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T H E S I S

on

GENERAL PARALYSIS of the INSANE

With Special Reference to its TREATMENT by MALARIA.

by

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INTRODUCTION

To ensure the successful treatment of any particular disease it is necessary that our knowledge regarding it should be made as complete as possible in certain important respects. Our conception of what constitutes the disorder must be clearly defined, its aetiology established, all the measures for its accurate diagnosis perfected, and its pathology thoroughly understood.

When regarded with these criteria in mind few diseases are so interesting historically and practically as General Paralysis of the Insane.

Ever since this disease was first described and isolated as a definite clinical entity it has borne a deservedly evil reputation. Until lately all undoubted cases have ended fatally in a short period of years. For long it remained mysterious and deadly; its cause could merely be guessed at, and, as a result, treatment was as undirected as it was unavailing. Constant research and observation gradually resulted in an accumulation of clinical and pathological data of interest and importance, without any apparent clue being

furnished with regard to the actual cause of the illness. While this was unknown treatment could only be directed to the relief of symptoms or to a frank adoption of empiricism.

Its choice of victim in a number of cases appeared cruel and inexplicable. Men were attacked when their lives were just approaching a full maturity, and indeed when their usefulness gave every indication of being above the average. They were often people who had led full, busy lives and whose future seemed assured. Once the disease appeared, the sufferer was reduced from the apparent health of early middle life to a state of paralytic dementia. In the space of three or five years the progressive deterioration of the mind became manifest, first, in a slight failure of judgment and memory, then in conduct that was bizarre and violent, and, finally, in the abolition of all ordered thought and action.

Hand in hand with this went a physical failure terminating in the general paralysis which gave the disease its name.

Such, therefore, was the repellant picture and dispairing outlook which characterised the disease for many years, and it is now with some thankfulness that one can discuss it with an increased knowledge and with considerable hopefulness.

Within the last few years, as a result both of the increasing perfection of our means of investigation, and of the brilliant observers who have put these means to use our know-

ledge of this subject has been greatly amplified, almost revolutionising this branch of medicine. The ætiology of General Paralysis is established; diagnosis can be made with practical certainty; and treatment is enlightened.

Undoubtedly this gratifying advance was made possible primarily by Schaudinn's discovery, in 1905, of the Spirochaete Pallida, the causal organism of syphilis; because this led Noguchi in his turn to show conclusively that General Paralysis was syphilitic in origin.

For many years it had been known that syphilis and General Paralysis were closely related, but there was no proof of its being a disease which was 100% syphilitic. Whenever this proof was forthcoming progress in diagnosis and treatment proceeded rapidly. For the same reason, naturally, the study of General Paralysis is now considerably bound up with that of Syphilis in general. It is even more definitely linked with the other so called para-syphilitic diseases affecting the central nervous system.

Nevertheless it has become apparent that the great light which was shed on the subject by the identification of the Spirochaete Pallida has merely served to show up further problems in sharp relief. Several of these are of acute present-day interest.

It is asked, for instance, is there a special neurotropic type of Spirochaete which causes General Paralysis,

or is the development of the disease dependent upon the patient's resistance? Why is there such a long latent period before the onset of symptoms?

Why are no Spirochaetes to be found in the cerebro-spinal fluid while they are swarming in the brain? Why do tabes, general paralysis, and optic atrophy not occur together much more often than they do? In casesof general paralysis when does the spirochaete settle in the central nervous system, and by what route does it enter?

None of these questions have yet been completely answered although some have been very fully dealt with and have received plausible and possibly accurate explanations.

For example, the possibility of there being a special type of spirochaete which from the initial infection of the patient would tend to produce general paralysis has received support from many observers.

The question arises from the fact that of all persons infected with syphilis only about 5% develop paresis later. In addition it has been shown that at some period during the course of cases of syphilis temporary infection of the nervous system and the cerebro-spinal fluid takes place in from 30 to 40 per cent.

The paucity of cases of paresis therefore cannot result from a proportional inaccessability of the central nervous system.

Of course before the part played by the Spirochaete Pallida had been proved, several theories that the disease was caused by some special toxin or organism were brought forward.

The Bacillus Paralyticans of Ford Robertson, and the toxin theory of Orr and Rows[1] form good examples. These naturally receive less serious consideration now; and the hypothesis usually advanced is that, granting general paralysis to be caused by a spirochaete apparently indistinguishable from that giving rise to ordinary syphilis, may there not be a type with special characteristics fore-ordained to cause paresis?

Either one must support this theory or else consider that the disease is determined by the soil in which the germ finds itself i.e. that 5 per cent of those who contract syphilis have a central nervous system which is inherently unstable in a particular manner, and which readily receives and welcomes the Spirochaete.

Naturally a third consideration might be that the whole matter was one of pure chance.

Mott[2] was one of the first to suggest that a neurotropic variety of Spirochaete might be at work, and this has been supported frequently in the literature since - by Noguchi,[3] Levaditi, Marie and others. Facts such as the following are certainly arresting. Many records are given of general paralysis or tabes developing in persons infected from a com-

mon source. It is well-known that wives of general paralytics are prone to develop neurosyphilis. Of husbands infected by paretic wives 10% contract General Paralysis as against 3·7% among ordinary syphilitics.

Although other factors may be at work some support to this theory is afforded by statistics of the racial and geographical distribution of the disease.

For instance, both syphilis and general paralysis are common in Western Europe and North America; but on the other hand syphilis is widely found in China, Japam, Turkey, India, Algiers and Abyssinia, while General Paralysis seldom occurs.

In addition Marie and Levaditi claimed to have distinguished differing strains of Spirochaetes by cultural and inoculation experiments; but this work is rather unconvincing in some respects, and has not been confirmed in others.

The arguments in favour of the disorder being determined by constitutional factors in the patient have also been well contested, however, and they can usually be studied under two heads. Firstly, that the determining factor is an inherited instability or vulnerability of the Central Nervous System, or, secondly, that the site of election may possibly be one result of treatment - for example, by the destruction of spirochaetes before sufficient antibodies have been acquired by the individual.

The first of these hypotheses is substantiated by clinical evidence which in its turn seems to be just as signi-

ficant as that already cited in support of the neurotropic Spirochaete theory. Thus, records are given of several members of a family being infected from quite different sources, but who have all developed General Paralysis or Tabes. Now if these are not coincidences one might readily conclude that the neurosyphilis resulted from a neuropathic heredity.

Again, with regard to the effects of treatment many interesting speculations have been based upon the ground that the formation of antibodies called forth by the Spirochaetal infection is an essential feature of cure and protection, and that some superficial but vigorous forms of early treatment may bring this natural response to a premature conclusion.

It is unwise, however, to take these speculations too seriously, especially as it has often been said that the incidence of paresis may be due to <u>inadequate</u> early treatment. It is certainly a fact that a great number of general paralytics seem to have shown excessively mild secondary syphilitic symptoms, and have presumably had little or no anti-syphilitic treatment in consequence.

It can be seen from the problems mentioned above, (which have been well reviewed by Stewart[4]) that the discovery of the Spirochaete, while of estimable value, has in many ways opened up a larger field for speculation than ever.

Having devoted more than eight years to the care and

treatment of the insane in three different and representative Mental Hospitals, I have naturally had continuous opportunity of studying the clinical manifestations of General Paralysis and the therapeutic measures for its relief. Even during the period I have been in contact with such cases I have seen signal improvements in the methods used. It is undoubted that the welcome spirit of hopefulness, which has been so justifiably aroused with regard to this disease, springs mainly from our improved knowledge of its aetiology.

The literature of General Paralysis is now copious, and in the present thesis I propose to deal concisely with the principal recent work, and to discuss modern methods of diagnosis and treatment. While the broader generalisations in this paper will be made on a personal study of over 100 cases, I intend to base my thesis mainly upon a series of twelve.

These twelve cases have all been treated by the inoculation of Malaria, and I hope to discuss principally this form of treatment.

The idea of attempting to cure or improve one disease by the experimental production of another is not a new one, but in few, if any, instances has the procedure given such promising results as the one under discussion.

Some years ago, for instance, an analogous measure was largely used in the treatment of malignant growths, sarcomata in particular. Injections of the virus of erysipelas and

bacillus prodigiosus were recommended by Coley, and some degree of success was reported by various surgeons in cases regarded previously as hopeless. Such gratifying results were rare however, and the use of Coley's fluid has for years been discontinued.

The treatment of General Paralysis by induced malaria has not been practised for a sufficient length of time for any complete pronouncement to be made upon its efficency, but my experience coincides with that of most of those who have recorded their results. I find that in a majority of instances some degree of improvement may be looked for, and that in a smaller proportion complete remission takes place.

In past years although General Paralysis was treated energetically by a very large number of different agents, and by many ingenious methods its mortality remained constant, practically no undoubted case escaping a fatal termination. The few recorded instances of apparent cures in the past are all open to some doubt as to diagnosis, and at best their appearance in the literature merely accentuates our realisation of the deadly nature of the disease.

More years must elapse before one may claim with any confidence that General Paralysis can be cured; but in view of the almost complete inefficency of former methods of treatment the results which are at present accruing are exceedingly striking, and must form my excuse for devoting particular

attention to Malaria therapy in this thesis.

HISTORICAL OUTLINE.

The history of the development of our knowledge concerning the diagnosis and treatment of General Paralysis resembles the disease itself in that it is most appropriately described in three stages.

During the first stage our conception of the disease was gradually clarified until it took its place as a definite clinical entity. In the long second stage the symptomatology and pathology were exhaustively investigated: and finally in the third, and present, stage aetiology has been established, diagnosis made certain, and treatment has become apparently fruitful.

It is now rather more than a century since General Paralysis of the Insane was first isolated and described as a well-marked clinical and pathological unit. In 1798 John Haslam published details of a case in which we can form a diagnosis of General Paralysis with certainty from the recorded symptoms and post-mortem appearances. He did not claim however that it could be taken as one example of a clearly defined class of disorder.

In succeeding years a steadily increasing amount of evidence appeared in medical literature, pointing to a dawning realisation that such cases were related and that they

showed striking similarities both clinically and pathologically. Cox, Esquirol, Pinel and Georget all described types of mental disorder, complicated by paralysis, which appeared to have many features in common both with regard to symptoms and course.

When compared with our present conception of Dementia Paralytica however, all these accounts fell rather short of completeness, displayed want of accuracy, and contained fundamental misconceptions regarding pathogenesis.

It was not until 1822 when A.L.J.Bayle presented his thesis to the Faculty of Medicine in Paris that one could say with certainty that for the first time this disease had been recognised and accurately differentiated from all others.

His thesis made it abundantly clear that the writer was aware that he was describing the well defined disorder which we now call General Paralysis of the Insane, that he recognised that the mental disorder and the paralysis develop together, and are intimately related to each other, and that the principal manifestations of the disease were caused by an inflammation of the meninges which he called Chronic Arachnitis.

With the appearance of Bayle's thesis one can say that General Paralysis became establised in its place among known and recognisable diseases, and the second stage of investigation began. For a number of years very little hopeful progress was made, in spite of the vast amount of careful and often brilliant work expended upon it.

It is true that all the clinical manifestations of its dual aspects - mental and physical - were extensively studied, and the post-mortem appearances produced by General Paralysis were particularly fully observed, but convincing proof of its aetiology, and accurate scientific methods of diagnosis were completely lacking. As a result treatment was undirected and unavailing.

Nevertheless definite advances in knowledge gradually accumulated and on looking back one can trace how each of these steps has consolidated work previously done and has led us to our present conception of the disorder. In particular investigators of Neuro-syphilis in general helped greatly to establish the true relationships of General Paralysis.

Thus we find that work done in the latter half of the 19th Century to describe accurately the histological changes occurring in syphilis of the Nervous System forms a good example. In 1858 Virchow investigated the lesions which were to be found in the nervous elements, and in 1874 Heubner demonstrated the characteristic features of the cerebral endarteritis, thus practically completing the histological picture.

Again, when Quinke first advocated lumbar puncture in 1891 a fresh diagnostic (and, later, therapeutic) aid was acquired.

With the study of pathological changes in the cerebro-

spinal fluid, thus initiated, the names of many prominent scientists are connected.

Widal[5], for example, was early on the field with researches into its cytology, and, later on, in 1903, its albumen content. His work and that of others such as Ravaut, Sicard and Nissle foreshadowed later developments. These developments pointed more and more to a direct connection between syphilis and general paralysis.

In 1905, however, a definite discovery of great value was made - and by a non-medical man. Schaudinn, the Zoologist, in a series of investigations regarding various Spirochaetes identified the Triponema Pallidum and established the fact that this organism was the causal agent of syphilis. In collaboration with Hoffmann he published the results of his researches and almost immediately the truth of his observations was confirmed by many observers. The profitable study of all syphilitic disorders received a great impetus from this advance, and it is undoubted that most of the modern development in the diagnosis and treatment of G.P.I. date from Schaudinn's discovery. Immediately the relationship of the Spirochaete Pallida to Syphilis was established the lines along which further research should be directed were made clear.

Thus the problem of accurate diagnosis was approached with special reference to the Spirochaete by way of the complement

fixation methods of Bordet and Gengou. On the other hand forms of treatment were evolved by Ehrlich and others which had in view the destruction of this organism by chemical means.

In 1901 Bordet and Gengou had increased greatly the delicacy of haemolytic immunisation tests by making use of the fact that when any antigen-antibody reaction occurs complement is used up, and that if an attempt is then made to perform a haemolytic experiment in the resulting medium no haemolysis takes place. They called this disappearance of complement in a mixture of antigen and antibody - fixation or deviation of complement, or the Bordet-Gengou phenomenon.

Wasserman based a series of experiments upon this phenomenon in order to discover a reaction which would demonstrate in a patient's serum whether infection with syphilis had ever taken place. Instead of using a pure culture of Spirochaetes he employed as antigen a watery or alcoholic extract of a hereditary-luetic liver.

His researches were eminently successful and in 1906 he published details of the now famous Wassermann Reaction. In this work he collaborated with Neisser and Bruck.

The test can still be carried out in its original form but since 1906 various modifications in its technique have been suggested, by Noguchi in particular, and some of these are now

generally adopted. The most significant of these changes is that it is now a general practice to use an extract of normal heart as antigen instead of that from a luetic liver.

As soon as the Wassermann Reaction became known investigators found that it was positive in the serum of the majority of general paralytics and tabetics. In 1908, however, Plaut, and also Wassermann, applied this test to the cerebro-spinal fluid and, when again positive results in such cases were the rule, another important link was formed in the chain of evidence connecting syphilis, as a causal agent, with General Paralysis - a chain which had been forming since 1857 when Esmarch and Jessen first discussed this relationship and cited three cases of paresis which they said were caused by syphilis.

In this matter, however, all doubts were finally wiped out and arguments rendered unnecessary by Noguchi's work. In 1913 he demonstrated the presence of large numbers of Spirochaetes in the brain of a patient who had died of General Paralysis.

This notable discovery was immediately confirmed; and of late years our knowledge of the characters of the spirochaeta Pallida has been augmented by similar examinations made under improved conditions. The names of Jahnel, Hauptmann, Dunlop[6] and Grant[7] are associated with this work. The last-named found spirochaetes in 62·5% of the brains in a series of 50

cases of General Paralysis.

I have indicated the impetus that Schaudinn's work gave to the study of the diagnosis of syphilis, and I have identified with this the name of Wassermann. In the same way the concurrent researches which were made in the realm of treatment may be observed. The pioneer work here was done by Ehrlich.

For many years the remedies most extensively used for syphilis were mercury in various forms, and Potassium Iodide. In the beginning of this century however arsenical compounds were increasingly employed. As a rule they supplemented mercury therapy, and this alliance proved highly successful in secondary and tertiary lesions. With General Paralysis, however, although they often gave encouraging results for a time, they did not affect the dreadful mortality rate to any appreciable extent. These arsenical compounds were numerous and were mostly arylarsonates.

Atoxyl, containing 22.8% of arsenic was first introduced and described as the Sodium Salt of Met-arsenic Acid Anilide, but it later proved to be identical with another anti-syphilitic remedy called Soamin (Sodium Para-amino-phenylarsonate).

Mercury Atoxylate which contains 23.7% of arsenic and 31.8% of mercury had a considerable vogue.

Arsacetin, Arsenophenylglycin, and Sodium cocodylate were three other arylarsonates which were much used. The last

named was rather less toxic than the others and was prepared as an Injection, an Elixir, and in Globules.

Although all these arsenical derivatives were undoubtedly valuable, the fact that they were introduced in such large numbers, and that each succeeding one usually ousted its predecessor in popular favour, showed that something much more efficient and less dangerous was required.

The painstaking researches of Ehrlich finally supplied this. In 1909, after a unique series of investigations he brought out Salvarsan (Di-oxy-Diamidoarsanobenzene Bi-Hydrochloride). It was called the Ehrlich-Hata Remedy and as it was the result of his 606th experiment he referred to it as "606". As an anti-syphilitic it was quickly found to be superior to anything that had previously been used and it was generally adopted. Soon after it came on the market preparations of a similar nature were manufactured in different parts of the world. Thus we find arsenobenzol appearing in France, followed by kharsivan in Britain, arsphenamine in America, and diarsenol in Canada.

Salvarsan is a pale yellow amorphous powder containing about 34% of arsenic. It is very unstable if exposed to air, and is kept in specially prepared ampoules on that account. It must be administered intravenously because of the extreme pain and even necrosis that follows its injection intramuscularly or subcutaneously.

Physicians administered it rather apprehensively at first on account of the toxic results which had sometimes followed atoxyl therapy. They soon found however that, granted careful technique, there were few dangers. The great majority of unfortunate results which did occur were due undoubtedly to faulty administration; and Nonne[8] said in 1913 - "There are no dangers ..... if it is not given in severe cases of arterio sclerosis, extensive nerve degenerations, advanced cases of diabetes, and in general marked cashexias, such as exist in Tuberculosis and Carcinoma."

Notwithstanding his highly successful introduction of Salvarsan, Ehrlich still continued his attempts to find something better. At his 914th experiment he evolved Neo-Salvarsan - Ehrlich-Hata Remedy 914, (Dioxy-diamidoarsenobenzene-mono-methane-sulphate). It is a yellow amorphous powder with a peculiar ordour, and about two-thirds as strong as Salvarsan (22% of arsenic). It is even more easily oxidised than "606", and therefore the precautions in its preparation and administration must be rigidly regarded. It has the great advantage over Salvarsan that it can be given intramuscularly or by deep subcutaneous injection.

Neo-Salvarsan gradually took the place of Salvarsan and in due course Neo-kharsivan, Neo-diarsenol, Neo-arsphenamine, and Novarsenobenzol appeared.

As I have stated already the arrival of the "606" and "914" drugs marked a big advance in the treatment of syphilis. It became a disease which could be controlled and cured with a degree of certainty formerly unknown. In spite of this however General Paralysis remained as obstinately immune to therapeutic interference as ever. This lack of response was felt to be due to the comparative impermeability of the choroid plexus to such drugs, and it was naturally proposed next that some means should be found to bring Salvarsan into more direct contact with the central nervous system. As the injection of the drug itself into the spinal canal was found to be quite impracticable the suggestion was made by Marinesco that salvarsanised serum should be used. The technique of this intrathecal method was perfected by Swift and Ellis who introduced it in 1912 as a mode of treatment in tabes. It was first used in this country for the treatment of General Paralysis by Prof. G.M.Robertson.[9]

This avenue of approach was extensively used almost immediately, and salvarsanised serum was given in a diversity of ways. Besides being injected into the spinal canal it soon became a practice to give it intracranially and intraventrically. Different modifications of this form of therapy are associated with the names of Ogilive, Levaditi, Wardner, Cotton, Purves-Stewart, Hammond and Sharp. Although these workers were able to report a measure of success in the treatment of

paresis the results were far from conclusive. Some clinical improvement, accompanied by modification in the cell count and the protein reactions in the C.S.F., was obtained in quite a large proportion of cases. It was obvious, however, that the comparative inaccessability of the Spirochaete because of its parenchymatous distribution was the factor which militated principally against success.

Of late years a large number of other forms of treatment have been suggested and tried out. Many of these aimed at producing an acute reaction with accompanying leucocytosis in order to raise the body-resistance. In some treatments this was supplemented by the supposed inhibitory effects of other pathogenic organisms upon the vitality of the spirochaete

A good example of this type of therapy was that suggested by Wagner von Jauregg who used mercury and iodide along with increasing doses of Koch's old tuberculin. Pilez used this method and in 1910 he reported encouraging results. Killed cultures of streptococci and staphylococci were employed in the same way. To promote leucocytosis and increase resisting power, Fischer and Donath used nucleinic acid and sodium nucleinate. Lecithins, spermins and other preparations have also been given with the same object.

The success which has attended the recent introduction of bismuth as an anti-syphilitic agent has naturally resulted in its being enlisted in the large and rapidly growing army of

remedies for general paralysis. It has been given mostly in the form of organic salts by intramuscular injection.

Once again, however, one has to record the same types of result - some remission of symptoms, modifications in the laboratory findings - but no hint of an unmistakeably curative agent having been found. It would appear that bismuth like many of the forms of treatment already mentioned must be relied upon more as a therapeutic ally than as a specific cure for paresis.

Before discussing the historical aspect of treatment by means of induced malaria, it is necessary to refer to one additional drug which has recently attracted much attention in treatment of neuro-syphilis. This is Tryparsamide, the sodium salt of n-phenylglycineamide-p-arsonic acid.

Although it was synthesised in 1915 by Jacobs and Heidelberger at the Rockefeller Institute it was not used clinicallyuntil 1920. During the five years between these dates it went through an exhaustive experimental stage.

With memories of the early arylarsonates still fresh, and with everyday evidence of the exact value and scope of the salvarsan and neo-salvarsan groups always present, it was obvious that yet another arsenical preparation would attract very little notice unless it had exceptional features to commend it.

Tryparsamide, however, was found to have properties valuable enough to command attention even at a period when the whole hori-

zon seemed to be covered by malaria therapy.

The most salient features which make it so useful in the treatment of neuro-syphilis have been summarised briefly by M. Brown and A.R.Martin.[10]

Some of the points they make are as follows:-

The drug possesses a marked affinity for the tissues of the central nervous system.

There is no known substance with an equal degree of spirochaeticidal action that possesses the same high power of penetrability.

The drug has a remarkable stimulating effect upon animal economy. It is capable of reinforcing the natural processes of resistance and promoting recuperation.

The drug yielded wonderful results in rabbits with trypanosomiasis, in which disease there is a distribution of organisms and of lesions in the C.N.S. comparable to those of cerebral syphilis in man.

Its value depends on its power of developing spirochaeticidal action in hitherto inaccessible foci, and of stimulating the processes of natural resistance. The same authors analysed reports on 2000 cases of neuro-syphilis treated by Tryparsamide and found clinical improvement in 30% and serological improvement in 75% Its use in paresis has also been favourably reported on in this country by Davie and Lees.

Malaria Therapy.

Although this form of treatment is one of the most recent, it has given more encouraging results with General Paralysis than any other.

In many ways it belongs to a much more ancient kind of therapy than do the majority of the remedies we have already mentioned. The specific chemical means, devised by Ehrlich and others for the destruction of the spirochaete, having proved ineffective, frank recourse is now made to a much older and more emphirical mode of attack. As far back as the days of Hippocrates it was noticed that some intercurrent febrile arrack often exercised a curative effect upon psychoses. This phenomenon has been remarked upon with increasing frequency throughout the centuries since, and many efforts have been made to turn this observation to some practical use. Inflammatory reactions were provoked in mental patients by a variety of irritant ointments and injections, febrile attacks being encouraged and induced in many different forms of psychosis. The results were often disasterous and always uncertain.

One of the most persistent investigators of the possibilities of treatment by means of induced physical reaction has been v Wagner-Jauregg,[11] to whom reference has already been made in this paper.

Since 1887 he has experimented with agents that produced fever or suppuration and it is on account of the encouragement

that his researches gave him that he continued so patiently.

He found that the means used could be divided into three classes and that, according to their efficiency in inducing remissions or improvements, they could be arranged in an ascending scale as follows:-

1. Chemical substance - e.g. sodium nucleinate, and milk.
2. Toxalbumins e.g. Tuberclin, and staphylococcal vaccines.
3. Living organisms of infectious disease.

His most striking results when using the above methods were got in the treatment of General Paralysis, and, favouring as he did the inoculation of living organisms, he next concluded that of these the plasmodium of benign tertian malaria was the best infective agent to use. Not only could this infection be very readily controlled when given therapeutically, but it also yielded a much higher percentage of remissions and apparent cures than did others which he tried.

In 1917 Wagner-Janregg used this method on nine cases with such good results that he brought it into use increasingly during the following years. In 1919 treatment of paresis by malarial infection became a routine measure at his clinic. Gerstmann, Weygandt, Kirschbaum and Delgado[12], impressed by his high percentage of remissions, followed his technique with similarly striking effect.

In 1922 the position among psychiatrists in Britain was

that they were confronted by successive reports from continental sources claiming up to 40% of cures in a disease hitherto regarded as fatal, and by a method apparently empirical. It became a scientific necessity that this form of treatment should be tested here. It was brought into use as a routine practice at several mental hospitals during 1922. Since then it has become almost universal and the literature on the subject has reached impressive proportions. The results given in this country by Graham, M^cAlister, Dunne, Rudolph,[19] Nicol and others[x], while showing a smaller percentage of complete remissions than do those of the earlier workers, indicate nevertheless, that a form of therapy far in advance of its predecessors is now in use.

In concluding this historical survey of the diagnosis and treatment of general paralysis one finds a rather humbling commentary upon our newest method in the following facts.

- Boerhaave in his "Aphorisms Concerning the Knowledge and Cure of Disease", written in 1728, says of insanity - "When all Remedies have been tired in vain, it has sometimes happen'd that various Tumours, Piles, Dysenteries, Dropsies, great haemorrhagies cure of themselves, and Tertian or Quartan Agues have cured this disease." Hippocrates knew of the curing of mental disorders by inducing febrile diseases and Galen describes a case of melancholia cured by intermittent quartan fever.

THE NEWER METHODS of the DIAGNOSIS of GENERAL PARALYSIS and their VALUE.

Before embarking upon the following analysis and discussion of newer diagnostic methods it is necessary to point out that these supercede in no way the estimation of physical signs and mental symptoms. No further mention will be made of these here as they do not come within the scope of this section, but it must be emphasised that they form an invariable preliminary to methods which are more associated with the laboratory than the consulting room.

1. Laboratory findings in the C.S.F.

It is by now a common-place that no unequivocal diagnosis of General Paralysis can be made without an examination of the cerebro-spinal fluid, and without obtaining positive results in at least four respects.

One must demonstrate :-

a. A positive Wassermann Reaction
b. An increase of globulum.
c. Pleocytosis and
d. a paretic curve with the Lange Gold Sol test.

The following are some of the tests commonly used to provide these and further confimratory data.

The Wassermann Reaction.

This is the most important and significant test we have. Its significance rests mainly on the fact that if a specimen of cerebro-spinal fluid gives an undoubtedly negative result it is highly improbable that it comes from a case of paresis.

When the Wassermann Reaction was first applied to the C.S.F. very few positive results were got. This was because in the technique which obtained in the early days relatively small amounts of spinal fluid were used. As soon as it became the practice to use larger quantities it was found that a positive Wassermann reaction was obtained in almost 100% of cases of general paralysis. The exact percentages quoted by numerous authorities vary between 96 and 100.

There are strong grounds for the belief that the presence of the Wassermann reacting substance in the spinal fluid is due to an increased premeability of the meninges and not to intra-meningeal formation of this antibody (Dujardin[13]). This would account for the fact that any meningeal inflammation ocurring in a syphilitic patient may give rise to a positive Wassermann reaction. Thus it is found that in the late Primary and in the Secondary stages of syphilis this test gives a positive result in a certain number of cases.

Fildes, Parnell and Maitland examined 1314 cases of syphilis and, with regard to the W.R. in the cerebro-spinal fluid, the following interesting results were got. In the late Primary state 3%, and in the Secondary stage 11% were positive. Dujardin and Fordyce also found a positive W.R. in the liquor of 10% to 11% of Secondary cases.

In untreated cases even higher percentages of positive results have been got - 12% in the Primary Stage, and up to

39% in the Secondary Stage (Schou).

Also in the period of latency which follows the disappearance of active signs of Secondary syphilis a certain proportion of fluids retain a positive W.R., and it is undoubted that it is from the ranks of such cases that late neuro-syphilitics are mostly recruited.

Many cases are on record however in which it has been shown that paresis, tabes, etc., can develop in patients whose fluid has been found negative to the W.R. in the latent period.

We can say with confidence that in (untreated) general paralysis one almost always gets a strongly positive Wassermann reaction in o.2cc or more of the cerebro-spinal fluid, This is accompanied unsually, though not invariably, by a similar finding in the blood serum.

This then gives us one essential item in the humeral syndrome associated with General Paralysis.

Sachs-Georgi Reaction.

Ever since the introduction of the Wassermann Reaction in 1906 attempts have been made to determine its exact nature, to make it simpler and if possible to replace it by a similar test of even greater specificity. Among the most interesting results of this quest are the Sachs-Georgi reaction and its modifications.

This reaction belongs to the group of flocculation methods and it was evolved by Sachs and Georgi in 1918. It

is simpler than the Wassermann test in that it is performed with serum + antigen + cholesterin only. The resulting fluid was at first incubated at 37°C for two hours, and after an interval of 18 hours it was examined for flocculi by means of a Kuhn and Woithu's agglutinoscope. It soon transpired that this reaction was not specific for syphilis, positive results being obtained from the blood sera of tuberculous and cancerous cases. Sachs and Georgi then recommended that the incubation at 37°C should be continued for 18 hours and this greatly increased the specificity of the test.

In the collected results of the two tests upon the sera of over 17,000 cases Baumgärtel found that the Sachs-Georgi and Wasserman Reactions agreed in 91.43%

In 1921 Dreyer and Ward[14] published a further modification which they called the Sigma Test. This differs principally from the original Sachs-Georgi in the constitution and preparation of the extract, the much greater precision in the diluting process, and the methods of reading and estimating the results.

Modifications of the Sachs-Georgi reaction, and flocculation tests generally cannot yet be said to have gone very far towards replacing the Wassermann Reaction, although an increasing parallelism among them is becoming apparent. Nevertheless before long these tests may have a proved specificity in addition to their present advantage of being capable of

giving some indication of the actual amount of reacting substance present in a given pathological fluid. This substance has been shown by Mackie[16] to be related to pseudo-globulin.

Protein Reactions.

The normal cerebro-spinal fluid contains from 0.2 to 0.25% of protein, consisting of albumen and globulin.

An increase of protein is associated with many pathological conditions, but in all of these states the albumen is in excess of the globulin. On account of the ease with which serum globulin can be identified the majority of tests for increased protein content are specific for this substance and not for albumen, and therefore as a result of the constant references to excessive globulin one is apt to overlook the fact that this is invariably accompanied by an even larger amount of albumen.

In General Paralysis for instance the albuminous bodies are present in the proportion of seven of albumen to three of globulin. This proportion indicates a relatively large increase of globulin compared with cases of non-specific meningitis for example.

Serum globulin is readily divided into Pseudo-globulin, Euglobulin and Fibrinogen, and of these the last two are only definitely present pathologically.

On account of the relatively great increase of globulin in cases of General Paralysis, and because of their simplicity

the tests of Pandy, Nonne-Apelt, Ross-Jones, and Noguchi are mostly employed upon spinal fluids which are thought to be of paretic origin.

Pandy's Test.

This test is more delicate and more simple than any of the others mentioned above. It consists in observing the result of adding one to five drops of cerebro-spinal fluid to a strong solution of phenol. With normal fluids no reaction, or, at most, a very faint opalescence is got. A positive reaction is indicated by varying degrees of turbidity. I have found it of interest to perform Pandy's test while the suspected specimen of cerebro-spinal fluid is being collected. When the lumbar puncture is made a drop of the fluid is caught in a test-tube containing 1cc. of strong phenol.

If the fluid is strongly positive this will give a definite opalescence. In any case other four drops are then taken, and on shaking the tube the resulting amount of turbidity, if any, can be estimated. If Dattner's lumbar puncture needles are used the spinal fluid will flow slowly enough for this procedure to be followed.

Of course a positive result gives us no definite information as to whether a case is suffering from General Paralysis or not, but this much is sure - if, in a syphilitic patient, Pandy's reaction is positive then there is some active luetic

affection of the cerebro-spinal system. If the reaction is negative then there is no active process going on.

Nonne-Apelt and Ross-Jones Tests.

If, to 1cc of spinal fluid, an equal quantity of Saturated Neutral Ammonium Sulphate solution be carefully added to form an under layer, a white ring will appear at the junction of the fluids in a positive case. This constitutes the Ross-Jones test.

Unfortunately a faint ring is sometimes got with normal spinal fluids.

The test-tube should then be shaken and laid aside for five minutes to half an hour, after which the degree of resulting turbidity, if any, should be read. A weakly positive fluid shows faint milkiness and a very strongly positive one precipitation.

This is the well-known Nonne-Apelt Reaction - Phase 1. It is the oldest of the globulin tests, and although it has always been applied most universally in Germany it is still used with confidence in this country and elsewhere.

The Noguchi Test.

In this test 0.2ccs of cerebro-spinal fluid is boiled with 1cc of 10% Butyric acid plus 0.2cc of normal 4% NaOH.

If the reaction is positive a flocculent deposit appears and settles within about three hours.

This test holds no advantage over those already men-

tioned and, like the Ross-Jones, it is not quite specific for syphilis.

Several other globulin tests are in use; such as Weichbrodt's where mercurie chloride is used, and Brandberg's which is a further modification of the Nonne-Apelt, but by far the commonest in the diagnosis of neuro-syphilis are those already described.

The Foam Test.

This is an exceedingly simple procedure which can only be used as a very rough guide.

If cerebro-spinal fluid be shaken in a test-tube a layer of foam appears and persists for some time if the fluid contains any excess of protein. Naturally this test is positive in nearly all pathological states of the liquor, and it is merely of value in indicating that a specimen is abnormal. The test is much used in America and it has been commented on by Levison[17] and others.

CYTOLOGY

In normal cerebro-spinal fluid large and small lymphocyte cells are found. There is no real line of demarcation between these two types as the small lymphocyte merely grades off into the larger variety. There are however fewer large ones than small ones. A few so-called "large mononuclears" may be encountered, but these also belong to the lymphocyte class.

Other types such as polymorphonuclear leucocytes are practically never found under normal conditions.

Modern methods of cell-counting, especially by means of the Fuchs-Rosenthal chamber, have now practically established that healthy spinal fluid should contain no more than 3 cells per cmm; certainly any count over 5 per cmm. should be regarded with suspicion.

In syphilitic disease of the central nervous system there is almost invariably an increase of cells in the fluid, small lymphocytes being in the majority. This has also been found even in cases where there was no apparent involvement of the nervous system. Thus numberous authors have recorded an increase of cells in early syphilis, late secondary cases and in the so-called latent period. For example Fildes, Parnell and Maitland in their examination of 1314 cases found over 5 cells per cmm in 14% of early primary cases, in 21% of late primaries, and in 30% of secondaries. Of these a number had a negative W.R. in the cerebro-spinal fluid.

Pleocytosis is specially marked, however, in metasyphilitic affections. According to Nonne (1921 Syphilis and the N.S.) it occurs in 90% of tabetics, 95% of general paralytics and 100% of cerebro-spinal syphilitics.

In General Paralysis the cells usually number from 50 to 300 per c.mm. but in some cases there may be as many as 600 or 900.

Of these cells the majority are lymphocytes: 5% to 20% of large mononuclears are often present however. Plasma cells are very constantly found in this disease and at one time their presence was considered to be peculiar to it. This is not so however. Besides occurring occasionally in tabes and cerebral syphilis they have also been demonstrated in cases of Tuberculous Meningitis. Polymorpho-nuclears, compound granular corpuscles and macrophage cells are often present, and more infrequently fibroblasts.

It has been shown repeatedly that if a series of lumbar punctures is done in one case the cells per cmm. are more numerous in the first specimen than they are in the last.

Lange's Colloidal Gold Reaction.

When a solution of sodium chloride is added to colloidal gold the mixture goes through shades of blue and violet and finally becomes clear. The decolorisation which takes place is due to precipitation of the gold particles by the electrolytic action of the salt. Similarly it is found that the addition of proteins to the gold solution has a like effect. In 1901, however, Zsigmondy discovered that if protein were added to Gold Solution along with the salt then the colloidal gold was protected by the protein and precipitation did not take place. He utilised this phenomenon in order to estimate the amount of protein present in certain solutions.

In 1912 Carl Lange endeavoured to use Zsigmondy's method

in a series of experiments with spinal fluids containing excess of protein. To his surprise he found that when a specimen taken from a general paralytic was employed the protein contained therein exercised no protective action upon the gold solution - precipitation occurred. He investigated further and found (a) that normal cerebro-spinal fluid gave no precipitation (b) that different and characteristic types of protection were afforded by fluids from cases of General Paralysis, tabes and meningitis. He showed in the form of a graph the varying degrees of precipitation which were got when 1 cc. of spinal fluid of progressive dilutions was added to 5 ccs of gold solution. Ten tubes of Goldsol were taken and to each cerebro-spinal fluid in strengths of from 1 in 10 to 1 in 10,000 was added. In cases of paresis complete precipitation was found in the first 5 or 6 tubes but this became rapidly less marked in the higher dilutions. With tabetic fluids decolorisation was very incomplete in the first two tubes but was much more noticeable in the 3rd and 4th, then fading out. In meningitis precipitation was found even further along in the series and was most seen among the highest dilutions.

His observations were confirmed by other workers, particularly by Miller, Brush, Hammers and Felton,[18] and it was obvious that a test for neuro-syphilis of great significance had been evolved. At first it was thought to be a certain

method for the diagnosis of general paralysis but later work has shown that the so-called "paretic curve" may be got in cases of cerebral syphilis, and, very rarely, in disseminated sclerosis. In spite of this, however, its value is great and the German school, as typified in Nonne, soon added the Lange Colloidal Gold reaction to their well-known "four reactions" for syphilis of the nervous system.

Pressure.

In concluding this seriatim review of spinal-fluid tests for General Paralysis one must mention that the fluid is usually under increased pressure - about 200 mm water or more. As this is also found in a number of non-specific affections of the central nervous system, however, its importance as a symptom in lues is rendered considerably less important.

Having made a survey of the most important liquor tests required before a diagnosis of paresis can be made, it is well to estimate how much reliance can be placed upon a diagnosis so reached.

It will be noted that in no case has it been possible to single out one test or reaction as being unmistakeably typical of the disease. Thus we see that, although a positive Wassermann reaction is essential, it is also got in all other forms of neuro-syphilis, and in addition it is encountered,

though in very rare instances, in non-specific affections like scarletina.

Also Lange's "paretic curve", while present in practically all cases of paresis, may occur nevertheless in other conditions in a very small number of cases.

Increased protein content in which a relatively large amount of globulin is present certainly is strongly suspicious but by no means pathognomonic; and a lymphocytosis also is not confined to paretic fluids.

It is when all these factors are present together in one specimen of cerebro-spinal fluid that the evidence in favour of a positive diagnosis is particularly weighty.

One is well aware that exceptions even to this are recorded in the literature, but the fact remains that one can afford to be more dogmatic in this matter than in almost anything else in the realm of medicine. If the spinal fluid of any patient has a strongly positive Wassermann reaction, shows a pleocytosis consisting mainly of large and small lymphocytes, has a definitely increased globulin content, and give a typical "paretic curve" with the Goldsol test then that patient suffers from General Paralysis.

When these liquor findings are supported by clinical evidence then the diagnosis becomes a practical certainty. The cases in which considerable doubt may arise are those

where one or two of the reactions mentioned are incomplete or otherwise unconvincing.

MALARIA THERAPY.

Several theories have been put forward to explain why therapeutic malaria has had such striking results in the treatment of General Paralysis, and while no particular one of these is completely satisfying it would seem possible that a combination of some of them would adequately cover the ground.

(a) What is perhaps the most ingenious of these is based upon the fact that the Spirochaete is a mesodermal parasite. As such it lives primarily in the walls of the cerebral blood-vessels but tends to migrate into the surrounding nervous tissue. This being ectodermal the parasite dies, and its toxins thus reach the ganglion cells and other structures of the parenchyma. Nature attempts to prevent this by an over-growth of neuroglia, but without success.

Malaria, however, causes a great increase of the glia surrounding the vessel walls, and when the spirochaetes make their way out they die as before but in this case they are unable to pass the glial barrier, and their toxins, failing to reach the nervous tissue, are re-absorbed by the vessels.

Attractive though this explanation is, it is nevertheless probable that it contains less of the truth than the two following. These are each more in the nature of highly important and closely associated factors than of isolated theories.

(b) In this hypothesis the high temperature is held to be the direct cause of spirochaete destruction in the central nervous system. It is quite undoubted, as I shall show later in this paper, that more successful results follow therapeutic malaria in which the patient has had long fevers with very high temperatures, rather than in cases where only poor malarial reactions have taken place. On the other hand it must be admitted that although the pyrexia may be of prime importance, it cannot be the only agency at work. Otherwise several other febrile diseases would prove equally valuable. Of these one need only mention Relapsing Fever, in which not only are high and prolonged rises of temperature produced, but in addition this is effected by an organism - the Spirochaete Duttoni - which has biological characters very similar to those of the Spirochaete Pallida. One would expect therefore that the results from therapeutically induced Relapsing Fever would be much superior to those from malaria. This is not so however.

(c) It is held by some that as a result of the malarial

attacks antibodies are formed which confer upon the patient an immunity against plasmodia of the malarial and spirochaetal types.

It is almost certain that this factor is operative but again one would expect Relapsing Fever to be much superior as an agent for inducing this immunity.

(d) In the Wagner Jauregg clinic they consider that malaria achieves its effects through a generalised activation of the bodywith a resulting increase of resistance. The series of infective pyrexiae causes a succession of strong stimuli to all the elements of the human body which combat disease. Lymph and blood systems are activated, antibodies are formed, and the human organism which had fallen asleep unresistingly under the syphilisation of years re-awakens.

This is one of the reasons why the Vienna school advocate so strongly the institution of active specific treatment after malaria, but deprecate it before.

Methods of Inoculation.

While at the Wagner Jauregg clinic I had the privilege of observing the inoculation of paretics with a malarial strain which has been used continuously since September 1919. At this clinic the original infection was got from a natural case, of Benign Tertian Malaria and it has now made about 200 passages through human hosts.

At the Retreat we have inoculated nearly all our cases

with infected blood kindly supplied to us by the Whittingham Mental Hospital. This strain of Benign Tertian, known as W.1., was started in 1922. A few months ago (in 1928) it was purposely allowed to die out after making 100 passages.

The following are the methods of inoculation in use: in all but the last of these the infection is transmitted by blood from a human host to the patent.

1. Subcutaneous. About 2 ccs of infected blood are infected under the skin in the subscapular region. The exact amount used is immaterial. At first itwas thought to be an advantage to scarify the underlying tissues with the point of the needle when making the injection, but this is unnecessary.

2. Intravenous. The blood is injected into the median basilic or other suitable vein. By this method the Incubation Period is usually shortened by a day or two. There are circumstances where this may be of importance.

3. Intracutaneous. At times patients travel "from a far country" in order to be inoculated and it is then necessary to infect them in such a way that the malarial Incubation Period is considerably lengthened. They will thus have time to return home before rigors begin.

   In such cases the Intracutaneous method is used. A single drop of blood is carefully injected into the skin tissues. Malaria will then not develop for from 28 to 40 days.

4. By Mosquito. In Britain many inoculations have been effected by allowing infected mosquitoes to feed upon the subject.

The special department of the Ministry of Health which maintains a supply of mosquitoes will send a few on application to any Hospital which requires them. They are brought

in small glass jars whose open tops are covered with gauze of fairly wide mesh. The skin of the patient's thigh is gently warmed with a hot water bottle and then the mouth of the jar is applied to it. The mosquitoes feed through the gauze. and the jar is removed when several are seen to be gorged. This method seldom fails.

It has several disadvantages, however, and in Vienna this procedure is never carried out.

Mosquitoes do not make good travellers and many die in transit. Their maintenance is a matter of expense and difficulty, and, as they have to be conveyed to Hospitals by a doctor specially detailed for the work, long delays may occur before they can be sent.

Methods of preserving and sending Malarial Blood.

There are but few centres in any country where there is always a sufficient number of General Paralytics under treatment to ensure a constant supply of malarial blood. Considerable attention has therefore been given to the question of how long the blood can be kept active, and how best to send it to different parts of the country.

The method which is most usually employed is to mix the blood with an equal amount of ½% Sodium Citrate solution. The simplest way to do this is to put 5ccs of citrate solution in a syringe, withdraw 5 ccs of blood from the donor into the same syringe, and then put the mixture in a test-

tube. This can then be sent away, packed in ice in a thermos flask, and the blood will remain active for 10 hours or more.

In cases where the blood has to be kept for a longer period Gelatine has proved to be a suitable medium. On account of a possibility of contamination with Tetanus the gelatine used shouldbe quite sterile. It must be melted at a temperature of 33°C and to 10 ccs of the fluid are added about 2 ccs of blood. In a few minutes the mixture becomes solid and it can be sent for long distances in this condition. On arrival it must be melted again and injected into the subject. At the Wagner Jauregg clinic malarial blood preserved in this manner has remained active for five days.

Selection of Cases.

In making use of malaria therapy one cannot afford to ignore the fact that patients, already suffering from a grave disorder, are being subjected to an additional illness of considerable severity. Almost every case of induced malaria shows at some period of its course signs of exhaustion and prostration.

On the other hand one cannot but view with amazement, firstly, the endurance which the great majority of paretics show during successive bouts of fever with a temperature of 105°F and over, and, secondly, the almost miraculous recuperation that

sets in immediately the infection is cut short by quinine.

Early cases in fair general health are of course ideal subjects, both with regard to their tolerance of malaria, and to their prospects of recovery from paresis.

More advanced cases are liable to exhibit alarming symptoms during their pyrexia, and usually they cannot be expected to make a complete clinical and serological recovery after it. Such cases often improve to a considerable extent as a result of the treatment and then remain stationary for an indefinite period.

It is inadvisable to inoculate paretics in the late stages of their disease. The risks attending such a course are very great, and, at the best one cannot hope to repair the gross damage which has already been done to the central nervous system. If they survive treatment they may live with arrested symptoms for a long period before succumbing to some intercurrent disorder.

Obese patients do not stand malaria well, and their progress must be watched with care in order that the rigors may be stopped if collapse is threatened. These cases do not seem to have the same resisting or recuperative powers as others, and they often show this with specific treatment also.

Paretics with cardio-vascular disorders should be treated with caution, but many of them go through it surprising

ly well. Thus one finds that pronounced mitral stenosis, cardiac irregularity, tachycardia, or myocarditis may contra-indicate immediate treatment, while mitral or aortic incompetence do not. In the former cases cardiac medication should be instituted before the malaria is given.

Renal cases and those with signs of disturbed liver function have not got a good prognosis. These are specially liable to develop into that exceedingly interesting but hopeless group - the Paranoid-Hallucinated Paralytics - to which I shall refer later.

From my own results, and from a study of the observations of others I have come to the conclusion that the best prognosis qua General Paralysis is to be got in early, expansive cases, even if they are of so marked a degree as to be noisy, violent, and excessively grandiose.

The Malarial Course and its Management.

After inoculation there is an Incubation Period, followed by a series of rigors or chills which are ultimately cut short by the exhibition of quinine. There is a rapid convalescence, and the malaria treatment per se terminates. The ensuing period is devoted to the observation of results, and to the institution of specific treatment. In most cases the patients should be seen at least every six months for several years, particular attention being devoted to examination of the cerebro-spinal fluid.

The Incubation Period[19] varies greatly. It may be from 5 to 32 days long. As a rule it is shorter in summer than in winter, in bed patients rather than in those who are going about. Intravenous inoculation also shortens it. In addition it has been shown by Dattner[20] that the length of the incubation period, and indeed, the whole course of therapeutic malaria is largely dependent upon the personal reaction of each patient to the infection. He inoculated two patients at the same time, from the same specimen of blood, kept them under identical conditions, and found that throughout each stage of their illness they showed definite differences from each other.

During the Incubation Period I have often permitted patients to remain out of bed, but have kept a careful watch upon the temperature. This procedure is followed in most hospitals; indeed, in Vienna, many paretics with but slight mental symptoms come to the Wagner Jauregg clinic for inoculation, go straight home, and return to the clinic after their firstrise of temperature. In some institutions, however, the patients are kept in bed during the whole incubation period. This is done at Horton Hospital, and the reasons given by W.D. Nicol[21] in favour of this practice are valid ones. He points out that warmth favours the development of the infection, that rest in bed tends to prevent the usual non-specific rises of temperature associated with General Paralysis, and that the

danger of intercurrent illness or serious accident complicating the issue is reduced to a minimum.

In a majority of cases the incubation period ends between the 8th and 10th days after inoculation - earlier in Austria. The pyrexial stage then starts. For three or four days the temperature climbs up rather irregularly, malarial parasites appear in the blood, and rapidly increase in number. Shivering is uncommon in these first days, but soon the temperature adopts the characteristic swing, and is then accompanied by rigors. The range of temperature increases with each rise for about the first four and then settles to a fairly steady limit of about 96.6° to 105°F. In ordinary circumstances one endeavours to allow 8 to 12 rigors to occur before terminating the infection.

When the chills are well establised they are very characteristic - as the temperature climbs rapidly the patient's shivering is often enough to shake the bed; he looks grey or livid, but although his expression is an anxious one he very often is not much troubled mentally by his experience.

He then becomes flushed, and his skin is burning to the touch. Profuse perspiration sets in and the temperature falls fairly rapidly. As the pyrexiæ succeed each other they tend to last longer and the patient gets progressively thinner and looks weaker. When one considers the rapidity with which patients "pick up" after the course one is forced

to the conclusion that this weakness is more apparent than real.

The temperature should be taken at least every half-hour during the rise and until the fall is established. Whem 105° F is reached tepid sponging is necessary. This has usually to be repeated several times during each bout. One should remember however the great value of high, prolonged temperatures and refrain from sponging unduly.

During the sweating stage the patient should be well covered, and be given plenty of water to drink. He feels much better afterwards if he sweats profusely. An Italian observer discovered experimentally that the perspiration from malarial tabetics is much more toxic to mice than is normal perspiration. It has been noticed that cases which do not sweat readily never do satisfactorily. They tend to collapse, and on that account the malaria usually has to be stopped prematurely.

As a rule one watches cases rather anxiously after the 7th or 8th rigors as they look so ill during the chills. It must be remembered however that a case rarely dies at these periods. The dangerous time is just after each rise, when there is a drop in blood-pressure which may be alarmingly extensive. If there is reason for uneasiness regarding the blood-pressure quinine has to be given.

Cardiac cases may require stimulants like Strophanthus, Camphor and Digitalin during the rigor.

Vomiting may occur after the first or second rise without causing undue alarm, but if it comes later in the course im-

mediate stoppage is necessary.

Nicol considers that the earliest suggestion of jaundice indicates that the fever should be terminated, but Dattner thinks that a little does not matter.

Delirium is common during malarial treatment but I have noticed that cases in which hallucinosis is marked and persistent rarely do well.

Although Benign Tertian is the type of organism which is always injected the majority of cases run a quotidian course throughout. Other irregular charts may be got, however, though much less frequently. Thus, among cases at Whittingham, J.D.Silverston has noted the following variations:-

a. Pure quotidian throughout.
b. Pure tertian throughout.
c. Initial 3 or 4 Quotidian, the remainder Tertian.
d. Initial 2 or 3 Tertian, the remainder Quotidian.
e. Continuous temp. for 3, the rest Quotidian or Tertian.

Interruption of the Course.

In cases that develop dangerous symptoms during the course the fever may be temporarily interrupted by giving one dose, or if necessary, two doses of Quinine gr V. The fever usually stops for about 10 to 14 days and then recommences, though in a milder form and with a Tertian type.

Should its return be delayed one can usually provoke a recurrence by injections such as milk, nuclein, phlogetan, tuberculin, or even by a cold bath. The Austrian school usually employ Typhoid Vaccine (25 millions).

Termination of the Course.

This is promptly and effectively done in every case by giving Quinine gr X t.d.s. for about four days, by which time parasites have disappeared from the blood. The administration should be started immediately after a bout of fever, because the quinine cannot stop "a chill" once the temperature has begun to rise. There is often a slight rise on the 2nd day accompanied by a slight feeling of malaria, but almost invariably the patient feels bright and fresh by the 3rd day. He is thin and anaemic however, and almost invariably has a herpetic eruption about the mouth.

Convalescence is very rapid but fresh air, generous nourishing diet and tonics are strongly indicated.

Results of Treatment.

Driver, Gammel and Karnofsky[22] made a review of the results obtained by 36 observers in different parts of the world, and they found that malaria therapy produced full remissions in 27.5% of General Paralytics so treated. Incomplete remissions were got in a further 26.5%

In three years 191 cases were treated by the mental hospitals of the L.C.C., and complete remissions were obtained in 33.5%.

In point of fact one finds that when comparatively unselected paretics are considered, about a third of the cases make apparent clinical recoveries after malaria therapy alone.

If cases are selected, however, and only early and strong ones are included, and if the malarial course is followed up by judicious specific treatment then the percentage of remissions is considerably higher.

The degree of improvement which may be hoped for in any given case depends to a very large extent upon the history, upon the personal reaction of the patient to malaria, and upon the after-treatment.

Thus, to take the first of these criteria, it is of importance to note whether a case is an early paretic or an advanced one. In those whose clinical history extends over less than 18 months the prognosis for a complete remission is good. Malaria appears to have the power of stopping the active general paralytic process at almost any stage of the disease. But whereas this often leads to a disappearance of all symptoms in cases of short-standing, nothing more than a state of arrest can be expected in later ones. In the Wagner Jauregg clinic I saw cases who had received treatment eight and nine years ago, and who were still stationary. Cure could not be hoped for in such as these on account of the grossly impaired state of the central nervous system.

The patient's type of reaction to malaria has also considerable prognostic significance.

In the course of the last few years one gradually became impressed with the fact that those patients, whose malaria

was severe but well-borne, tended to provide most instances of satisfactory remissions. Dattner[23] has made an investigation of this feature and has clearly demonstrated a relationship between the amount of fever experienced and the prognosis. He divided 150 treated cases into four classes according to the way they reacted to malaria. He studied the cases both with regard to the height of fever reached with each rigor, and with regard to the number of hours each rigor was sustained.

In the first class he placed those whose bouts were highest and longest, and then graduated the rest through the other classes down to the fourth, which contained defintiely poor reactors.

The following striking results were got:- of the 14 patients in Class 1 11 made complete remissioms, while out of 23 in Class 1V only 5 remitted.

Paranoid-Hallucinated-Paralytics.

While discussing prognosis in relation to patients' reactions while undergoing treatment I may with propriety draw attention to a type of general paralytic of some importance in this connection.

The first patient to whom I gave Malarial treatment in this Hospital was a man with the classical type of mental symptoms. He was elated, grandiose, excited and facile. During treatment however he became very hallucinated, imagined

that electric wires were connected under his bed, and that he was being persecuted by a man called John, under the floor, whose voice he could hear, and with whom he conversed day and night.

When the malaria was stopped these mental symptoms remained, and it was found that his former old-fashioned paretic characteristics had quite gone. He was neither grandiose nor elated, he was simply paranoid and hallucinated. He was suspicious and he took all the fantastic precautions usually associated with hallucinated paranoiacs.

Here, it might be argued, was a case upon whose characteristic general paralysis, had been superimposed malaria, and mirabile dictu the result was paraphrenia! Certainly, apart from the physical signs, and the strongly positive spinal fluid one might call it that.

This opens up a field of speculation upon what one might call "the universality of mental symptoms." There would appear to be a large but fixed currency of possible symptoms of mental abnormality, and although certain disorders usually draw upon selected groups of these symptoms, nevertheless these same disorders may at times bring forward symptoms not usually supposed to be in their province at all.

Thus practically any mental symptom may be associated with any mental disorder.

One would like to know what factors there were in this

alliance - or antagonism - between general paralysis and malaria which resulted in a paraphrenic state.

Upon enquiry I found that other observers, who had usually not commented upon the fact, had seen isolated cases after malaria with almost identical symptoms of hallucinosis and persecution.

In addition it must also be noted that similar cases were collected and described by Plant and Jacob in so-called non-progressive paretics, some years before the introduction of malaria therapy.

In 1924 investigation was made in Vienna regarding 41 of these Paranoid-Hallucinated Paralytics, all of which had matured after malaria therapy.

It was demonstrated that the prognosis in such cases was bad. Of the 41, no less than 22 died, 15 were in asylums and only 4 were at home. Although Dattner is of the opinion that malaria is not responsible for this change in the mental picture, I think this is open to considerable doubt, and that malaria therapy and, possibly, the exhibition of salvarsan may cause it in paretics who have cardio-vascular disorder and deficient liver function.

It is certainly a fact that in the paretics I have seen treated, those who showed really marked hallucinosis during their course of malaria have all done badly.

EFFECT of MALARIA THERAPY upon
the CEREBRO-SPINAL FLUID.

Almost without exception one finds some improvement in the cerebro-spinal fluid reactions after a malarial course.

In this connection it is interesting to remember that, following any syphilitic involvement of the fluid, morbid reactions appear in the following order - lymphocytosis → globulin increase → W.R. and Gold Sol positive. After treatment in general paralysis the reverse order holds good. There is a rapid improvement in the cell count, then a decrease in the globulin, and then at a later period modification of the Wassermann and Goldsol reactions.

In one of the earliest papers in Britain, dealing with this branch of the subject Grant and Silverston (Lancet, 1924, I, 540) published their results obtained with 40 cases. As the times of the withdrawal of the fluids following the fever treatment varied from one day to thirteen months, their findings lacked the value which they would have had if all the examinations had been made at a fixed period, say four months, after treatment. Nevertheless they showed very well that chronological order mentioned above in which the improvements in the fluid follow each other. They found that the lymphocytes decreased in 91.9%, that the protein content became less in 49%, and that a combined improvement in the cellular content, the globulin, and the W.R. of the fluid occurred in 20.2% of all cases. There was an improvement in the gold sol reaction

in 20.3%.

There is no doubt that in most of the successful cases serological modification lags behind clinical improvement, so much so that, at first, Wagner Jauregg thought there was but little connection between them.

If a long view is taken, however, it is found that the two do correspond; given sufficient time well remitted cases will show a parallel alteration in the cerebro-spinal fluid, as the following very significant figures show (Klin Woch May 1928).

Of 129 paretics, treated at the Wagner Jauregg Clinic, whose history has been followed since 1922, 81 are still living.

In 1928 the C.S.F. was tested in 70 of these, i.e. 80% and they were divided into three groups thus

a. 36 who had Normal Findings in the C.S.F.

b. 27 who had Weakly Positive Findings in the C.S.F.

c. 7 who had Positive Findings in the C.S.F.

From Group a. 32 were at Home and 4 in Asylums.

" " b. 19 were at Home and 8 in Asylums.

" " c. 2 were at Home and 5 in Asylums.

I think these figures are conclusive. Besides showing that improved spinal fluid reactions accompany good remissions they provide a striking testimony to the efficacy of the modern treatment of general paralysis.

It must be stated, however, that these cases all received a course of Salvarsan after their malarial treatment, and it is of this that we must now speak.

Specific After-Treatment.

For a year or two after the introduction of Wagner Jauregg's therapy many observers contented themselves with giving malaria alone in order that later remedial efforts should not complicate the issue.

All their results, including my own, confirmed the fact that, without any after-treatment, malaria did produce good remissions in at least a quarter of the cases treated.

It was soon apparent, however, that when some form of Salvarsan course was added the proportion of remissions improved and their quality was better, especially with regard to the spinal fluid findings. We have seen that before this era the rôle of specific remedies in General Paralysis was a depressing one; but with the advent of malaria therapy they have come to play a highly important part in treatment.

It is necessary that such remedies should be given after the fever and not before.

Wagner Jauregg considers that not only is it better thus, but actually that preliminary arsenical medication is actively prejudicial. It is hard, perhaps, to follow the Vienna school entirely in all their views on this matter, but they certainly bring forward some startling facts against the pre-

mature exhibition of salvarsan in metalues (Wien, Klin, Woch, Jan. 1928).

They aver that salvarsan and its derivatives given during the latent period of syphilis may cause or at least precipitate the onset of general paralysis.

At the Wagner Jauregg Clinic the youngest paretic, with the shortest incubation period, had been the most vigorously treated; while the oldest, with an incubation period of 45 years, had received no treatment at all.

Of those who were untreated during latency 60% had full remissions, against 3% of treated cases.

Of the dead or progressive cases, 26% had been untreated, and 66% treated.

After the onset of paresis the duration of life appeared to be shorter among those who had had specific treatment in latency; for example three cases who died 2, 6 and 9 months after the onset of general paralysis had all had exceedingly energetic specific treatment.

In my view Wagner Jauregg and Dattner[23] stress this aspect of specific therapy unduly. It would seem likely that a majority of cases that have been vigorously treated during latency must have merited it because of the persistence in them of disquieting features - obstinate symptoms, markedly abnormal spinal fluids, and the like - and that all the pre-

ventative means employed have merely emphasised the fact that their malignancy had been apprehended from the beginning.

Apart from these interesting speculations, I think there is no doubt that every case treated by malaria should receive a course of arsenic shortly afterwards. The non-specific treatment having aroused the fighting forces of the whole body, and having rendered the spirochaetes more accessible and more vulnerable, they are thus much more open to successful attack by specific remedies.

As this general physical re-activation holds good for only a limited period, the series of arsenical injections should be started in about three weeks or one month.

In Vienna the best results follow a course of Tuberculin, Bismuth, and Neo Salvarsan.

Very shortly after malaria the patient receives bi-weekly injections of Koch's old tuberculin, starting with the minute dose of 1/1000 and working up to 1 cgm at the end of three or four months. In the 3rd or 4th week after the fevers, specific treatment in the form of Spirobismol(a Bismuth preparation) and Neo-Salvarsan is started. The latter is given until a total of 5 gms have been injected, no single dose exceeding .45gm. When the course stops no further treatment is given, and the patient's spinal fluid is examined every six months.

In 1922 Wagner Jauregg arranged 129 malarially treated

paretics into four groups according to their after-treatment (Klin.Woch May '28 P14)

Group 1 Received a Salvarsan course in daily small doses

" 11 Received No Salvarsan.

" 111 Received 6 Salvarsan injections in the ordinary way.

" IV Received Salvarsan course associated with Dercum's drainage.

In 1925 he found:-

Group 1 - 15 good remissions out of 30 cases.

" 11 - 8 good remissions out of 32 cases.

" 111 - 16 good remissions out of 33 cases.

" IV - 13 good remissions out of 34 cases.

By 1928 the figures were:-

Group 1 - 17 remissions out of 30.

" 11 - 11 remissions out of 32.

" 111 - 17 remissions out of 33.

" IV - 12 remissions out of 34.

This shows that the best results are got when the salvarsan course is given in small daily doses, but that an ordinary series of 6 injections, while being more convenient, is only a little less effective.

Dercum's procedure is ingenious but this investigation shows that it has none of the advantages which were hoped for it. His idea was that before giving the salvarsan intravenously one should draw off 20 to 25 ccs of cerebro-

spinal fluid. He hoped that the secretion of fresh fluid, thus called forth, would be impregnated with arsenical material.

The figures quoted above show once again how superior are the results of malaria plus salvarsan, to those of malaria alone.

For several years Tryparsamide, in preference to Neo Salvarsan, has been used in Britain and America as a means of after-treatment. It can be given in conjunction with Bismuth and its results are encouraging. I usually prescribe nine intravenous injections - 2 of 1 grm, 2 of 2 grm, and 5 of 3 grm.

Mention of this drug has already been made in this Thesis (Page 21), and further information may be got from the observations of Davie[24] (J.M.S. April 1927), Brown and Martin,[25] Neymann and Singleton and Lees.[26]

NOTES on CASES.

Case 1. Male: Aet. 42 yrs: Commercial Traveller: married.

Admitted - 8th November, 1923.

History - For about four months prior to admission patient's mental attitude and behaviour gradually altered. From being a kind and indulgent man be became irritable, fault-finding and exacting.

Ten days before admission he had an attack of Influenza, and his gravely disordered mental state developed then. He became grandiose, garrulous, and foolish, spent money recklessly, and lost all insight.

He is said to have contracted Syphilis 15 years ago for which he had a course of pills.

On admission - He was in a highly exalted and restless state.

Pupils were equal, contracted, circular and reacted very sluggishly to light.

There was tremor of the tongue but no speech impairment. Deep reflexes were exaggerated.

Cerebro-spinal fluid - Wassermann + + +, globulin increased, Cells - 117 large and small lymphocytes per cmm. (Goldsol not done).

Inoculated at Whittingham Mental Hospital with 4 ccs of malarial blood (W.1. strain of Benign tertian) from a non-specific case.

Incubation Period - 6 days.

The chart shows the typical first stage of induction with climbing temperature. Then the second stage with the onset of bouts reaching 103°F or over, but with a Tertian pattern. Finally the third stage of quotidian rigors.

He had 10 rigors of 103°F or over before

quinine was given. It is of importance to note, however,(a) that the rigors were all short in duration, and were all well below 105° (b) that the patient became very hallucinated during the fever.

After the malaria the patient picked up very rapidly and showed considerable mental and physical improvement.

In two months he was given intrathecal injections of Neo kharsivanised serum.

I have already referred to this case in this Thesis (page 54). The hallucinosis which arose during the malaria became more marked and the patient finally showed all the mental characteristics of a case of paraphrenia.

Nearly two years after treatment his cerebro-spinal fluid gave strongly positive paretic reactions. In December 1927 - four years after - the result was much the same i.e.

Ross-Jones +	Colloidal Gamboge 222220
Pandys +	Wassermann + + +
Acetic Anhydride +	Cells-21 large and small
Lange's Gold Sol	lymphocytes
5555554321	per cmm.

He is now partially demented and very slowly progressive. The paraphrenic colouring has quite gone.

Case 2. Male: Aet 41 yrs: Farmer: Widower.

Admitted 1st May, 1922.

This case shows the striking effect of malaria upon a patient in whom the disease was very advanced. For 4½ years after treatment the mental and physical symptoms have been completely arrested and at a much higher level than they were before.

History. Patient showed mental symptoms of paresis for two years before certification became necessary, and on admission in 1922 he was found to be quite an advanced case.

He was boastful, excitable and emotionally unstable; he was grandiose and extravagant; his memory and judgement were much impaired.

Pupils were unequal and reacted sluggishly to light.

There was tremor of the lower facial muscles and tongue. The tendon reflexes were much exaggerated.

The Cerebro-spinal fluid on May 24th, 1922 showed increased globulin, 11·3 cells per cmm, and a strongly positive Wassermann reaction.

After admission his condition progressed rapidly. He became dull, apathetic and more enfeebled mentally.

In March 1923 he had a siezure with a resulting paresis of the left arm and leg. From then on he became more and more helpless and demented. Siezures got increasingly frequent until at the time of inoculation they were of almost daily occurrence. He was inarticulate, paralysed, and incontinent.

8th February, 1924. Inoculation with blood from Case 1. This was done principally to keep the malarial strain alive in the Hospital.

Incubation Period 10 days.

Chart showed 1st stage of invading temperature for 5 days and then typical quotidian rigors. Nine rigors over 103° were allowed, and the temperatures were satisfactorily high - 3 being up to 105·6°.

Shivering was not quite so marked as usual and the patient did not stand the course very well; he became very weak and had pronounced secondary anaemia.

He improved with wonderful speed and very soon was better mentally and physically than he had been for over a year.

Since the day after inoculation he has never had another siezure.

He is quietly grandiose and facile, but he can look after himself in most respects, and is able to

move about the ward with the help of the furniture.

Cerebro-spinal Fluid in 1927 indicates this "arrest" strikingly by its modification from the true paretic picture.

Ross Jones	Faintly +
Pandys	Faintly +
Acetic Anhydride	Negative
Lange Gold Sol 1112210000	= weak luetic curve
Colloidal Gamboge 112000	= weak luetic curve
Wassermann	+ +
Cells	4·3 large and small lymphocytes per cmm.

This is not now a general paralytic fluid, and the question of the Case being one of Cerebral-Syphilis might be debated. I am inclined to class it as a case of General Paralysis however.

Case 3. Female: aet 37 yrs: shop-assistant; married.

Admitted 12th February, 1924.

A case of unsuccessful treatment in a rather advanced paretic who reacted very poorly and inadequately to malaria.

There was a history of mental and physical deterioration for over two years before admission. From being clean, tidy and industrious she became dirty, careless and slovenly. She had had several attacks of "weakness" affecting the right side;

there had also been transient aphasia.

On admission one found her facile and mildly elated, with grave impairment of the general intelligence.

There were twitching movements of her face; her speech was very slurring; her tongue was trombone-like in its movements.

Deep reflexes were much exaggerated and her movements were inco-ordinated.

Cerebro-Spinal Fluid 20th February, 1924.

Ross Jones +

Pandys + +

Lange Gold Sol 55553210000 = Paretic Curve.

Colloidal Gamboge 222220 = Paretic Curve.

Wassermann + + +

Cells 77·6 large and small lymphocytes per cmm.

February 25th, 1924 Inoculated with 4 ccs malarial blood from Case 11.

Incubation Period 10 days.

Charts show 1st Stage of Induction with climbing temperature for 3 days.

2nd stage with Tertian tendency for 2 days.

3rd stage with Quotidian rises.

The patient reacted very poorly. Only three times did the temperature reach 103°. It was never over that figure. Parasites were particularly numerous in the blood.

The course was stopped after eight poor bouts as the patient's condition was unstaisfactory. Anaemia and exhaustion were prominent; she had epistaxis once, was very excited and hallucinated for two days and latterly was sick several times. Prompt administration of quinine was therefore indicated.

Results were very unsatisfactory.

She showed no real mental or physical improvement. During the following year there were two slight malarial recurrences. She has had several siezures.

Cerebro-spinal fluid. November 1927.

Ross Jones +

Pandy's +

Acetic Anhydride +

Lange Gold Sol 5555543210 = Paretic Curve

Colloidal Camboge 222220 = Paretic Curve

Wassermann Reaction + + +

Cells 176 Large and Small lymphocytes per cmm.

At the present time - 4 years after inoculation she is fat, partially demented and becoming more helpless.

Case 4. Male: Aet 50 yrs: Accountant: Married.
Admitted - 25th May, 1923.

An advanced case who died shortly after treatment.

In February 1924, when he was Inoculated the patient was in the late stage of General Paralysis. He was partially demented with vague grandiose delusions and was wet and dirty in his habits.

He was a noticeably poor reactor, and the malaria was cut short after he had had eight rigors of 102° or over. The highest temperature recorded was 104·6°.

His pulse was poor throughout the fever, and he was weak and debilitated at the end of it, though considerably more alert mentally.

A week after the malaria had been stopped he developed serious vomiting for two days.

His state became progressively worse, and he died on March 27th, 1924.

Case 5. Male: Aet 45 yrs: wholesale Grocer: Married.
Admitted 17th September, 1924.

A case showing an excellent and prolonged remission in an early paretic with expansive mental symptoms.

The patient had been elated, grandiose and irrational for two months before admission.

Pupils were contracted and had a very sluggish light reflex.

The tendon reflexes were much exaggerated.

Cerebro-Spinal Fluid-examined before admission - showed increased globulin; typical paretic curves with the Goldsol and Colloidal Gamboge tests; strongly positive Wassermann Reaction; lymphocytosis.

14th October 1924 - Inoculated with W.l. strain of Benign Tertian malaria.

Incubation Period - 7 days.

The patient reacted well but the charts were irrugular and atypical.

He had eight rigors of 103° and over, the highest being 105.2°.

Several bouts were unusually prolonged, however, the temperature not going below normal for as long as 48 hours at a time.

He stood the treatment very well, and improved physically and mentally with great rapidity after it.

On December 2nd, 1924 - one month after the exhibition of quinine his Cerebro-Spinal Fluid was found to be modified i.e.

Ross Jones +

Pandy's +

Lange Gold Sol 5443210000

Colloidal Gamboge 222210

Wassermann Reaction - Positive.

Cells 5.6 large and small lymphocytes per cmm.

On December 8th he had a malarial relapse, and, very unusually it was not abortive.

He was allowed seven more rigors of 103° or over before quinine was given.

His mental and physical state was remarkably good after it and he was discharged on January 1st, 1925, in a state of remission.

Cerebro-Spinal Fluid - January 7th, 1925 - a month after preceding report:-

Ross Jones +

Pandy's +

Lange's Gold Sol 5542210000

Colloidal Gamboge 221000

Wassermann Reaction-Positive

Cells 4 lymphocytes per cmm.

The patient returned to his home in Paris where he has successfully carried on a wholesale grocery business ever since.

He received a course of specific treatment at home but we have not been able to obtain from him any data regarding the present state of his cerebro-Spinal Fluid.

In April 1927 - more than two years after leaving the Retreat he writes thus:-

> "I am glad to say that I am quite well, and "after a short treatment of six months with my "doctor my blood was negative. I am doing "my affairs as usual, but am not worrying as "our business is now progressing very satis- "factorily, I am naturally taking care of "myself, and I might say that I never felt "better."

Remarks ;

(a) A good remission in a very early case with grandiose symptoms, after a very atypical fever course, but one in which reaction was good.

(b) A malarial relapse which did not abort as usual after 3 or 4 rigors.

(c) Shows early modification of the Gold sol and Colloidal Gamboge curves in the C.S.F., also the rapid change in the cytology.

Case 6. Female: Aet 30 yrs: Medical Practitioner: Single.

Admitted 14th November, 1925.

An advanced case that had a good malarial course and improved greatly afterwards, but then relapsed.

This case has an interesting and tragic history, syphilis having probably been acquired innocently while the patient was a medical student.

Seven years before admission she had a large sluggish ulcer on her neck, also a rash which has appeared at intervals since.

In 1921 - four years before admission - she

became inclined to trip over her words when agitated. It was not until 1923, however, that some definite speech defect got obvious. Since then this had gradually increased. For two years she had occasional tremor of the right hand.

In 1924 she tried to learn to drive a car, and was very difficult to teach - rather stupid. At times also she had ankle clonus when her foot was on the clutch.

In 1925 she collapsed and had transient stiffness of the right hand. Tremors and speech impairment became very marked.

She then became stupid, confused, delusional and possibly hallucinated.

The specific nature of her illness had not been suspected as several doctors had failed to find signs of organic disease of the nervous system.

In November 1925 her cerebro-spinal fluid was examined and was found to be positive for General Paralysis in all respects except the cell count.

On admission - she was found to have no insight, and although tremulous, ataxic and weak she boasted of her strength and power - said she had built the world and owned it all.

Speech defect was very pronounced and of the

typical paretic type. There was general ataxy and inco-ordination of voluntary movements, also some spastic weakness of the right side. Pupillary contraction to light was present, but badly maintained.

19th November, 1925. Inoculated with 4 ccs of citrated malarial blood (W.l.) sent by train from Whittingham.

Incubation period - 17 days.

Reaction to malaria was vigorous and the patient became very weak and debilitated.

On three occasions the temperature rose above 105^{0} and tepid sponging all night was necessary. Quinine was given after the 8th rigor as she looked so ill during each.

Afterwards she got on exceedingly well both mentally and physically; she studied the British Medical Journal, and was interested in her surroundings. Her speech defect become much less noticeable and her gait steadier.

Cerebro-Spinal Fluid 15th February, 1926.

Ross Jones	Faintly positive.
Pandy's	Positive.
Lange's Gold Sol	4443210000 = modified paretic curve.
Colloidal Gamboge	221000 = weak paretic curve.

Wassermann Reaction Positive.

Cells 2.6 lymphocytes.

She was discharged much improved on February 18th. 1926.

In August 1926 we received a letter from the patient which showed that her mental improvementcontinued.

From a report in August 1928, however, one finds that the remission was maintained for only one year. The patient then had attacks of depression, and became progressively enfeebled mentally and physically. Unsuccessful attempts to re-induce malaria were made by those in whose care she was.

She is now bed-ridden and dementing.

Case 7. Male: Aet 42 yrs: Cashier in Bank: Married. Admitted 20th November, 1925.

This is an interesting case of a tabo-paretic who received energetic specific treatment for over six years before he developed paresis. After malaria therapy he had a full remission which has been well maintained for over 2½ years.

He was infected with Syphilis in 1911, and he was treated with mercury and iodides.

In 1917 while on active service he had slight leg pains for the first time. He was three times

wounded after this, and on each occasion he was treated for rheumatism while he was in hospital.

In August 1919 tabes dorsalis was diagnosed and the following list shows how vigorous and enlightened was the specific treatment.he received.

1919 August to November	- 9 Intravenous injections of Galyl. Blood W.R. - Positive.
1920 November	- 11 Intravenous injections.
1921 January	- Blood W.R. - Negative.
November	- " " " - Positive.
1922 February	- 9 Intravenous injections.
March	- Blood W.R. - Negative.
September	- " " " - Positive

Three months on Iodides.

1923 January	- Blood W.R. Fairly strongly positive.
March/April	- 6 Intravenous and 6 Intrathecal injections
July	- Blood W.R. Very slightly positive.
October	- Blood W.R. - Positive.
November	- Blood W.R. Very slightly Positive.
Oct/December	- 3 Intravenous and 3 intrathecal injections.

Further treatment also in 1924 and 1925.

All this time he was carrying out his duties efficiently as Cashier in a Bank. For a few weeks before admission to the Retreat, however, he was extravagant, boastful, and full of rather ambitious schemes.

Suddenly he became violent and excited, and was finally admitted on an Urgency Order on November 20th, 1925.

He was silly, irrational and deluded - said he was going to take a flight round the world in order to start women's window-cleaning companies in every large town. He was often restless and violent.

He had Argyll-Robertson pupils; his speech was impaired; there was tremor of the lower facial muscles and tongue; knee-jerks and ankle-jerks were absent.

The Cerebro-Spinal Fluid showed:-

Increased globulin: Pleocytosis - 56 large and small lymphocytes per cmm: Positive Wassermann Reaction.

December 14th. 1925 - Inoculated with blood from Case 6.

Incubation Period - 10 days.

The patient reacted very satisfactorily, his final temperature beong 105.8°F. The course was stopped after 8 rigors.

During the malaria his lightning pains were very severe. Afterwards he was very weak, anaemic and amaciated. He was also in rather a septic state -

with faruncles in his nose and on his wrist, also a facial abscess

Within three weeks his condition had improved marvellously. He added a stone to his weight in a fortnight and was almost normal mentally.

Cerebro-Spinal Fluid - March 1926.

Ross-Jones +

Pandy's +

Lange Gold Sol 4443210000

Colloidal Gamboge 221000

Wassermann Reaction - Positive (+, ½, o)

Cells 2.3 lymphocytes.

This demonstrates a rapid disappearance of the lymphacytosis, also modified paretic curves with the Gold Sol and Gamboge tests.

The patient left the hospital in March 1926 with a good remission. He returned to his work at the Bank, and has done it faithfully and well for 2½ years, during which time his salary has twice been raised.

I examined this patient in September 1928 and found him quite normal mentally: the usual signs and symptoms of tabes were present.

Cerebro-Spinal Fluid - Sept: 1928.

Ross-Jones Negative

Pandy's Negative

Lange Gold Sol 1110000000

Colloidal Gamboge 100000

Wassermann Reaction Negative

Cells 2.6 Lymphocytes.

Remarks. This case forms a remarkable commentary upon the failure of specific treatment to prevent the onset of General Paralysis. It shows, however, a full remission with practically normal C.S.F.

Case 8. Male: Aet 41 yrs: Spirit-taster: Married. Admitted 3rd July, 1926.

A case in which hallucinosis was a very prominent feature of the fever course, and in which the prognosis is unsatisfactory.

The patient had shown mental symptoms for 3 months before admission - he became reckless, extravagant and boastful. Speech impairment developed rapidly. He had no alcoholic tendencies - pace his occupation!

On admission. He was elated, restless, and, at times, violent; memory and judgement were very defective; he had no hallucinations.

There was marked tremor of the lips and tongue - speech was very slurring. The pupils reacted sluggishly to light.

Cerebro-Spinal Fluid 7th July, 1926.

Ross-Jones +

Pandy's +

Acetic Anhydride + +

Lange Gold Sol 5555543210 = Paretic Curve.

Colloidal Gamboge 222110 - Paretic Curve.

Wassermann Reaction + + +

Cells 4 4 lymphocytes per cmm.

4th August 1926, Inoculated by means of mosquitoes brought by Dr. Morgan from the Ministry of Health.

Incubation Period - 13 days.

His chart shows pseudo-tertian rises for the first week of fever, and quotidian thereafter.

During his course the most notable feature was the development of pronounced hallucinosis and delusion. He became morose and difficult as a result. He had 10 rigors - the highest being 105·8°, but the majority were much below this.

After treatment, although his physical state improved greatly, he continued to have constant hallucinations of sight and sound accompanied by ideas of persecution.

He was transferred to another Hospital in November 1926.

Report from Dr. M.A.Archdale, Sept. 1928

states that the patient remained hallucinated and delusional for some months.

In January, 1927, he received 5 weekly intravenous injections of Tryparsamide gm 2. He gradually improved and went home in June, 1928. In September, 1928, the patient's wife states "he is much improved in all ways; he is just like he was before he took ill." This is a good result in one who was so hallucinated, but I fear that even yet the prognosis may not be very good and that a relapse may occur.

Case 9. Male: Aet 38 yrs: Master Baker: Married.
Admitted 17th November 1926.

An interesting case of a depressed paretic who became hallucinated and frenzied during fever treatment, who remained in a semi-paranoid state for 18 months, and who is how at home enjoying a fair remission of mental symptoms.

The patient had been an excellent baker and organiser of his own and his father's business, but for nearly two years before admission he gradually became less inclined for work and less competent. For the last two months of this time he was definitely melancholic and slept badly.

There was a history of syphilis (well treated).

Two years ago he suffered from severe headaches and pains in the legs.

On admission. He was retarded, depressed and dispairing - but pleasant and anxious to co-operate.

On the physical side the only signs that might be indicative of general paralysis were slight tremor of the tongue, and marked exaggeration of the tendon reflexes. (The ankle-jerks were well present.)

Cerebro-Spinal Fluid.

Ross-Jones +

Pandy's +

Lange Gold Sol 5555543210

Acetic Anhydride Negative.

Wassermann R. +++

Braun Husler +

Cells 27·3 lymphocytes per cmm.

A definitely paretic fluid.

Inoculated with 2 ccs - citrated blood (W.1. Strain)

Incubation Period - 13 days.

Immediately after the Incubation Period ended the temperature began to climb rapidly. He had a rigor almost daily - 103°: 104.2°: 104.8°: 105.8°: 105.8°. With each rigor he became wildly excited and hysterical. The last two rigors mentioned resisted tepid sponging and as the patient got so ex-

cessively violent the malaria was interrupted, after 6 rigors, by three doses of quinine gr 4 on successive days. This stopped the fevers and the parasites began to disappear from the peripheral circulation.

He was very depressed and complained of numerous distressing disorders of sensation - some of which resembled tabetic manifestations - pains in the legs, choking feelings in the throat and chest etc.

The malaria returned after an interval of 29 days, but on this occasion it had to be stopped definitely after 3 rigors on account of the patient's extraordinary reaction.

His outbursts of frenzied hysterical violence and terror were more extreme than I have seen in any mental case. At these times he shouted and screamed, said he was dying, and tried to damage himself in a most impulsive and determined manner.

He had had 9 rigors in all, and for a month after treatment his condition gave cause for considerable anxiety. He was much exhausted and still gave way to attacks of intense excitement.

After this he improved rapidly in his physical state, but as months went on he went through a succession of strange paranoid hallucinated phases accompanied by euphoria and facility.

He wrote copiously and foolishly but his writing was beautifully and accurately executed. Indeed at one period he used to write The Lord's Prayer neatly and distinctly upon a piece of paper the exact size of a threepenny bit!

In August 1928, however, there was a marked improvement in his mental state and he went home on leave. He was still inclined to be paranoid, hallucinated and a little facile, but he was quiet, agreeable and orderly in his conduct. His memory was excellent.

Remarks. The notable feature in this case was the extraordinary mental effect of the malarial treatment. The fevers were badly borne and it was thus impossible to give a really efficient course.

Although the patient has a fairly good remission and is fit for his work, one fears that the prognosis is not good, because of the part played by hallucinosis during and after treatment.

He is to be given a course of Tryparsamide while at home.

Case 10. Male: Aet 45 yrs: Mining Engineer: Married.

Admitted 9th July, 1927.

This is a most disappointing case. After malaria therapy the patient made a perfect mental remission for a few weeks. Then he gradually became hallucinated, but with full insight. This progressed,

however, until he got intensely delusional and delirious and finally died.

He was found to have early Optic Atrophy 2 years before admission; this was accompanied by exaggerated tendon reflexes, Negative blood W.R., but strongly positive liquor W.R.

He was vigorously treated with mercury and with sulpharsenol injections.

For a few weeks prior to admission, as his C.S.F. was found to be obviously paretic in reactions, he was again given a course of specific treatment. He altered mentally, however, became difficult to manage and came to The Retreat. On Admission He was then elated, happy and fatuous; his memory and judgement were gravely impaired.

He had Argyll Robertson pupils, slight speech defect, and very exaggerated deep reflexes.

Cerebro-Spinal Fluid. August 1927.

Ross-Jones +

Pandy's +

Acetic Anhydride +

Lange Gold Sol 5555432100 = Paretic Curve.

Colloidal Gamboge 222100 = Paretic Curve.

Wasserman Reaction + + +

Braun Huslar +

Cells 15 lymphocytes per cmm.

Inoculated with 2 ccs citrated blood (W.1.Streain)

Incubation Period - 19 days.

He reacted well and had 10 good rigors, almost pure Tertian in type. During the fever treatment he was grandiose, facile, restless, and rather markedly hallucinated.

After treatment he improved with great rapidity and in a month appeared to be perfectly sane, and rational.

The Cerebro-Spinal Fluid (8th November 1927) a fortnight after treatment showed abolition of the pleocytosis and modification of the protein reactions.

Ross-Jones Faintly +

Pandy's Faintly +

Lange Gold Sol 5555432100 = Paretic Curve

Colloidal Gamboge 222220 = Paretic

Wassermann Reaction + +

Cells 3.6 lymphocytes per cmm.

He then began to complain about noises in his right ear, and said that he heard everything repeated twice. He had good insight at first, but soon his thoughts also were repeated to him. The

hallucinatory state progressed and he got acutely miserable. He started repeating things constantly to himself, was desperate and confused, and rapidly fell back mentally and physically. He became delirious, and had outbursts of wild hysterical violence rather similar to those which characterised Case 9.

Congestion of the lung-bases developed and he died on 31st January, 1928.

Case 11. Male: Aet 35 yrs: Pork Butcher: Married.
Admitted 3rd November, 1927.

In this case general paralysis developed in spite of most energetic and sustained specific treatment in the latent period. The patent, an early, grandiose, and robust paretic, has made an excellent remission after malaria treatment. The History of his pre-paretic specific treatment is of great interest. The patient contracted syphilis in 1918 and was treated and pronounced cured after a negative Wassermann.

Five years later his wife, whom he had married in 1921, was found to have a positive Wassermann in the blood. The patient's blood was then discovered to be positive also.

For the next five years he was thoroughly treated with Novarsenobillon, mercury and potassi -

ùm iodide in repeated courses. During this time his blood Wassermann reaction fluctuated in the following interesting fashion:-

December,	1923	Positive
March,	1924	Negative
August,	"	Negative
December,	"	Doubtful in undiluted serum
February,	1925	" " " "
June,	"	Negative
September,	"	Weakly Positive (1 in 5)
December,	"	" " (1 in 6)
June,	1926	" " (1 in 4)
September,	"	Negative
January,	1927	Negative
April.	"	Doubtful
October,	"	Weakly Positive.

For a few months before admission he was rather strange in his manner at times, and in the last week or two this became very pronounced.

On admission - 3rd November, 1927. He was incessantly garrulous and elated, full of grandiose ideas, most irrational, and at times violent.

Pupils were sluggish in reaction in light.

The speech was slightly but quite unmistakeably slurring. Deep reflexes were exaggerated.

Cerebro-Spinal Fluid 8th November, 1927.

Ross-Jones +

Pandy's +

Acetic Anhydride +

Lange Gold Sol 5555543210

Colloidal Gamboge 222220

Wassermann Reaction + + +

Cells 152.6 lymphocytes per cmm.

A typical paretic fluid.

17th November, 1927 Inoculated with 2 ccs of citrated blood (W.1. strain).

Incubation Period 23 days (? effect of winter)

The rigors were almost pure tertian throughout. The reaction was strong at first, five fevers being well sustained over 104°F, four reaching 105°.

In the 3rd week, however, the temperature fell away remarkably and ranged between 100° and 102·4°.

During treatment the patient was exceedingly restless, noisy, destructive, and degraded in habits. His delusions of grandeur were remarkable. He stated his intention of swimming the Atlantic, but later qualified this by admitting that he would keep in the wake of a liner and thus get the benefit of the suction; he identified himself with the Deity, with Earl Haig, and with the author of this Thesis!

He also was hallucinated, but this was not a marked feature.

After treatment the patient improved both mentally and physically in a most striking manner.

He left the Hospital on 14th April, 1928 in a

state of remission.

Cerebro-Spinal Fluid - 14th March, 1928.

Ross-Jones +

Pandy's +

Acetic Anhydride ÷

Lange Gold Sol 444321000

Colloidal Gamboge 222210

Wassermann Reaction + ÷ ½

Cells 9.3 lymphocytes per cmm.

This shows great improvement in the cytology, a definite modification of the Gold Sol curve, and slight improvement in the W.R. - 4 months after treatment.

The patient was given a course of Tryparsamide after his return home and I examined him in September, 1928 (9 months after treatment) His remission was excellently maintained - he was quite normal mentally - and he was working well and happily.

Cerebro-Spinal Fluid, September, 1928.

Ross-Jones Faintly Positive

Pandy's Faintly Positive

Lange Gold Sol 4444320000

Colloidal Gamboge 210000

Wassermann R. +

Cells 4 large and small lymphocytes per cmm.

Remarks. A striking remission after malaria and Tryparsamide. The liquor appears gradually to be approaching normal

Case 12. Male: Aet 42 yrs: Cloth Merchant: Married.

Admitted 26th February, 1928.

A case with depressed symptoms who reacted very strongly to malaria and who has made an excellent remission.

History. Six months before admission patient got married: two months later he lost all his money. He became dull and depressed, and lost all initiative.

On admission. He was found to be exceedingly retarded, hesitant, dull and depressed. He was also rather facile and confused.

The pupils were unequal and showed an exceedingly sluggish light reflex. The deep reflexes were much exaggerated.

Cerebro-Spinal Fluid. March 2nd, 1928.

Ross-Jones +

Pandy's + +

Acetic Anhydride +

Lange Gold Sol 5555543210

Colloidal Gamboge 222220

Wassermann Reaction + + +

Cells 41 lymphocytes per cmm.

21st March, 1928, Inoculated with 2 ccs citrated blood (W.1. strain).

Incubation Period - 8 days.

The fever course in this case was a perfect one and well-borne.

The temperature showed well the initial irregular climbing stage for 5 days, with a tertian tendency, then a series of quotidian rises.

The patient was allowed 12 fevers of 103° or over, Nine of these were over 105°, the highest reaching 105.8°, and they were each well sustained in duration.

In this case as in all the others tepid sponging was carried out whenever the temperature was over 104°F.

The patient was quiet and orderly throughout. His depression, facility and retardation were always present, but during bouts he was mildly delirious and confused.

After treatment mental and physical recovery occurred quickly and the patient left the hospital on 21st May, 1928, in a state of full remission. While at home he was given a course of Tryparsamide.

He reported to me in September, 1928, - 5 months after treatment. He was in good health, and, al-

though a trifle talkative and euphoric, he was undoubtedly getting on very successfully in business once more.

Cerebro-Spinal Fluid - September, 1928.

Ross-Jones +

Pandy's +

Acetic Anhydride +

Lange Gold Sol 555432100

Colloidal Gamboge 222110

Wassermann Reaction + + +

Cells 4.3 large and small lymphocytes.

Remarks.

This case is taking quite a hopeful course. The liquor findings are in agreement with the fact that although there is a good mental remission it is not perfect. The protein reaction, the Gold sol and Gamboge reactions and the cell count are all becoming satisfactorily modified.

Observations upon the Series of Cases.

Of the 12 cases treated with Malaria -

4 ($33^{1}/3\%$) made good remissions.

3 (25%) were much improved.

3 (25%) were ultimately not improved.

2 ($16^{4}/6\%$) died.

While one is well aware of the impossibility of com-

piling reliable statistics when these are based upon insufficient data, it is nevertheless worthy of note that exactly one third of my cases had good remissions. This figure has been got very constantly by other observers when dealing with unselected cases. Were selection carried out then of course the proportion of remissions would be much higher.

Several in this series, for instance, had a hopeless prognosis from the beginning.

This is well shown by studying the cases with regard to the duration of their paretic symptoms before treatment.

Six of the cases I have described had shown symptoms of General Paralysis for six months or less before treatment, and all the full remissions took place in this group. This emphasises the need for early diagnosis and treatment.

One third of the cases developed paresis in spite of having received the best of specific treatment beforehand.

The Vienna school might venture to hint at propter rather than post hoc in this connection.

In the majority of reports and discussions upon the results of malaria therapy no reference is made to hallucinations and their signficance; and in no instance have I found comments upon the type of frenzied outburst with its strong hysterical colouring which occurred so strikingly in

one case in this series, and of which milder imitations were evident in several others.

I have seen somewhat similar attacks only in one or two cases of alcoholism, and in one case of cerebral tumour.

The presence of hallucinations of sight, hearing and visceral sensation , during and after treatment, was a prominent feature in four instances. Of these one died, one sank into dementia, and two have rather dubious partial remissions.

This bears out the contention that this symptom is of grave prognostic significance.

The Incubation Periods varied from 6 to 23 days, and there is no definite sign in this series of the period being longer in winter and shorter in summer. Indeed both the shortest and longest occurred in winter months.

The effect of therapy upon the Cerebro-Spinal fluid is of importance, but it is essential that in this matter observations must be carried out over a long period. It is only by taking this long view that one can estimate the effects of treatment, control the patient's recovery, and correlate the clinical and serological pictures.

Unfortunately, of the cases described in this thesis, the majority of the apparently successful ones have not been under observation long enough to warrant definite statements in the matter.

Nevertheless the fluid has been examined in all the cases, before and after treatment at least, and a periodical study of the fluid is being carried out in most of them.

In every instance where comparison has been possible there was some improvement in the fluid after malaria. Of the eight cases so examined the cell count was greatly modified or normal in all.

The protein reactions were modified in five.

The Gold Sol and Colloidal Gamboge tests were modified in four.

The Wassermann Reaction was modified in four.

In one instance (Case 7) the cerebro-spinal fluid is practically normal.

Specific after-treatment in for form of Tryparsamide has been given in half the cases, but as this has been done so recently in several of these, it is too early to attempt an assessment of its value.

It is an interesting fact that of the twelve cases described, eleven were married.

CONCLUSIONS.

1. The best method at our present disposal for the treatment of General Paralysis is by the induction of malaria, followed by some form of specific treatment, preferably

tryparsamide.

2. The prognosis for a complete remission is very much better in early cases than in more advanced ones.

3. Cases with remissions should be followed up for several years, examination of the cerebro-spinal fluid being made every six months.

4. It is now possible to venture upon a prognosis very soon after the malaria treatment has been completed. If a case has been of short duration, has had 8 to 12 lengthy rigors with high temperatures, and has not been markedly hallucinated, then it is probable that a good remission will result.

5. Specific treatment during the latent period of syphilis often does not give encouraging results, and in certain cases the use of therapeutic malaria in secondary syphilis would appear to be advisable. More success might then follow the subsequent administration of arsenical preparations.

6. Wagner Jauregg's use of malaria is a triumph for the biological method of approach in treatment, and for this reason one cannot accept this particular form of therapy as the final word in the treatment of general paralysis.

Undoubtedly the formation of anti-bodies, and the stimulation of the inherent defence mechanism of the organism play the greatest part in the efficacy of this

agent, and it is highly probable that before long it will be supplanted by immunising methods of greater precision, and capable of more accurate standardisation and application.

Finally I would pay tribute to the greatness of Wagner von Jauregg. While he is to be congratulated upon the happy outcome of his patient researches, he may also be envied for his good fortune in being able to claim that as a result of his efforts, general paralysis may now be banished from the list of maladies called "mortal".

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