy.
As soon as pyrexia was terminated, he began to shew a steady improvement, and took an interest in everything about the place, the "home-instinct" soon being seen. His progress was rapid, and he was allowed parole in the Hospital grounds, finally being discharged early in January 1926.

This case has been once to see his friends, and looks well, and is back at light work. He shews, perhaps the best of all our discharged cases, the almost total disappearance of any obvious physical signs of General Paralysis, and has only a slight suspicion of a slurring speech.

Case 81. T.A.G. Grocer. Admitted 20th June 1924. Aged 47. Admitted with a history of changed disposition for 18 months and a recent history of grandiose buying of useless articles. Admitted with a wide spread psoriasis all over trunk and legs. Lingual and labial tremor, unequal and acentral pupils with no reaction to light. Excessive knee-jerks. Slurring speech and grandiose manner and ideas. Weight 8st 3lbs.

C.S.F. 5555543110. Globulin positive. Cells increased. Treated with malaria in July 1924, and for nearly a year he remained in a facile and dull condition, without shewing any improvement. Almost all this time he was on arsenic for the psoriasis. In October 1925 he commenced to take a keen interest in his surroundings, and in everything connected with the place, and worked well. The improvement steadily continued, although he always remained somewhat dull. He was discharged in early March 1926, weighing 10st 11lbs.

This patient shews a by no means uncommon type of recovery: in the first instance the grandiose ideas left him, and for some considerable time he was melancholic and could not be roused. Then, almost with no warning, he commenced to shew a mental improvement corresponding to the physical betterment, and this continued steadily. An additional point of interest in the case is that he has been receiving arsenic for a period of almost two years, as treatment for the psoriasis, but such medication does not seem to have caused any real amelioration of the **paretic** state: this bears out the experience one has gained that little benefit accrues from anti-syphilitic treatment in the after-manifestation of the specific disease: except for its tonic properties, arsenic in any form seems to have no effect on the mental state, and one cannot point to any case where the administration of the anti-syphilitics can be ~~said~~ to have had a real effect on the disease per se.

Case 88. J.C.C. Comedian. Admitted January 1925. Aged 46. Admitted with an excellent family history, and had only a history of one illness, dysentery. Admitted in an anaemic condition, with marked lingual and labial tremors, increased knee jerks, fixed and unequal pupils shewing lack of reaction to light. Mentally was grandiose, yet retained his sense of humour, for he promptly offered the Medical Officer two Daimler motor cars, and, when laughed at, as promptly said they were to be obtained at Woolworth's price, as he owned that place.

Weight 8st 9lbs.

C.S.F. 555554300. Globulin positive.

Treated with malaria within a week of admission, and from the date of the first rigor he commenced to improve mentally. Physically he was but poor, and the lingual and labial tremors became very marked indeed in the pyrexia.

Before the pyrexia was terminated, the patient seemed well on the way to displaying an ordinary insight, ordinary coherence of thought, and was laughing at his foolish delusions.

As soon as he got up, he became quite as useful as any Attendant, and spent the whole of his time trying to help patients who were bed-ridden. His habits improved before the end of the pyrexia, and never became faulty.

As soon as possible he was sent out to the Farm to work and was given parole. He did, according to the word of the Farm Bailiff, the work of two men, and was contented, happy, and absolutely reliable.

He was discharged in November 1925, and went home to his work. Since that date letters have been received from him saying he is doing fairly well. His C.S.F. shewed but little alteration, and he put on a stone of weight.

Case 89. F.W. Motor engineer. Admitted January 1925. Aged 33. Admitted with a history of dysentery, jaundice, and enteric. Had increased knee jerks, pupils acircular and fixed. Labial and lingual tremor. Slight incoordination. Was grandiose, facile and somewhat childish. Weight 9st 13lbs.

C.S.F. 5555541000. Globulin positive.

Treated with malaria almost on admission, and during the pyrexia became even more grandiose than on admission, and was extremely emotional. His habits were very faulty.

He was difficult to treat with quinine, as he shewed quite a resistance thereto and his blood was positive to malaria for a fortnight after pyrexia ceased.

The only real improvement found in the first month after treatment was that his habits improved, but he remained facile. In April 1925, he became somewhat melancholic, and much too emotion, but in May he commenced to pick up both mentally and physically.

Soon after, he was put into the parties which work outside, and he rapidly regained his health, with a steady return of mental fitness.

He was discharged in early January 1926, weight 10st 10lbs, with no alteration in his C.S.F. except that the globulin content was diminished. He still slurred his speech, but not so markedly.

Since discharge he has obtained clerical work, and has both written and visited the Hospital.

The two cases last quoted seem to me to be sufficient justification for the malarial treatment. Both were admitted with well-marked physical and mental signs of General Paralysis of the Insane, and both were beginning to go downhill. Both were finally discharged, and are living a useful life, and, one hopes,

will continue to do so. It is perfectly true that neither case has been away from the Hospital very long, but each was observed to be mentally fit long before he was discharged.

From each, the Hospital received very willing and loyal service over a period of six months or more, and never once did these two patients cause either trouble, annoyance, or anxiety. Both did work in the grounds, and, when they came back to the Wards, expressed their gratitude to the place by endeavouring to make the lives of their less fortunate fellows more comfortable. J.C.C. kept his ward happy and contented by his piano playing, whilst F.W. also tried in every way he could to be of use.

Both were discharged in good health, and with excellent mental capabilities: both knew the causation of their trouble, and could give a rational and coherent account of all that had taken place, whilst neither shewed any mental signs of the Disease.

One feels that neither of these two patients would have been of use in the world at present if a "remission" had been unprovoked. Indeed, one does not, and could not, expect that a remission would have been found in both cases, even had there been one in either case. On this, therefore, the justification of the malarial treatment may rest, for neither case was noticeable to an untrained eye on discharge.

A third, and final, case may be quoted, which adds confirmation to the results.

Case 97. R.B. Admitted April 1925. Clerk. Aged 50. Admitted with labial and lingual tremors, excessive knee jerks, irregular and fixed pupils, and in a confusedly grandiose condition, declaring he was King of Liverpool and London. His habits were filthy. He was totally disorientated for time, place, and personality, and was acutely emotional. Weight 9st 10lbs. C.S.F. 5555554300. Globulin positive. Treated in July 1925, and became of the manic depressive type in pyrexia. In August he continued to be confused but his habits were clean. In September he commenced to shew a definite improvement both mentally and physically, and never relapsed. He was able to realise that continued detention here would prevent his obtaining a pension, and set himself to work saying that he would prove that he was getting better. This he did, by conduct, speech and his letter writing about his business affairs. Except for a certain slowness in his ways, which was said by his employer to be natural, he shewed no

mental signs of General Paralysis, and was discharged early in March 1926.
Weight 10st 12lbs.
C.S.F. slightly altered, with negative globulin.

The foregoing, then, are details of most of our discharges, and on these must our justification of the malaria treatment rest. In no case has any selection been made to treat apparently early cases. They have been treated as soon after admission as possible, wherever it was felt that they could withstand even a short period of pyrexia, and they were all treated alike and received the same preparation.

A discharge of 15% is proof that malaria does induce, at least, at partial "remission" if it is nothing more, for the percentage of natural "remissions" is not so high, nor is it found in the type of case one has to deal with here: a patient is not sent to a Workhouse Infirmary for certification until his conduct prevents his remaining at home, for frequently he is the only breadwinner of the house. We, therefore, receive him in a presumably advanced stage: yet malaria therapy has enabled us to discharge 15 cases to their homes to continue their daily work.

It has, in addition, helped to keep alive 41% other patients, many of whom would have been dead ere this. It has altered the faulty habits of many of our patients, and allows them to exist on an equality with others in the Hospital, instead of being a nuisance to everyone.

No more justification for this severe therapy seems necessary in the minds of those who endeavour to carry it out, and though it may be at present empiric, it is rapidly being accepted all over the world.

CONCLUSIONS DRAWN FROM THE MALARIAL THERAPY.

From the experience of some 130 cases of General Paralyt~~ics~~ics who have been at one time or another under one's individual care, one is possibly able to base an opinion as to some of the results of the malarial treatment of the disease, and one has to confess at the outset that the therapy is by no means a panacea, whilst the results are, at times, bitterly disappointing.

Nevertheless, with a record of cases extending over three years, one can make an attempt at generalisation, and the first conclusion one comes to is that the view of General Paralysis as a disease which can "stabilise", but which is usually fatal within three years, is the only justifiable opinion to accept. In support of this one can instance 25 cases admitted, all of whom died, 24 in this Hospital at varying dates after admission, and the other after transfer.

When one has to deal with such a fatal condition, one is prepared to run almost any risk in the endeavour to find some agent which will reduce the mortality, and from published work of others, information privately given, and from one's own somewhat limited experience, one is bound to say that the treatment of General Paralysis of the Insane by malarial therapy is, at least, quite hopeful.

The three years limit of life is generally accepted, always with the proviso that there may be some remission: such remissions are, however, frequently theoretical, and do not lengthen life.

On the other hand, one can point to four cases who have actually been in this Hospital for three years or over, who are still alive and in fairly good health, whilst one has improved mentally to such an extent that there is a reasonable possibility of his discharge in the near future.

Thirteen others have been in the Hospital for over two years eight of whom are in good health, three in fair condition, whilst two are but little improved.

In the period of twelve months ended December 31st 1923

RESULTS OF MALARIA TREATMENT FROM NOVEMBER 1923

TO MARCH 31st 1926.

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<u>Admitted.</u>	<u>Not treated.</u>	<u>Treated.</u>	<u>Died.</u>		<u>Treated.</u> <u>In incubn.</u>	<u>After</u> <u>malaria.</u>	<u>Removed.</u>		<u>DISCHARGED.</u>	<u>Remaining.</u>
			<u>Not treated.</u>	<u>Treated.</u>			<u>Not</u> <u>treated.</u>	<u>Treated.</u>		
125.	25.	100.	24.	12.	31.		1.	1.	15.	41.

Of the 41 remaining it is expected to discharge within the next three months 3 more cases at least, whilst three others may go back to their friends much improved.

ANALYSIS OF THE RESULTS OF THE MALARIAL TREATMENT OF GENERAL
PARALYSIS OF THE INSANE.

Total admitted.	Treated.	Not treated.	Died.		Removed.		DISCHARGED.
			Not treated.	Treated.	Not tr'd.	Treated.	
				In Incubn.	After malar.		
125.	100.	25.	24.	12.	31.	1.	15.

Leaving 41 presently in Hospital, of whom at least three will be discharged before the end of May 1926.
Three others are sufficiently well to go home to their friends as soon as arrangements can be made.

therefore, we admitted 48 General Paralytics of whom 17 received no treatment, and who are all now dead.

Of the 31 treated, 15 are alive in Hospital, 4 have been discharged, and the remainder have died.

This, therefore, seems justification enough for the continuation of the treatment, based though it is on somewhat empiric lines, for no other treatment has shewn the power to prolong life to this extent. The fact that there are 41 cases still in Hospital, all of whom have been treated, and that none of the 25 admitted and who were not treated have died, seems to make the treatment worth while.

If, however, one could only point to physical results it would perhaps be but small justification: one can, and has, shewn that 15 cases out of the 100 treated are back at their work, or are at least leading useful lives, and as time goes on this number will be augmented for some of the patients are now shewing signs of long-awaited mental improvement to correspond to their physical well-being.

Therefore, one can sum up the series of one's cases, and say that 15% were considered to be sufficiently improved to be sent to their homes, and, from information received, they are continuing at the work they have obtained for varying periods since discharge.

In addition, 41% have definitely improved in health or habits, and this is the more noticeable in regard to the ataxicity of gait, the presence of lingual tremors, and the control of the habits. This figure of 41% is very conservative, and includes all those discharged or removed, and those presently in hospital, although some of the latter class have had to be included in the designation "not improved" as they have not recovered sufficiently long from malaria to allow of a correct assessment to be made.

One therefore feels that at least the malarial therapy has justified to some extent the claim that its originators made for it.

Reviewing our results in general one feels that the additional work imposed by the treatment of General Paralysis by malaria has been well worth while, for of our 125 admissions, those untreated all died, whilst of the 100 treated, the death rate is only 43%, which includes several cases who were inoculated as a last resource. Of the 12 who died in the incubation period, five died of inter-current disease having no relationship whatsoever to the malaria, and of these 12 cases 7 died early in the incubation period, before the plasmodium could have taken much toll of the system.

Having in mind these figures, it would seem reasonable to consider that the death rate at present, when every case is treated soon after admission in the hopes of stabilising the disease at an earlier stage, is nearer a figure of 20%, such as is given by Graham of Belfast, or that of 27% given by Whittingham Mental Hospital, who have a larger series of cases than is available to quote from than at most Hospitals in this country.

Our discharged cases have been reviewed earlier, but it would seem hopeful that these cases, mainly under observation here for many months before discharge, have resumed their normal work and have been certified by ~~xxx~~ other Doctors as being quite able to be about in the ordinary way.

A very conservative policy is adopted in this Hospital in discharging General Paralytics, and quite a number presently with us would be able to be at home, but for the fact that the homes are not always sufficiently prosperous to maintain them when work is difficult to get.

Of the 41 patients in Hospital even including the recently treated cases, 23 are well able to do ordinary ward and manual work, and those who are in the convalescent wards seem to take an even greater interest in their work than do the ordinary recovering patients who have suffered from other psychoses.

In summer, many of our General Paralytics work on and about the Farms of the Hospital and bear a very high reputation with the Farm Bailiff for the amount and quality of hard work they can do.

That a permanent cure is not to be expected, one is perfectly prepared to find. One has, however, to take into consideration the figures of the Continental workers who have had longer experience than has been available in this country: from these sources, in published information and private communications, one is led to believe that the "stabilisation", or the remission, is known to have extended over considerable periods of time varying up to ten years, at the end of which time the ex-patient was still performing arduous duties which required considerable mental ability. (Delgado, of Lima).

That life is prolonged beyond the "three years limit" one can substantiate even from the limited cases under review. With the increased tenure of life comes an additional facility for usefulness, and this is exemplified in our cases discharged.

The disappearance of tremors and the ataxic condition in general, together with the increased physical well-being is very marked, but in no case has any alteration in disorganised reflexes been observed.

From the patient's point of view, and that of the Hospital too, even though the mental condition may not respond to the therapy, the alteration in habit from ~~stagnant~~ faulty to clean is of vast importance, even though one could not point to an increased length of life. When one can, it is easy to appreciate the immense amelioration which is found by all in touch with the patient, when the habits become better.

And, though the first attack of malaria may only shew an increase in good health, one is looking forward hopefully to the results to be obtained by the second attack.

Malaria therapy, empiric though it may be, is justified. It is more than justified: it is essential.