UNIVERSITY OF GLASGOW

THE EVALUATION AND DIFFERENTIATION OF MENTAL DISORDERS ASSOCIATED WITH SYPHILIS OF THE NERVOUS SYSTEM

DONALD LACHLAN MACKENZIE, M.B., Ch.B., D.P.M.

A THESIS FOR THE DEGREE OF DOCTOR OF MEDICINE

MARCH 1950

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

CONTENTS

CONTENTS (Continued)

INTRODUCTION

(a) Historical

The earliest references to Syphilis of the Nervous System, in medical literature, appear as far back as the middle of the 16th Century, when Amatus Lusitanus described headache of syphilitic origin, and Botali observed that blindness might result from syphilis of the brain. During the following two hundred years many descriptions of a neuropathological nature are recorded, but one of the clearest descriptions of cerebral syphilis was that of Morgani, in 1761, who described gummata of the brain as well as pathological lesions in the smaller arteries. Almost a hundred years elapsed, however, before the knowledge of neurosyphilis was placed on a sound basis by the studies of Virchow (1847). Fournier, in 1876, expressed the view that Tabes Dorsalis was a disease which owed its origin to Syphilis, but it was not until 1894 that he propounded the doctrine that General Paralysis, like Tabes, was a consequence of Syphilis, and that they might properly be regarded as one disease affecting different parts of the nervous system. His views were, however, not

universally accepted until, in 1905, Schaudinn and Hoffman discovered the Spirochaeta Pallida, and, in the following year, Wasserman brought out his serum diagnosis. The final proof came seven years later, in 1913, when Noguchi demonstrated the Spirochaete in brain tissue.

The recognition of Syphilis, as a factor in the causation of mental disorders was, however, very scant until the latter half of the 19th Century, when the possibility of General Paralysis being luetic in origin was first raised. Until then, probably only Syphilomania (later classified with Syphilitic Insanity by Skae), held any ground. Shaw quotes Fournier as referring to a mental form, as one of his six forms of cerebral syphilis. This mental form he stated, existed in two varieties, the Depressive and the Expansive. In addition, he also described a Syphilitic Pseudo-General Paralysis, which he differentiated from 'real' General Paralysis under eight principle headings. Two of these headings are of great interest:-

> "The lesions differ--- in Syphilis, those of the meninges predominate, while in General Paralysis, those of the cortex".
>
> "Cure, possible in syphilis, is almost impossible in General Paralysis".

Here Fournier differentiates between a meningeal and a paranchymatous disorder, by means of either the pathological findings, or by the response to treatment. The inference being that to differentiate on clinical grounds is likely to be difficult. Folsom, on the other hand, in discussing syphilitic insanity stated...

> "there are no diagnostic marks to distinguish it from insanity not caused by syphilis, except in a certain proportion of cases of organic syphilitic disease of the brain".

General Paralysis, which, from the psychiatric point of view, is invariably considered the most common form of syphilitic mental disorder, was not universally recognised as being due to syphilis until the early part of this century. Nevertheless, Haslam, in 1798, unbeknowingly described a case which is now regarded as the first to be mentioned in the literature, and in a later part of the second edition of his book (1808) he drew attention to the frequent association of paralysis with insanity, and of mental feebleness with elation and feelings of well-being. Esquirol, in the beginning of the 19th Century, made several references to the disease, but it was left to Bayle in 1822 to recognise the disease as an entity, which he at that time called "Chronic Arachnitis". He separated it from other forms

of mental disorder, and claimed, from his observations, that there was a definite pathology as its basis, and that it was manifested in life by a recognisable set of mental and physical signs and symptoms. Four years later Calmeil published details about the disease and named it 'General Paralysis'.

In this country, literature on the subject is sparse during the first half of the century, but in 1858 Bucknill and Tuke published their manual of 'Psychological Medicine', and in it classified the various forms of insanity, all of which, they averred, could be 'complicated by General Paralysis or Epilepsy'. In the later edition, (1874), they defined General Paralysis as:-

> "A disorder marked by general and progressive loss of co-ordinating power over the muscles, especially those of speech and locomotion, combined with mental enfeeblement, always tending to dementia, and frequently characterised by a sense of well-being or actual delusions of an exalted character".

Maudsley, in his "Pathology of Mind" (1878) regards General Paralysis of the Insane as the most definite and satisfactory example of a clinical variety of mental disease. He attributes it to sexual excess, though he mentions, in passing, that some writers deem syphilis to

be the most frequent cause. He also describes varieties of General Paralysis which begin with, or are associated with, symptoms of Tabes Dorsalis.

From this time on, the question of the syphilitic origin of General Paralysis is met with frequently. Clouston, (1883), concludes his chapter on General Paralysis with the opinion,

> "I do not think there is any proof that it is syphilitic in origin".

Mickle (1886) was non-commital, while Folsom, in the same year stated that,

> "recent investigators find syphilis to be a part of the anticedent history of from one half to three quarters of the cases",

and that some writers

> "think that so large a proportion can be accounted for only by some specific relation between the two diseases".

Savage, in 1892, wrote,

> "Syphilis may produce mental disorder by causing loss or destruction of nerve tissue, such as organic dementia; it may cause sensory troubles leading to mental disorder; or it may cause disorder of nutrition and function, which may lead to ordinary insanity or epilepsy".

With regard to General Paralysis his view was

> ".... we consider syphilis is one of its most common causes. We believe it acts in different ways in different people, and affects different parts of the nervous system, but that its tendency is to start a process of degeneration, which ultimately produces the ruin we recognise as General Paralysis, and that it may play the sole, or only a partial cause".

Krafft-Ebing's experiment in 1897 went a long way towards the theory of "No Syphilis, no General Paralysis", but two years later Mott did not accept this dictum unconditionally. Bianchi, in 1904, in his chapter on General Paralysis, also wrote,

> "Numerous observations have clearly shown me that no difference exists, in any stage of the disease, either in symptomatology, or in course, between progressive paralysis arising from syphilis, and that from any other cause".

Kraepelin in his lectures on Clinical Psychiatry (1904), however, states....

> "The disease seems always to develop after syphilitic infection, ... and it must seem questionable if cases which have not been preceded by syphilis are really of the same kind as the bulk of those observed".

However, with the discovery of the Wasserman reaction in 1906, most authorities were finally agreed that syphilis was a necessary precursor of General Paralysis. Mainly owing to Mott's teaching, General Paralysis and Tabes Dorsalis, were still regarded as Parasyphilis, but this doctrine was finally abandoned when, in 1913, Noguchi and Moore discovered the spirochaete in the

brains from cases of General Paralysis.

(b) General Trends

From Haslam's time, until the introduction of the Wasserman reaction, the diagnosis of General Paralysis and "syphilitic insanities" had depended on clinical examination of the physical and mental states. As a result the descriptions of the disorders in the text-books of the period could not be surpassed for detail of signs and symptoms. Various types and stages were described, and prognosis was formulated accordingly. The prognosis in General Paralysis of the Insane was invariably given as fatal, and many writers went so far as to state that any cases classed as recovered must have been wrongly diagnosed. Syphilitic insanity and Syphilitic Pseudo-General Paralysis, on the other hand, were given a more favourable prognosis, due to several factors, but mainly because there was a possibility of curing the syphilis.

With the establishment of the relationship of General Paralysis to Syphilis, and especially with the

Wasserman reaction available as a diagnostic test, a tremendous change in the attitude towards General Paralysis took place, particularly in diagnosis. Many cases formerly not considered as General Paralysis, and not even classed as Syphilitic Insanity, were grouped under this label, while other cases, which would undoubtedly have been so classified, were eliminated by the Wasserman. This trend towards laboratory diagnosis was further emphasised in 1912 when Lange introduced his Colloidal Gold Reaction, with its differentiation of "Paretic", "Luetic", and "Meningeal" curves.

In 1910 Ehrlich and Hata had introduced the arsenobenzol compound known as "606", or Salvarsan, for the treatment of Syphilis, and together with Mercury, Bismuth, and Potassium Iodide, formed a promising therapeutic armament, which, not unnaturally, was enthusiastically and optimistically directed against a disease which had hitherto been deemed incurable. The results were disappointing and we find Mott declaring in 1914,

> "Candidly, I do not think any measure of success has attended any of the methods of treatment so far

employed for General Paralysis".

Nevertheless, strenuous efforts were being made, by investigators in many countries, to produce drugs of less toxicity and greater therapeutic power. The trend in relation to General Paralysis had now completely shifted to treatment, with the result that "a clinical picture accepted for nearly a century before laboratory tests were invoked in the diagnosis", (Brander), became neglected. The introduction of malarial therapy by Wagner-Jauregg in 1917, and of Tryparsamide in 1923 by Lorenz and Hodges, raised so much optimism that the diagnosis of General Paralysis became nearly as routine as the treatment. During the next few years the literature on the subject of the treatment of General Paralysis became so abundant, and claims of cure so frequent, that following a provocative paper, read by Brander at the Annual Meeting of the Royal Medico-Psychological Association in 1928, a special committee was appointed to discuss the entire subject. Despite this, or perhaps because of its non-committal findings, the tendency even to the present day, is to be dependent on laboratory findings, and to classify the majority of cases of Intracranial Neurosyphilis with mental symptoms,

as General Paralysis of the Insane. Even cases lacking the characteristic physical and/or mental symptoms are so designated and treated. The prodigious literature on General Paralysis is mainly concerned with new methods of laboratory investigation, or refinements in treatment. Only sketchy clinical descriptions of patients appear in papers, and in arriving at the diagnosis the emphasis is invariably on serological findings. Such, I feel, has been the trend during the 150 years since General Paralysis was first described - from a distinct clinical entity, such as was described by Haslam and Bayle, to a comprehensive group of conditions which have, by neglect, been lumped together under the original term of General Paralysis of the Insane. One might even say that the disease, isolated by Bayle and Calmeil from the mass of insanities, has, with the swing of the pendulum, and the passage of time, become once more obscured.

SECTION II.

OBSERVATIONS WHICH ACTUATED THE INVESTIGATIONS, AND STATEMENT OF THESIS

As a student, and so far as I am able to recall, my conception of cerebral syphilis as a mental disorder was General Paralysis, and the picture of this disease in my mind was of a grandiose, expansive, delusional state, accompanied by certain definite neurological and serological signs.

I had not been long in the Mental Hospital service, however, before I had noted that most of the cases diagnosed as General Paralysis did not conform to this type. Very rapidly I came to recognise that the mental picture varied in an exceedingly wide range, and that neurological signs also were by no means constant. Even serological findings showed differing results, but one almost constant feature was the Lange Colloidal Gold reaction - a paretic curve was, as far as I could judge at that time, invariable, and seemed to be the sign which clinched the diagnosis.

In reviewing a number of cases I noticed that, not infrequently, some had been diagnosed as Mania, Melancholia, Primary Dementia, Delusional, or Confusional Insanity, though within a short time this diagnosis was altered to conform to the serological picture. What impressed me most was that these cases had been diagnosed by very experienced Psychiatrists, and I was forced to the conclusion that without other methods of confirmation, the clinical picture must have been indistinguishable, on admission, from true states of Mania, Melancholia, and so on.

The question which thrust itself at me at this stage was, "Is it possible that many cases of mental disorder are lumped together as General Paralysis of the Insane merely because there is serological and/or neurological evidence of syphilis?"

I decided to collect details of all cases of General Paralysis admitted to the hospital over a definite period and to investigate and study them with three objectives in view. These objectives are the aims

of my thesis which is to prove....

(1) That General Paralysis of the Insane, as defined and described throughout the 19th Century, is still a recognisable entity, but, in modern times, a much rarer disease. Treatment may arrest the progress of the disease, but cure, in the true sense of the word, is not possible, because it is primarily a degenerative disease of the parenchyma.

(2) That many cases, designated as General Paralysis are, in fact, psychoses of a non-organic type, in which the neurosyphilis is not necessarily the precipitating agent, but in which, if not treated or inadequately treated, the effects of the neurosyphilis may eventually cloud the original disorder, by secondarily involving the parenchyma.

(3) That it would be advantageous to differentiate between General Paralysis and other Insanities with Neurosyphilis, and to classify the latter as, for example, Mania with neurosyphilis or Schizophrenia with neurosyphilis and so on, in order that treatment appropriate to the psychosis could be initiated, where indicated, in addition to antisyphilitic measures.

SECTION III.

METHOD ADOPTED TO ARRIVE AT CONCLUSIONS.

I propose to show that General Paralysis can be separated from other psychoses associated with neurosyphilis, by considering.....

(a) The mental states.

(b) The neuropathology of the conditions.

(c) The neurological signs.

(d) The serological findings.

(e) The response to treatment.

In so doing, I shall refer to the literature on the several subjects, and also to a series of 539 cases, admitted to the County Mental Hospital, Rainhill, Lancashire, between January 1925 and December 1938. This series, comprising 421 male and 118 female patients had all been classified, at one stage or another, as General Paralytics. The conclusions to be drawn from the study of such a series of cases have limitations:

(1) In nearly two-thirds of the cases I was dependent on the recorded observations of others, and, especially with neurological findings, this could lead to discrepancies.

(2) With few exceptions, the cases were certified prior to admission, and therefore, from the psychiatric point of view, might be considered well established.

(3) Previous histories were inadequate in most cases.

(4) There was no systematic follow-up scheme for the remissions in the series.

There are advantages, however, from the view point of my thesis:-

(1) All cases contained a mental statement in the form of the "7 day's notice" to the Board of Control which had, in practically every case, been made by the same reputable Psychiatrist.

(2) The same serological tests were used in all cases --- (Blood and c.s.f. Sigma Reactions; Colloidal Gold Reaction; Foam test; and Globulin estimation)--- and the readings assessed by the same technician.

The main results of my study of this series of cases are set out in tabulated and graphical form in the Appendix, whilst reference will be made in the text to these tables and graphs.

SECTION IV.

GENERAL OBSERVATIONS ON CASES

My case material consists of the 539 cases diagnosed at one stage or another while in hospital, as General Paralysis, and admitted to Rainhill Mental Hospital, Lancashire, during a period of 14 years. A detailed list of the annual admissions is contained in Table I (Page 148). Perusal of this table shows several points of general interest. The first striking feature is the incidence of such a diagnosis as between male and female patients. Though many more women than men were admitted to hospital, with all types of mental disorder, among those diagnosed as General Paralytics there were 22 more men than women admitted in an average year. The actual proportion of men to women was 4 : 1, which is in keeping with the generally accepted ratio in standard works during the past 40 years. The average annual percentage of male General Paralytics admitted was 11·9, a figure which indicates that this type of disorder plays by no means a minor role in the causation of insanity among the male population. As only 2·9 per centum of females admitted, in an average year, were given this diagnosis, the role, or possible role, of

syphilis as an aetiological factor would not appear to be so serious among women. From this table it will also be noted that though the actual number of cases of "General Paralysis" varied considerably from year to year, and in the sexes, the total percentage of these cases each year, varied within very narrow limits. This fact is, perhaps, better illustrated by Graphs I and II (Pages 149 and 150). The point is of special interest in view of the many opinions given that General Paralysis is less frequent in relation to other disorders than in former years. It is probable that these opinions were formulated on actual numbers of cases, and without reference to the total numbers of certified admissions.

Table II (Page 151) shows the actual numbers of cases, diagnosed as General Paralysis, who were admitted, discharged, and who died, each year throughout the period under review, and these figures are also presented in another form in Graph III. The latter shows very clearly the steady fall in actual numbers of admissions which, as already pointed out, could indicate erroneously, that the incidence of "General Paralysis" was on the wane. It is also important to consider this observation from

the point of view of the 'type' of mental state presented. Later in this thesis it will be contended that more than half the cases which had been diagnosed as General Paralysis should more correctly have been diagnosed as a fundamental reaction-type psychosis with neurosyphilis. In other words that Mania, Melancholia, Schizophrenia, and so on, existed in the presence of a neurosyphilitic infection, and that these mental disorders could, and almost certainly would, have arisen in the absence of syphilis. The fact that the diagnosis "General Paralysis" varied directly with the total certified admissions each year, would appear to support this contention, as no one has indicated that the fundamental disorders, such as schizophrenia or melancholia, are on the decline, though no doubt, the actual numbers vary directly with the total numbers admitted each year to hospital.

The numbers and percentages of patients admitted, and their progress while in hospital, are given in Tables III and IV (Page 153). All cases discharged, though not necessarily recovered, were considered, for the purpose of this investigation, to have shown improvement with treatment. Similarly those cases remaining in hospital

at the end of 1938 were looked upon as improved in the sense that treatment had arrested the neurosyphilitic disease process. Though not strictly accurate conclusions, the error must be so small as to be safely disregarded, and, in any case, it would be neutralised by those cases who did show arrest of the disease process, without mental improvement, but eventually died in hospital and were included in the deaths.

The improvement refers then to the beneficial effect of treatment on evidence of activity of the syphilis, as illustrated by those who were able to leave hospital and those still in hospital. On this basis, the tables show that improvement with treatment occurs more frequently among females than males and that the overall improvement rate in the series of cases is 38%. This figure is well within the limits given by most investigators.

When one studies the period of residence in hospital prior to discharge or death, it is found that the bulk of patients remained in hospital less than one year, and that more than 60% were discharged or died in less than 6 months. The patients who received treatment were the

only ones investigated from this aspect, and the results are shown in Graph IV (Page 154).

The ages of patients on admission were considered in order to determine if age could be a prognostic factor. It was found that age incidence varied little from that stated by authorities throughout the years, the vast majority of patients being aged between 36 and 55, and, that age on admission in males did not influence the prognosis to any extent. In females, however, though the numbers were relatively small, the prognosis was excellent in those under 35 years of age - 60% showing improvement. Graphs V and VI (Pages 155 and 156) illustrate these points.

In Table V the mental condition on admission of all patients is shown, and whether they died, were discharged, or remained in hospital. Though reference to this table will be made in later parts of the text, I feel it would be pertinent to mention a few points of general interest. The cases tabulated as unclassifiable include cases of Tabo-paresis, in which the paresis had supervened on a

diagnosed Tabes; cases of Juvenile Paralysis; of Congenital Defect; and one or two who died so soon after admission that a reliable assessment of the mental state could not be obtained.

The ratio between males and females in the combined first two groups - which I intend to prove are cases of Dementia Paralytica - is approximately 4 : 1. In the other groups it varies enormously. In the Manics it is nearly 1 : 1 ; in the Melancholics 2 : 1 ; in the Schizophrenics 2·5 : 1 ; and in the Paranoid states it is 15 : 1 . The significance, or otherwise, of these figures is not at all clear, but may have some bearing on prognosis. In these last four groups the rate of improvement, as indicated by discharges and those remaining in hospital, is 47%, as compared with only 29% in the other two groups, and an overall improvement rate of 38%. The group showing the highest degree of benefit from treatment is the Paranoid state in which the rate is 55%. Next in order are Mania 44%, Melancholia 43%, Schizophrenia 40%, Confusional state 32%, and lastly the Demented group, 24%. These figures and percentages are found in Tables VI - VIII (Pages 158 and 159).

The presence, or absence, of neurological signs was examined in order to decide if there were any group of signs which could differentiate between Dementia Paralytica and Meningo-vascular syphilis. No positive conclusions could be drawn from the analysis made. In 103 cases no neurological signs were elicited on examination on admission. Of these, 28 were of the Demented or Confused types, that is, 11% of the total cases in these groups. This compares with 74, or 27%, of the other groups. One case was unclassifiable. The 74 cases who showed no neurological signs with mental states of Mania, Melancholia, Paranoid states, and Schizophrenia, will later be shown to have been cases of Latent or Asymptomatic Neurosyphilis. The other cases showing these reaction-type psychoses, showed neurological signs varying from a slight to a marked degree, and the main changes are enumerated in Table XI (Page 161), while the results of the analysis of all cases, and whether discharged, in hospital, or dead, are shown in Tables IX and X (Page 160). A further investigation was made into the mental states on admission of all cases showing no neurological signs, but no significant conclusion could be drawn from the results, which may be

found in Tables XII - XIV (Pages 162 and 163). It will be noted, however, in Table XIV, that, while in Groups 1 and 2, the percentage improved with treatment, and showing no neurological signs, is less than half the percentage improved in all cases in these Groups. In the other Groups (3,4 and 5) the percentage of cases, improved with treatment and showing no neurological signs, is even higher than in the Groups as a whole. This finding is in accordance with the opinion of most investigators, with regard to Latent Neurosyphilis, and will be discussed in greater detail later in the text.

It was possible to examine the cerebrospinal fluid in 517 cases and the routine test used were...

(1) The Dreyer-Ward Sigma Reaction.

(2) The Foam Test.

(3) The Ross-Jones test for Globulin.

(4) The Lange colloidal gold reaction.

The Sigma reaction in the blood was carried out routine on all admissions, and that in the cerebrospinal fluid where any indication of neurosyphilis was suggested.

The Sigma reaction is a flocculation test and it was

compared with the Wasserman reaction, and the findings reported in a special report of the Medical Research Council. Some of the conclusions in this report can be summarised as follows:-

a. Complete, or almost complete, agreement between the tests.

b. Divergence occurred in sera with low Sigma readings, in other words, border-line cases.

c. The Sigma persists longer than the Wasserman in cases under treatment, and generally falls regularly. It is, therefore, more sensitive to antisyphilitic drugs.

d. Sigma seldom or never gives a false positive.

e. Like the Wasserman, a negative Sigma does not necessarily mean no syphilis.

f. The Sigma reading seems to correspond to the intensity of the clinical picture.

g. It is a valuable method for determining the progress of a case under treatment, and for testing the effect of different remedies -- a factor not possible with any other method.

As a diagnostic test of syphilis the Sigma was found positive in the blood in my cases, with almost unfailing regularity. In 70 cases, however, the reaction was negative in the cerebrospinal fluid. This finding, however, of a positive blood reaction and a negative c.s.f., is considered by most authorities to indicate a meningo-vascular syphilis rather than a parenchymatous infection, and will be considered more thoroughly later. The intensity of the Sigma reaction in the blood and/or cerebrospinal fluid did not give any indication as to prognosis (Table XV (Page 164)) other than that where the reaction was greater in the fluid, the prognosis is somewhat less promising than when the reaction in both blood and fluid is equal, or when the fluid reaction is less intense than that of the blood. The readings in female patients, generally speaking, were less, or weaker, than in males. On the assumption that the Sigma units indicate the degree of infection rather than the extent of damage, this may explain the better prognosis of neurosyphilis among women who receive treatment.

The Foam test and the Globulin test were positive in all cases and I feel the most one can assign to them is

that they indicate the presence of neurosyphilis but do not identify the variety. A quantitative test for globulin might be of diagnostic value, but all so far devised are complex to perform and unreliable.

The Lange colloidal gold reaction is a useful confirmatory test for clinically diagnosed General Paralysis, but in itself it is not a reliable indicator. The paretic curve, so named from its almost constant occurence in confirmed General Paralysis, is found very frequently in other varieties of neurosyphilis, and not uncommonly in non-syphilitic conditions. It would, however, appear to indicate involvement of the parenchyma, and it would also seem that the zone with the greatest precipitation indicates the degree in which the parenchyma is damaged, the paretic indicating extensive destruction. Perhaps the most important function of the Lange lies in its sensitivity to treatment with antisyphilitic remedies. It is the most persistent of all tests, and the progress of a case can be judged by its gradual return to normal, over usually a period of years. Nicole confirms this impression in a series of post-treated cases.

In my own series of cases a Lange curve, approaching the paretic, or actually paretic, was found in all but 23 cases. In these latter, a mid-zone or luetic curve was given in 16 cases, and a meningeal in 7 cases. At different stages subsequent to treatment, 117 cases were re-examined, and in the majority some indication of a return to normal was found. Of 31 cases remaining in hospital, for periods of from two to twelve years after treatment, whose cerebrospinal fluid was re-examined, fourteen had completely negative findings, and only two cases showed no change in the Lange - one 4 years after treatment (Malaria and Tryparsamide followed by Pyrifer, Neokharsivan and Bismuth) and one $2\frac{1}{2}$ years after a course of Pyrifer, Bismuth and Neokharsivan.

Various treatments and combinations of treatments were used on 414 patients during the fourteen years in which my cases were admitted. As will be seen from Table XVII (Page 165), Malaria or Pyrifer alone, or combined with Tryparsamide, or the latter alone, were the only treatments given to 342 of these patients. From this Table, and also Tables XVIII and XVIIIA (Page 165), it will be apparent that the combined treatment of Malaria

or Pyrifer and Tryparsamide, gave by far the best results. The method of treatment was to start with weekly injections of Tryparsamide and, during this course of 12 injections, to inoculate with Malaria, or give 10 rigors with Pyrifer. This procedure could account for the apparently poor response to Tryparsamide alone, as many patients, started on a course of treatment, had died before pyrexial treatment could be commenced. A detailed list of the other treatments used will be found in Table XIX (Page 166). The most efficient of these treatments were those in which Pyrifer was combined with Neokharsivan and Bismuth, and the improvement rate of 62%, is not only well above the overall improvement rate, but the response to the type of treatment suggests that the cases were almost certainly examples of Meningo-vascular syphilis. Even after the syphilitic origin of "General Paralysis" had been proved beyond argument, it was found that ordinary antisyphilitic remedies had little effect on prognosis in many cases. Carlill, and others, describing cures with such drugs, admitted that their cases should, more likely than not, have been diagnosed as Interstitial Neurosyphilis - the differentiation arising from the known fact that ordinary trivalent arsenical drugs could

not pass into the cerebro-spinal fluid. The introduction of malaria therapy produced many statements of "cured" paresis, but it was not until the advent of Tryparsamide, pentavalent arsenic, that it was apparent the disease process in General Paralysis could be permanently arrested, as witnessed by the return to normal of the Lange. Even so the use of trivalent arsenicals and bismuth was continued and was considered the treatment of choice in meningovascular conditions. Adams in 1941 expounded that Paresis calls for fever and tryparsamide, and "Cerebrospinal syphilis for Neoarsenobenzol, bismuth, and occasionally tryparsamide". My own figures, and experience, are in accord with this opinion, though, in modern times, penicillin and a combination of arsenicals would appear to be the treatment of choice.

SECTION V.

MAIN DISCUSSION OF CASES.

Classification.

It was possible, with reasonable accuracy, to divide the mental states of patients on admission into six main groups:

(1) Those cases in which Dementia predominated.

(2) Those cases in which Confusion was the most pronounced feature.

A further sub-division was possible in this group:

(a) Confusion with extreme restlessness.

(b) Confusion with emotional lability.

(c) Confusion with exaltation.

(3) Those cases of a Schizophrenic type.

(4) Those cases with features of Mania-melancholia.

(a) Mania.

(b) Melancholia.

(5) Those cases of a paranoid type (persecutory as a rule).

(6) A very small percentage of cases which could not be reasonably classified under any of the above headings.

It is possible from this grouping to postulate that the mental picture can be that of an organic-reaction type psychosis -- that is, of dementia, or a confusional state leading to dementia, and including acute Fulminating General Paralysis of the Insane -- on the one hand, and, on the other, the picture can be of Schizophrenia, Manic-depression, or a Paranoid state. The first two groups, therefore, could be called General Paralysis, but the other groups almost certainly are psychoses occurring independently of the syphilitic process, in the first place, though the latter is possibly the main exciting cause, and could secondarily overshadow the original picture.

(i) CASES EXHIBITING PROGRESSIVE AND PROFOUND DEMENTIA.

(a) Assessment of Dementia

Another name for General Paralysis of the Insane, unfortunately not now in common use, is Dementia Paralytica. Unfortunately, because such a name indicates much more clearly the essential clinical features of cerebral parenchymatous syphilis -- a dementia accompanied

by paresis.

Earlier descriptions of General Paralysis mention among the "varieties" a demented form. Folsom describes it as.....

> "consisting in a very slowly advancing mental impairment, making progress side by side with muscular loss of control and power".

A demented type of General Paralysis is mentioned frequently in the literature and in most of the present day standard text-books on Psychological Medicine. The overall opinion appears to be that it is a progressive type which shows little or no response to treatment. The disease process may be arrested by treatment, but the dementia remains, and life is merely prolonged for a few years. Reeve went as far as to state that.....

> "To succeed in prolonging life when the patient had already attained the stage of dementia is frankly not worth while".

Mott described Dementia Paralytica many years ago as a primary atrophy of the neurones, and as such postulated the essential feature of the disease as dementia. From the histo-pathological point of view, it has been well established that the greatest amount of

wasting in Dementia Paralytica, is in the frontal region. Shaw Bolton has emphasised that the amount of this wasting varies directly with the amount of dementia existing in the patients. He further demonstrated that the pyramidal layer of nerve cells in the frontal cortex develops, pari passu, with the development of the psychic powers of the individual, and is the only layer which appreciably varies in depth in normal brains; and that the polymorphic layer, the first to develop, is the last to fail in dementia, and probably subserves the ordinary functions, such as attending to their own wants. He showed, by a series of micrometric examinations of the cortex, a marked resemblance between the condition of the cortex at birth, when mentation is about to begin, and at death, in the final stage of primary decay of the prefrontal cortex, when the mind had practically gone. It is also of interest to note that Bianchi's conclusions, after frontal ablation in monkeys, were in keeping with Shaw Bolton's findings. His animals no longer showed any restraint or resourcefulness, and utilization of past experience was absolutely wanting. Watson has described the changes he found in the cortex in General Paralysis, and, besides typical vascular changes in the meninges and

neuronic tissue, with glial proliferation, stresses the great destruction of the smaller pyramidal cells in the prefrontal region, as compared with that in the central and calcarine areas. Lamination is completely destroyed in the frontal region, whereas it is still fairly definite in the central area, and normal in the calcarine. These findings are in accord with the frontal cerebral wasting which is so typical in the brains of General Paralytics.

Of the patients in my series of cases, 75, or 12%, could be classed in my first group, where dementia predominated. Of these, 57 had died by the end of 1938, and 32 came to post-mortem. In all but one case the diagnosis was confirmed by the marked frontal wasting; by the frontal, parietal and sylvian opacities in the meninges; by the varying degree of dilatation of the ventricles; by the decortication on stripping, particularly meso-frontally; by the more or less oedematous nature of the brain; and by the granulations in the Ventricles, and especially in the region of the calamus scriptorius. The only other findings of note were, a large sub-dural haemorrhage in one case, optic atrophy

in another, and carcinoma of the stomach in a third. In the case not confirmed at post-mortem, the patient, aged 58, would appear to have been diagnosed in the absence of any but mental signs of gross and relatively rapid dementia.

(b) Neurological Signs.

Mott stated that unequal pupils, fixed to light and sometimes to accommodation, was the most important early physical sign of General Paralysis. Tremor of the muscles of the face, hands and tongue; slurred speech; exaggerated tendon reflexes; and iridoplegia were given by H.W.Lewis, in 1897, as the four cardinal neurological signs of General Paralysis. Henderson and Gillespie in their description of the physical signs of Dementia Paralytica concur in this view, but stress that all these signs are variable. They also believe that loss of accommodation response, and optic atrophy, occur more usually in cases of General Paralysis which are associated with Tabes Dorsalis. Worster-Drought also emphasises the variability of all these signs and that in many cases

pupillary reactions, and tendon reflexes, are normal.

Treatment is said to produce improvement in neurological signs. Head and Fearnsides cite numerous examples in which improvement occurred in all directions. Most other investigators, however, are more conservative in their estimations of neurological improvement. Tennent found that considerable improvement could be expected in speech, tremor, and inco-ordination, but he did not consider that pupillary changes showed any alteration. He quoted various authorities whose investigations led to similar conclusions. My own experience leads me to the same conclusions, for though I have frequently observed marked amelioration in speech, reduction of tremor, and improved co-ordination, I cannot recall having seen any change in reflexes or pupils.

Among my cases in Group (i) the variability of neurological signs was marked. In all cases the findings are those recorded on admission. In nine cases no evidence of neurological involvement was elicited. In all other cases some or all of the cardinal signs were

apparent -- in 48 cases marked ophthalmoplegia was noted; in 27 cases tendon reflexes were grossly exaggerated, while in 15 cases reflexes were absent; and in 17 cases speech was very slurred.

From the neurological examination of cases in Group (i) no clear cut diagnosis could be made, though the presence of pathological eye changes can be said to be the most frequent neurological accompaniment of those cases in which dementia predominated.

(c) Laboratory Examinations

Dattner, whose monumental book on "The Management of Neurosyphilis" is recognized universally as the standard work on serological reactions, states in this book.....

> "there is not a single test that can be considered as exclusively characteristic of a specific type of neurosyphilis".

He, however, agrees

> "that in the vast majority of instances the cases which do not give a colloidal gold reaction will not prove to be Paresis".

In addition he states himself in accord with Kilduffe,

who had declared that a diagnosis of General Paralysis should never be made unless, in addition to the 'paretic curve', increased globulin content, increased cell count, and positive blood and c.s.f. Wasserman reactions are also found. On further reviewing the literature he arrives at the final opinion.....

> "We find that none of the spinal fluid syndromes, per se, enables us to arrive at a proper differential diagnosis as to the exact pathological processes in a given case of neurosyphilis, since even a complete paretic humoral syndrome, which is considered as most specific, may be misleading. But this is not surprising, for here, as in other fields of medicine, one is dependent on more than the laboratory findings".

Worster-Drought asserts that in the absence of a paretic curve he would hesitate to make a definite diagnosis of General Paralysis, though.....

> "In a few instances, however, the Lange curve may be 'luetic' in type".

These opinions appear, from perusal of the literature, to be conclusions that are generally accepted, and may be couched in another way. Where clinically and neurologically the diagnosis points to General Paralysis, positive c.s.f. findings confirm the diagnosis, but in the absence of mental or neurological signs,

positive c.s.f. findings need not necessarily make the diagnosis.

In my group of cases, the dementia and neurological signs, pointed to the diagnosis of General Paralysis. In only one of these 75 cases was a paretic curve not found. In addition to dementia, his tendon reflexes were absent, he had Argyll-Robertson pupils, his blood and c.s.f. Sigma Reactions were positive, but his Colloidal Gold reading was 1123421000. He was treated with Malaria and Tryparsamide, and when he died, two years later, the diagnosis was confirmed by post-mortem examination. Two cases had a positive blood Sigma, paretic curves and negative c.s.f. Sigma. One of these cases was examined post-mortem and the diagnosis confirmed. Only one case had a negative blood Sigma and positive c.s.f. findings.

(d) Effects of Treatment

During the 19th Century, General Paralysis of the Insane was regarded as an invariably fatal disease, and

even when syphilis was accepted as the cause, treatment had little effect on what was known as the progressively dementing type. With the advent of malaria and tryparsamide hopes were aroused that this type would benefit, but several authors who classified their cases into clinical types, (Bamford, Smyth, Tennent), found that other types benefitted more than the dementing type. Nicol and Hutton mention "the bad prognosis associated with the dementing case". Muncie also states...

> "The simple dementing type has a more unfavourable prognosis than the types with strongly affective features".

Of those in Group (i) of my series of cases, 47 received treatment, but 38 of them died in hospital. Of the remaining 9, one escaped, and one was transferred to another hospital. The other seven were all discharged, unimproved mentally, to the care of friends, but five of them were known to have died within a year of leaving hospital.

From the above observations I contend that I am justified in classifying those cases in my first group as true Dementia Paralytica, but feel that there can be

few people who would disagree that a picture of progressive dementia, relatively rapid, with or without evidence of muscular paralysis, and with positive serological findings indicative of neurosyphilis, should not be so diagnosed.

(ii) CASES IN WHICH CONFUSION WAS PROMINENT

Assessment of Mental State

In my second group are patients in whom, on admission, the predominant picture was mental confusion, but who, in the main also showed varying signs of dementia. Included in this group are the exalted, grandiose, expansive cases, who typify the classical text-book G.P.I., and who represent 27% of the group, but only 8% of the total cases in the series. It was found possible to further sub-divide the 'confusionals' according as to whether the confusion was associated particularly with extreme restlessness, with emotional lability, or with exaltation.

It is of interest to note that Nicol and Hutton, in

their classification of clinical types of G.P.I., include the Grandiose, the Manic, the Melancholic, the Dementing and the Confused; and that they consider "the differentiation between definite confusion and dementia presents great difficulties".

Shaw Bolton, in his work on Amentia and Dementia, defined mental confusion as a symptom-complex, which probably precedes all dementias, which is the result of a toxic process, and in which the prominent features are disorientation; more or less complete inability to retain impressions, even when frequently repeated; illusions of identity, such as mistaking total strangers for acquaintances, friends or relatives; and rapidly varying and quite unsystematised delusions. This is the earliest description of confusion which I have met with in the literature, and it differs in few respects from the changes described by Henderson and Gillespie, in the intellectual sphere, in Organic reaction-type psychoses, in which they include Dementia Paralytica,....

> "...there is impairment of comprehension, interference with elaboration of impressions, defects in orientation and retention, difficulty in activation of memories, and marked fluctuation of the level of attention".

Bevan Lewis, though he does not mention syphilis as a factor in the causation of mental disorder in his text-book, quotes Campbell's work on the 'Neuro-muscular changes in General Paralysis' in support of the theory that the changes secondary to the primary brain lesions are identical to "the conditions found in the group of primary toxaemic neuroses, dependent on an intrinsic toxic agent".

Henderson and Gillespie, in discussing the infection-exhaustion type of organic psychosis, write....

> "Where....confusion is present, it is a good working rule to search for a physical, especially a toxic or septic, basis",

but they do not mention syphilis as an infection commonly producing psychoses, yet they comment favourably on Fildes and McIntosh's view that.....

> "The 'parasyphilitic' diseases are due to an exacerbation of Spirochaeta pallida about nerve elements which are in a state of hypersusceptibility. This state is induced as a reaction to an intoxication occurring in the secondary period, and the spirochaetes taking part in the exacerbation are remnants of those which produced the original infection".

Similarly, Muncie, in his chapter on the Support disorders (Dysergasia), does not include Syphilis in his

tabulated list of causes, though later, in discussing Dementia Paralytica, he writes,

> "....paresis has become the least significant of mental reactions.... Its greatest theoretical interest at this date is in the differentiation of dysergasic (toxic, infectious, etc) from anergasic (acquired organic deficit) reactions. The reversibility of the process, in whole or part, suggests the need for the determination of the factors, short of actual cell destruction, responsible for the well-known clinical features which were thought to be anergasic, but which in whole or in part yield to treatment".

Weil, in his text-book on Neuropathology, is much more definite on the toxic effects of syphilis and makes frequent reference to "the histo-pathologic changes that may be produced by the toxins of Treponema Pallida within the brain and spinal cord".

The tendency would, therefore, appear to be to regard Dementia Paralytica as a chronic infective and degenerative disease process, due to the direct action of the Spirochaeta Pallida, with a possibility that toxic effects of the organism may produce variations of the clinical picture.

(a) Confusion with Restlessness

I consider that only by admitting the possibility of a toxaemia can one account for the extreme confusion met with especially in the 'so-called' acute, fulminating cases of G.P.I. This would appear to be borne out by Smyth's investigation into the relation of the Spirochaeta Pallida to the pathological changes of Dementia Paralytica. Though he was able to demonstrate Spirochaetes in 38 of 52 cases, he found them few in number, or absent, in the acute variety, with a mental picture of marked confusion and rapid exhaustion, and a histological picture of gross neuronic destruction, vaso-dilation of the cortex, and slight or no neuroglial reaction in the deeper layers. The slight, or absent, cerebral wasting in these cases, is explained by Shaw Bolton as due to the rapid course of the disease, and the consequent imcomplete removal of the products of degeneration. Kraepelin describes in detail a case which he states is typical of those cases in which the whole course of the "illness is rapid and stormy". He terms such cases "Galloping Paralysis" and mentions confusion, and extreme restlessness and excitement, as the outstanding symptoms. Shaw quotes Voisin as stipulating an "Acute

General Paralysis, in which the course is rapid, the stages are confounded, and death occurs early as a rule".

Survey of Cases

Of those cases in my series, dying within one month of admission, -- 51 or 70%, were grossly confused and violently restless. Age bore no relation to the type of illness, the majority corresponding in proportion to the age incidence throughout the series of cases. Nor did either sex preponderate other than in the greater proportion at which males acquire the disease. In only 11 cases was it possible to commence treatment with tryparsamide or malaria, the majority rapidly exhausting themselves, despite all efforts to restrain them. Neurological signs were marked in 30 cases, absent in 9 cases, while, in 12 cases, only slight evidence of neurological involvement was elicited. 23 cases came to post-mortem -- 20 (14 males and 6 females) were confirmed as Dementia Paralytica, and three could not be confirmed histologically, despite positive neurological and serological findings. No unusual phenomena were discovered, with the exception of evidence of a subdural haemorrhage in one female. In three cases it had not

been possible to obtain cerebro-spinal fluid, but in one of these cases the fluid was examined post-mortem and gave positive readings. In all other cases the Sigma was positive in Blood and c.s.f., the Colloidal Gold Reaction gave a strong 'paretic' curve, the foam test was positive, and globulin was increased. The only other observation which need be mentioned, is, that the fluid Sigma reading was greater than that of the serum Sigma in rather more than half of the cases, whereas this occurred only in 75 of the remaining 466 cases in which a comparison could be made.

From this evidence I feel justified in postulating that an acute fulminating type of Dementia Paralytica, due to a cerebral toxaemia, manifested clinically by a state of profound confusion and extreme restlessness, and associated with neurological and serological evidence of neurosyphilis, occurs more frequently than is commonly indicated.

The other cases in my series, in which confusion and restlessness predominated, differed only in severity

from the fulminating type - 28 cases left hospital, relieved to some extent, but showing evidence, to some degree, of intellectual reduction. There were nine cases remaining in hospital at the end of 1938. All had received treatment -- 6 Malaria and Tryparsamide; and 3 Pyrifer and Tryparsamide. All showed evidence of severe dementia, though one male was still capable of simple routine work under supervision. The average age on admission was 46 years, and the average period in hospital since admission was six years. All showed improvement in serological reactions, which on admission had been 'Paretic', and two cases showed completely negative findings.

From the above observations I feel that one is justified in diagnosing as Dementia Paralytica, those cases, in which Confusion and restlessness are the outstanding features of the mental picture, especially when associated with positive serological findings. One can also conclude that in a proportion of cases the prognosis is inevitably fatal, and that in others, though the disease process may be arrested, some degree of feeblemindedness remains, and that the end result is a gross dementia.

(b) Confusion with Emotional Lability

The second sub-division of the confusionals which I have made in my series of cases, is one which is, more or less, universally recognized as a 'type' of Dementia Paralytica. The older writers regarded it merely as a stage in the progress of the disease. Folsom, for example, considered confusion with temporary outbursts of excitement or anger, and rapid changes in the emotional state as indications of transient vaso-motor disturbances in the brain. He described such changes as being prodromal, and especially liable to be overlooked as indicators "of the period of invasion of general paralysis of the insane". More recent writers mention the emotional lability present in some cases, but apparently do not consider it other than an occasional happening. For example, Tennent apparently includes this 'type' in his Simple Dementias. Muncie mentions lability of mood only as a general symptom of the main disorder. I consider that there are sufficient cases in my series to justify a separate description of those confusional cases in which emotional lability was at one stage a prominent feature. There is no doubt that the

condition progresses, relatively rapidly, to dementia, and that other evidence, neurological, serological, and pathological confirms it as a variety of Dementia Paralytica. It is, moreover, felt that though the main presenting symptom is confusional, the subsidiary picture is so different from the other two varieties of the Confusional group as to warrant further observation and description. These cases, 14 in number, proceeded to dementia, without showing either the extreme restlessness of the first sub-division, or the expansive exaltation of the third. Serologically all tests were positive. All showed marked neurological signs, including, in nine cases, Argyll-Robertson pupils, a proportion incidentally, much higher than any type of case examined. Treatment was begun in all cases, and one course of malaria and tryparsamide was completed, except in two cases, who died within a few weeks of admission. Only one case remained in hospital, in a demented state. Two had been discharged to the care of friends, and the remainder died within an average of six months of admission. At post-mortem, seven cases which were examined, were confirmed histologically as Dementia Paralytica, and no unusual findings were recorded.

From these observations little difference emerges compared with the Demented group, other than in the initial mental picture. Progress, as noted, was towards dementia, but the instability of mood, the liability to anger, excitement, depression or laughter, on slight provocation, was quite different from the dull, apathetic demeanour of the straightforward demented type. Possibly, if an adequate assessment of the previous personality of these cases had been made, one would have found them to be emotionally unstable, childish, inadequate, self-centred types. The syphilitic process, on this hypothesis, would merely act, in its initial stage, to aggravate these features. At all events, one can, I believe, agree with Folsom, in that this type does occur, though, perhaps, it is but a stage in the course of, and progress towards, Dementia Paralytica.

(c) Confusion with Exaltation

Confusion with exaltation, in my series of cases, comprises the type of cases described as the classical examples of General Paralysis. It conforms to the earliest description of the disease, and this group can,

in fact, be isolated from the other types described as General Paralysis, by adhering to Bucknill and Tuke's definition, which I have already quoted:-

> "A disorder marked by general and progressive loss of co-ordinating power over the muscles, especially those of speech and locomotion, combined with mental enfeeblement, always tending to dementia, and frequently characterised by a sense of well-being, or actual delusions of an exalted character".

In more recent times, the mental confusion has been stressed by all writers on the subject, either as a symptom-complex, or in detail, such as disorientation, liability to mistake identity, impairment of memory, and inability to concentrate. The outstanding feature, however, of all descriptions, is the obvious sense of well-being apparent in all such patients, and expressed in ideas of exaltation or grandeur. Ideas of grandeur are not infrequent in other psychoses, but, in Dementia Paralytica, it is the expansiveness associated with the ideas that is so typical. Discrimination and judgment are utterly lacking, and, consequently, the grandiosity knows no limits. The extravagance of the delusions, and the emotional exaltation, are so striking, that, according to Mickle,

> "....attention has been too withdrawn from other, and equally common, facts pertaining to the mental order of symptoms".

Mickle stressed that such expansiveness and exaltation were not constant, and were interrupted, even if only temporarily, by hypochondriacal ideas, childishness, peevishness, or simple dullness and stupidity. In the more detailed of the present day text-books, such as Henderson and Gillespie, similar descriptions are given, though in many books and articles the impression gained of the 'Expansive' type of Dementia Paralytica is one of a delusional state, proceeding, relatively rapidly, if untreated, to dementia.

Survey of Cases

I found it easier to classify my confusionals with exaltation than any of the other groups in my series of cases. The only reason I can advance for this, is that few doctors find it difficult to describe, in writing, the symptomatology of patients exhibiting expansive and grandiose ideas, whereas to record accurately and describe manic, melancholic, schizophrenic, or even demented cases, requires much wider psychiatric experience. The certificates on reception orders, usually written by

General Practitioners, would bear this out, as, other than in delusional states, their certificates tend to be brief, vague, and non-committal. As a result, a detailed description of the mental condition of these patients was always found, and it left no doubt as to the clinical diagnosis. The neurological and serological examinations confirmed the diagnosis, in every case, and, those cases which ultimately came to post-mortem, proved the clinical diagnosis correct. One observation which may be noted from Table V (Page 157), is that, of 47 patients in the Group, only three were females, and this proportion of 16 males to 1 female is only found in one other type -- the confusionals with emotional lability. In all others the proportion of cases as between the sexes was much nearer that encountered in standard text-books, namely 1 female to 3 or 4 males.

Discussion on Cases with Confusion

Such then are the three sub-divisions of the confusional group of cases. I believe that I have demonstrated that such types occur, and that such a division is a useful prognostic indicator. For instance,

those cases with Confusion and Emotional lability have a much poorer prospect of survival than the other types of confusion - only three out of fourteen showed any benefit from treatment, i.e. only 21%. The patients, with Confusion and Exaltation as predominant features, showed the best response to treatment - 16 out of 47, or 36%, showing some arrest in the disease process. With restlessness as the main accompaniment of confusion, 37 out of 116, or 32%, gained some benefit from treatment. It should be stressed, however, that in all cases one could generally speak only in terms of 'Hospital' recovery, as distinct from 'Social' recovery, and rather the arrest or slowing down of a disease process, than actual cure. This conclusion is in keeping with that advanced many years ago by Mott, and expressed in similar terms by Tennent, Henderson and Gillespie, Weil, Worster-Drought, and many others. Mott wrote,.....

> "The mental aspect which is usual in General Paralysis, is the presence of a dementia of a progressive character; whatever else may be present, the only constant factor is this Dementia, and any temporary improvement of it is rare".

In a previous work, in discussing syphilitic arteritis he stated,.....

"It cannot be supposed that brain tissue can be

> regenerated when softening has taken place, nor can it be supposed that the scar tissue in diseased arteries or the atheromatous process of degenerated arteries can be influenced by drugs. It is not, however, denied that their administration may prevent progress of the disease, and thus allow other parts of the brain to take on function to some extent".

Henderson and Gillespie state that they still hesitate to speak of General Paralysis in terms of recovery.

Tennent expressed a similar view and added....

> "....any claim to recovery arouses in most minds grave doubts as to the diagnosis. In many cases under review a marked degree of improvement has been noticed as a result of treatment. In estimating these results one has to take into account the findings, if any, at clinical examinations, together with the social usefulness of the patient".

He believed that the effect of treatment is influenced by the duration of the mental symptoms prior to treatment, by the age of the patient, and by the clinical type of the illness. Also that the chances of a successful outcome diminished in direct ratio to the duration of the mental symptoms prior to treatment. Worster-Drought, in discussing prognosis, writes in terms of "Complete Remissions" and of "about 30% of cases recovering", though later, in his section on the therapeutic mechanism of malaria, he states.....

> "....In cases responding favourably to treatment, there is a definite recession of pathological changes in the brain, although, of course, nerve cells and fibres once destroyed cannot be replaced"

Weil is much more cautious.....

> "The interpretation of the histological picture, following fever therapy, is extremely difficult, because one does not know the condition of the brain before treatment..... It seems, however, to be established, that the degenerative process affecting the cortical neurones is arrested. Those observers, who have described a restoration to more normal conditions, assume a regenerative ability in the neurones, that has never been demonstrated, under other conditions, in the human brain".

Cases with confusion as the main symptom-complex proceed, if untreated, fairly rapidly to dementia. If treated, the syphilitic infection and destructive process is arrested, but there is always some residual evidence of feeblemindedness. Such cases then would appear to be, with the demented group, a definite disease entity, described as Dementia Paralytica. Some of the cases classified as Dementias, pure and simple, could, conceivably, have shown confusion, at one stage or another, before the dementia became profound. There is no question, however, that the cases classified as 'Confusional' terminated in dementia, and at this latter stage were indistinguishable from the Demented Group.

I contend, therefore, that Dementia Paralytica, or, as it is more popularly named, General Paralysis of the

Insane, is a disease of the cerebrum, due to the Spirochaeta Pallida, or its toxins, and evidenced clinically by a rapidly progressive dementia, which may, or may not, be preceded by a state of mental confusion associated with extreme restlessness, emotional lability, or expansive exaltation.

The question of the parts heredity and psychopathy play in the incidence of General Paralysis is one which, even to the present day, is not satifactorily answered. Though I would not go so far as Adams, who has stated that the spirochaete.....

> "serves simply to liberate underlying trends, the result being not paresis, but neurasthenia, hysteria, manic-depressive, schizophrenia, paranoid state, or other fundamental reaction types, with syphilis as the precipitating agent only",.....

I do believe that in a large proportion of cases hereditary factors or constitutional deficiencies are demonstrable, and that the majority of opinion agrees that General Paralysis occurs in such subjects more frequently than in well-adjusted people of stable stock.

Savage, for example, wrote that his experience

led him to believe that Syphilis did affect the nervous system of those who by "age, habit, or inheritance are nervously weak".

Lugaro maintained that in any organism there could be hidden weaknesses which might render it more vulnerable to one morbid agent than another.

Mott, many years ago, stated that.....

> ".....one would predict the development of the disease rather from their personal history than from their family history".

The inference from this statement is that heredity plays no part in the development of Dementia Paralytica, but in the same study we read.....

> ".....If we regard General Paralysis as a process of premature decay of the nervous system, affecting the structures latest and most highly developed, it is not reasonable to suppose that.....syphilis can play no part in the production of this disease, ...more particularly on those.....<u>which inherit a locus minoris resistentiae</u>".

This view of the disease particularly exhibiting itself in individuals with some prior neuronic defect, was stressed further by Bolton, who declared that General Paralysis only occurred in those individuals with defective cortical organisation, and who, in any case, probably would have developed a primary dementia, even

in the absence of syphilis.

Haskins believes that, if we investigated the past life of the individual paretic, we would find a definite relationship between the individual's make-up and the type of reaction that he develops.

This theory, and it can be no more, may account for the relatively small percentage of individuals, among those with serological evidence of neurosyphilis, who ultimately develop Dementia Paralytica. Dattner states that at least 35% of patients with syphilis show spinal fluid changes in the first two or three years following infection, but that not more than 25% will ultimately show clinical evidence of neurosyphilis, and less than 10% parenchymatous changes. The fact remains, however, that in a certain small proportion of syphilitics, a particular part of the cerebral hemispheres becomes affected by a primary neuronic destruction. The part of the brain so diseased is the fronto-parietal region, and particularly what is known as the prefrontal area of the cortex. As mentioned previously, this neuronic degeneration is illustrated, macroscopically, in all but a few of the fulminating cases, by gross

wasting of the convolutions, the wasting varying directly according to Shaw Bolton, with the amount of dementia existing in the patients. In other words as the destruction of the neurones by the Spirochaete, or its toxins, in the frontal lobes, proceeds, so do the mental changes become apparent. I have already mentioned Bianchi's experimental production of symptoms, similar to those in the plain demented forms of General Paralysis, following the removal of the frontal cortex in monkeys. Shaw Bolton, himself, goes further, in his researches into the functions of the frontal lobes, by relating the destruction of different parts of the cortex to the production of mental symptoms. The delusional state he regards as a secondary development,....

> "having as its basis a deficient power of co-ordination of psychic processes, -- (as a result of primary atrophy) -- and an inability to correctly interpret, and suitably co-ordinate, present experience in the light of past..... The capacity to develop delusions is present long before accident or environment determines the particular variety.....but the primary causal factor -- (neuronic destruction) -- progresses more rapidly than does the delusional state, and hence in some cases mild, and, in others, more marked, dementia eventually becomes evident".

This hypothesis, in other words, based on a scientific study, and, bearing in mind the rapid destruction of nerve elements, explains feasibly, not only the production

of the dementia in General Paralysis, but also the peculiar expansive delusions found in the disease. The confusion is attributed more to the toxic affects of the syphilis, and it varies in degree with the intensity of the toxic state.

This latter opinion receives confirmation in a report by Gordon (1941) on a group of cases with mild secondary manifestations of syphilis, who presented mental symptoms normally found in toxic-infectious psychoses. In all the cases vigorous anti-syphilitic treatment had a rapid and efficacious effect on both the psychic and physical aspects.

Various other more recent studies of the effects of injury, and operations, on the frontal lobes, serve to give support to my contention, that the first two groupings into which I have classified my cases, are really one and the same disease. Rylander, in a follow-up of 32 cases, in which part of the frontal lobes had been removed, summarised his findings as:-

1. Intellectural deterioration - 21 cases

2. Diminished inhibition of affective responses. - 25 cases
3. Distinct Euphoria - 20 cases
4. Restlessness - 14 cases
5. Loss of initiative - 12 cases

All these symptoms form the main mental pictures in my demented and confusional Groups.

Freeman, Watts, and Lyerly, give further evidence of the loss of function, consequent on the involvement of the frontal lobe. They mention as the usual secondary results of lobotomy, euphoria, evasion, moria, innattention, poor judgment, and....."a divorce between imagination and affect, as it concerns the individual himself".

Brain and Strauss, in discussing the exact plane of the cortical incision in Prefrontal Leucotomy, write

> "if it is made too far posteriorly, the effects will be profound, amounting in extreme cases to the Organic reaction-type psychosis and dementia".

This statement, implying as it does, that, if too much of the frontal lobes, (or thus their functions), are removed, an organic reaction-type psychosis is produced,

must be compared with the destruction of cortical neuronic elements in the frontal cortex in General Paralysis, which is an organic reaction-type psychosis. This comparison having been made, we are at once reminded of the three main changes which Henderson and Gillespie enumerate as comprising the organic syndrome:

> "(1) In the intellectual sphere there is impairment of comprehension, interference with elaboration of impressions, defects in orientation and retention, difficulty in activation of memories, and marked fluctuation of the level of attention".
>
> "(2) Affective disorder in the form of emotional instability, the patient laughing or weeping, without sufficient cause, and often in an explosive way".
>
> "(3) Character-change in the form of conduct foreign to the patient's natural disposition".

These changes are illustrated in Dementia Paralytica by the symptoms occuring in the two first groups of my cases.

I have already given a summary of Watson's enumeration of histological changes in the cortex in Dementia Paralytica, (Page 33). Similar descriptions may be found in the works of Ogilvie, Biggart, and Weil.

In all these descriptions, the changes are mentioned as being most marked in the frontal cortex.

Worster-Drought mentions that the orbital surfaces of the frontal lobes are particularly affected in many cases of Dementia Paralytica. Lesions of this area (Area 11), according to some authors quoted by Cobb, are followed by emotional disturbances. This, in turn, could explain many of the disorders of affect which are encountered in cases of General Paralysis.

Having separated and classified these cases; having demonstrated the clinical, neurological, serological, and pathological findings common to them; having correlated the symptomatology to the pathology; and having reviewed the relevant literature; I feel that I can finally complete my definition of Dementia Paralytica, and incidentally, the first objective of my thesis, as follows:-

(1) Dementia Paralytica is a disease, especially affecting the nerve elements in the frontal areas of the cerebral cortex, due to

the action of the Spirochaeta Pallida, or its toxins, and evidenced clinically by a rapidly progressive dementia, which may be preceded by a state of mental confusion, associated with either extreme restlessness, emotional lability, or expansive exaltation. It is primarily a degenerative disease of the neurones, and as such, cure is not possible, though arrest of the disease process, by treatment, can prolong life, and even permit some social rehabilitation.

(iii) CASES WITH OTHER MENTAL SYNDROMES

In arriving at my first conclusion, I have discussed the views of neuropathologists and psychiatrists, and I have attempted to demonstrate that, in the disorder known as Dementia Paralytica, the pathological changes in the brain are expressed clinically in a definite pattern. In other words, that Dementia Paralytica, being a primary neurone-destroying disease, is limited clinically to a picture of a relatively rapid and progressive dementia, with, in the majority of cases, a preceding, and accompanying, confusion, possibly due more to the toxic effects of the Spirochaete, rather than to its direct action. That is, diffuse cortical neuronic loss will always be recognised clincially in mental states of confusion and/or dementia. If this conclusion is accepted, one must, ipso facto, exclude other mental syndromes which are commonly classified as General Paralysis. At first sight this would appear to be an impossible task, because many cases have been described in the literature, with such other clinical pictures, and in which the diagnosis has been confirmed, macroscopically, at post-mortem examination. I contend, however, that such cases could have been, and almost certainly were, cases in which the neuronic elements were

not primarily, but secondarily, involved. I believe that many cases, in which the original infection was in the meninges or the blood vessels, were primarily non-organic reaction type psychosis, and that, with the spread of the infection to the nerve elements of the cortex, an organic reaction-type pyschosis was ultimately superimposed. I do not deny such a course of events, nor that it could be extremely difficult in some instances to separate, on clinical grounds, cases with a primary neuronic disorder from those with a purely meningo-vascular lesion, but I do believe it is possible to do so in the majority of cases. It has been stressed by succeeding authorities on neurosyphilis, that the treatment of non-parenchymatous varieties should be attended with almost universal success. If, therefore, one could, from the clinical examination and history, differentiate between primary and secondary involvement of the cerebral neurones, or prevent the latter, prognosis would likely be much more favourable.

In the following pages I shall attempt to prove that, in my series of cases, such a differentiation is is possible, and that, by a study of the literature on

the subject, a similar conclusion can be reached.

(a) Analysis of 270 Cases

Among the 539 cases, diagnosed as General Paralysis, which I have collected, 19 were not classifiable on the facts noted at the time of admission. Of the remaining 520, I have already discussed the reasons on which I consider that a diagnosis of Dementia Paralytica was justified in 250 cases. These are the cases in the first two groups in my classification - (a) Dementia, (b) Confusion progressing to Dementia. There remain 270 cases, which it will be my effort to prove, should, in general, have been diagnosed as a particular Psychosis with evidence of Neurosyphilis. Reference to Table V (Page 157), shows that cases fall into three main groups:-

(1) Manic-Depressive.

(2) Schizophrenia.

(3) Paranoid States.

The Manic-depressives are further sub-divided as to the phase presenting at the time of admission, and on this basis, of the 115 cases in the group, 50 are classed as

Mania, and 65 as Melancholia. In the Schizophrenia group are 72 cases, and though some showed hebephrenic features, the bulk were catatonics. 83 cases came under the heading of Paranoid states, (including Paraphrenia), or Delusional Insanity, and the majority of these patients expressed persecutory ideas, were evasive, and morbidly suspicious, but were well-orientated and showed no evidence of mental confusion.

I should once more emphasise that the mental state for the purpose of this classification was assessed entirely from the mental state exhibited on admission. The certificate on the Reception Order, and the admitting physician's estimation of the mental state, were taken into consideration, but the governing principle was the Medical Statement, or 'seven day notice' as it is often termed, to the Board of Control. A diagnosis is not essential in this statement, but frequently in my series of cases one was given. Though this made classification in these cases easier, the diagnosis, though not altered, was not accepted at its face value, but only after appraisal of the statement in detail. This statement, during the years applicable to my series of cases, was

almost invariably written by the Medical Superintendent of the Hospital, the late Dr.E.F.Reeve, who was also the lecturer in Psychological Medicine to the University of Liverpool. His certificates were clear and concise, and rarely left any doubt in one's mind as to the mental picture.

In the following pages I shall attempt to justify my action, in separating these 270 cases from those which I have already classified as true Dementia Paralytica, and, in proposing that each would have been more accurately diagnosed as a simple psychosis with neurosyphilis.

(b) Mental States

These cases, as has been shown above, fall into four main diagnostic groups, which are equivalent to the usual types of mental disorders among the non-syphilitic population in mental hospitals. It will be noticed also that the proportion of cases in each group corresponds approximately to the frequency of such disorders in patients with no manifestations or suggestion of syphilis. The mental state was such that, with no other findings,

one would not have hesitated to allocate each case to its respective group. The manics exhibited typical psychomotor activity, flight of ideas, and an elated, unstable mood. Delusions were abundant, but fleeting, unsystematised, and illogical. Speech was incoherent at times, but merely from inability to express rapidly enough all the ideas apparantly requiring simultaneous expression. Confusion was more apparent than real, and, as is the case in ordinary mania, memory for attacks was remarkably clear. Where confusion was more sustained the diagnosis of Mania was not made, but the case was included under Confusion with restlessness.

Where Melancholia was the diagnosis, the patients showed depression, of varying severity, with retardation. They tended to be solitary, and asocial, to look, and be, miserable and dejected, and to express ideas of guilt or unworthiness. They showed little interest in their environment but were well orientated, and could, though with difficulty, give a coherent and reliable account of themselves.

Though for the purposes of this investigation the

presenting state of Mania or Melancholia on admission to hospital is used for the purpose of diagnosis, it was not uncommon to find alternating states appearing when the patients had been resident for some time. Periods of normality, though generally very short, were also not infrequently noted. When such alternating or circular states occurred it was considered that the diagnosis of Mania-melancholia was more firmly established. Some cases of confusion with emotional lability presented difficulties in differentiation, but the guiding factors were always the mental confusion, and the tendency to expansiveness in the delusional content, whether of a euphoric, or depressive nature. In other words, care was taken, as far as possible, to include as Manic-depressives, only those cases showing no ascertainable evidence of intellectual impairment.

The criteria borne in mind in the classification of Schizophrenics were similarly, the absence of signs or suggestions of gross dementia, and the presence of apathy, negativism, impulsiveness, bizarre delusions and hallucinations, mannerisms, and flexibilitas cerea. There can be little doubt that some cases of schizophrenia

have been included in my first two groups -- those I consider to be true primary parenchymatous neurosyphilis -- especially the simple and hebephrenic types, but those cases which I have classified as Schizophrenia displayed sufficient characteristics of this psychosis for only a small error to be possible.

Under paranoid states I have grouped those cases which, according to the Board of Control's former classification, would have been diagnosed as Unsystematised Delusional Insanity. Some cases of Paranoid Schizophrenia will probably have been included as, with a diagnosis based on findings observed within a week of admission, errors in assessing the type of delusional state are more than possible. The standard adopted, however, in classification, was the presence of suspicion, evasiveness, and even hostility, together with varying or changeable delusions, sometimes accompanied by hallucinations, and invariably with a persecutory trend. The patients were generally well orientated, could respond to questions relevantly, if somewhat reluctantly, and discuss on general topics with reasonable clarity. A diagnosis was given to 63 cases in the medical statement,

and in no case was it found necessary to alter this from the observations recorded on admission. Mania was the diagnosis in 14 cases; Melancholia in 27; Dementia Praecox in 13; and Delusional Insanity in 9. Five of these cases were only recognised as Neurosyphilitics, and diagnosed as General Paralysis, at post-mortem examination. Two cases had been regarded, during life, as Melancholics, and one each as Dementia Praecox, Delusional Insanity, and Mania respectively. Only one of these five cases had presented neurological signs - loss of light reflex - and all had negative blood Sigma reactions. Post-mortem examination of the cerebrospinal fluid, however, was carried out in four cases, and all tests were positive.

(c) Neurological Examination

No neurological signs were elicited in 74, or 27%, of these cases under review. This compares with 28, or 11%, of the cases which I have already dealt with, and classified as Dementia Paralytica. In other words, 27% of the cases which presented mental symptoms on admission, which were indistinguishable from ordinary non-organic type psychoses, in addition showed no evidence, in the form of demonstrable signs, of disease of the nervous

system. One is, therefore, left with the conclusion that these 74 cases were diagnosed as General Paralytics on the presence of positive serological reactions in the cerebrospinal fluid. It is much more likely, as a survey of the literature will later show us, that these cases were cases of asymptomatic, or latent, neurosyphilis with a concurrent psychotic disorder, and, as I have contended, not General Paralytics. The incidence of the asymptomatic cases in relation to the various psychotic types is shown in Table XII (Page 162). On examining this table, one is struck by the difference in numbers between the cases benefitting by treatment, indicated by discharges and those patients remaining in hospital, as compared with those cases in Table XIII and XIV (Page 163), who comprised the remainder of the patients with no neurological signs, and who have been classed as Dementia Paralytica. Only 14% had not died among the Dementias, whereas 51% had shown some degree of improvement, with treatment, in the other category of cases. This, I believe, clearly indicates that the latter were cases of Interstitial Neurosyphilis, or latent neurosyphilis, which all authorities are agreed respond most favourably to antisyphilitic measures. In other words, this observation

upholds my belief that the correct diagnosis of these cases would have been the manifest psychosis and neurosyphilis.

The remaining cases displaying obvious psychotic syndromes, showed in addition, from mild to marked, clinical evidence of disease of the central nervous system. Evidence of speech impairment was slight, and was found in only 22 cases. Abnormality in the deep reflexes of the lower limbs was elicited in nearly two-thirds of the cases, and of these, one-third - 30 - showed absence or diminution, while the remaining 67 cases showed increased responses. The most consistent neurological signs were, however, significant of damage to the cranial nerves, - pupillary abnormalities, loss of light reflex, optic atrophy, facial tremor, and lingual tremor. Cranial nerve palsies are much more frequent, as would be expected, in meningeal infections, than in primary parenchymatous conditions, and, therefore, their common occurrence in the groups of cases under review, would at least suggest that the cause here was meningo-vascular neurosyphilis rather than parenchymatous. Tables IX to XI (Pages 160 and 161) give these figures in detail.

Primary optic atrophy is considered by most authorities as being a special variety of the tabetic process, though the aetiology of it is still obscure. A condition of Tabo-paresis is also well recognised and two varieties of this occur. The descending type which is in reality a spread of the cerebral degenerative process to the cord; and an ascending type which results from an extension of the parenchymatous infection in the cord to the cerebral cortex. The latter is the more common origin, and Worster-Drought is of the opinion that fully 50% of the cases of Tabes with optic atrophy develop General Paralysis. He also considers that a small proportion of cases show mental symptoms from....

"a supervening attack of one or other of the phases of a manic-depressive psychosis".

In my present series of cases optic atrophy was found in 16 patients. A diagnosis of tabo-paresis, from associated mental and neurological signs, was definite in 12 cases, but the other four patients who had been blind for periods of up to four years prior to admission, showed clear-cut mental pictures of mania and melancholia. Two recovered from their psychotic episodes, and were eventually discharged after treatment. The other two died

seven months after admission, following a series of seizures.

(d) Post Mortem Findings

As 46% of these cases, which I am attempting to exclude from the Paretic groups, showed, with treatment, at least arrest of the disease process, I feel that the response to treatment indicates, in these cases, a form of neurosyphilis less disastrous than Dementia Paralytica. The cases in these groups who died and were examined post-mortem had, on the average, survived for a period of several months, and all showed cerebral wasting to some degree, though evidence of meningo-vascular involvement was also generally demonstrated. I do not consider that these cases disprove my contentions, as, though a terminal diagnosis of Parenchymatous neurosyphilis was justified, the probability of this being secondary to a Meningo-vascular infection could by no means be discounted. The clinical picture could be explained, and related to the post-mortem findings, in the following manner. During life the neurological and serological signs indicate the existence of a syphilitic process, and the

latter, in the first place, occurs in association with a fundamental reaction-type psychosis. Later, as the parenchyma becomes involved, the syphilis modifies the psychotic picture, and, finally, the original psychosis is completely masked by the dementia resulting from gross secondary neuronic destruction, which is demonstrated, macroscopically, at post-mortem examination, by cortical wasting. This secondary neuronic degeneration can frequently be so similar to primary degeneration that differentiation, with any certainty, is impossible. Dattner no doubt had this in mind when he stated that pathologists frequently found it impossible to distinguish Meningo-vascular syphilis from General Paresis in advanced cases.

From the time of Mott's researches to the present day, neuropathologists declare that gummata are not found in Dementia Paralytica. In seven of my cases gummata were discovered on examination of the brains, and yet the findings, in other respects, were considered sufficiently typical macroscopically, to confirm a diagnosis of General Paralysis. I am inclined to accept the view that the presence of gummata imply a diagnosis of a primary

interstitial neurosyphilis, and therefore, that these cases were not true Paretics. Though we are concerned with only a very few cases of this type, I believe that the conclusion is another point in favour of my contention that General Paralysis is a distinct disease entity, and that other neurosyphilitic disorders are frequently confounded with it, especially in the later stages.

(e) Serological Examinations

Dattner, and others, have stated that there are no cerebrospinal fluid syndromes which can be considered diagnostic of any particular variety of neurosyphilis, though in conjunction with other findings, they may aid diagnosis. I have considered the mental pictures in these several groups of cases, and found them sufficiently atypical to propound the opinion that they are not fundamentally cases of Dementia Paralytics. I have shown that in a large proportion of these cases the evidence, or otherwise, of neurological signs, likewise creates doubt. Finally, I have considered the findings in those cases which were examined post-mortem, and I have endeavoured to prove that a terminal similarity to General

Paralysis need not necessarily mean General Paralysis. Though the view expressed by Dattner is, in essence, true, a study of the serological reactions in my series of cases is considered necessary. I have already dealt with the laboratory findings, in the 250 cases which I consider to be examples of Dementia Paralytica, and I have shown that, where a diagnosis on proved clinical principles has been made, characteristic reactions in the cerebro-spinal fluid, can confirm the diagnosis.

The tests used throughout my cases were:

(a) The Sigma Reaction.

(b) The Foam Test.

(c) The Ross-Jones test for Globulin.

(d) The Lange Colloidal Gold Reaction.

Watson, who was neuro-pathologist at Rainhill for many years, gave his reasons, in a paper, for limiting the tests to these four.

The Sigma reaction, as a diagnostic test for both neuro- and somatic syphilis, was preferred to others because it was

(a) equally reliable to the Wasserman

(b) was much simpler than the latter to perform

(c) "The reaction is standard, is more definitely quantitive, and comparative results can be obtained by independent workers".

The colloidal gold reaction, he found from experience was the most reliable, and the most delicate, of the colloidal tests.

The cell count was abandoned as a routine procedure as it did not compensate for the time and labour involved.

When all the tests mentioned were positive he considered a reliable laboratory diagnosis could be given, and he believed, from prolonged trial, that it was better to rely upon a limited number of tests, carried out with meticulous care, than to attempt a greater number of tests, some of which might have to be hurriedly completed.

These tests were used, where indicated, in examination fo the blood and c.s.f. of all cases being reviewed in this section, and an analysis of the findings show that the foam test was positive in every case, and also that

globulin was increased. A diagnosis of neurosyphilis is, therefore, confirmed by positive results from these tests, but, as will be demonstrated later, they do not indicate the variety of neurosyphilis. The Colloidal Gold Reaction showed a paretic curve in all but 22 cases and the blood Sigma gave a positive reading in the majority of cases. The c.s.f. Sigma reaction was, however, negative in 68 cases and considerably weaker than the blood Sigma in the majority of the others. This fact, of a positive blood and a negative cerebro-spinal fluid Sigma, is found commonly in neurosyphilis, and irrespective of the test used, but the unit reading used in the Sigma, permits of greater accuracy in comparing the strengths of reactions. As most authorities on neurosyphilis regard this sequence of findings as indicative of meningo-vascular syphilis, I consider that the cases giving a negative Sigma reaction in the c.s.f. among my cases can definitely not be regarded as cases of General Paralysis, and that those with a weaker reaction than that in the blood should, at least, be regarded as doubtful.

Consideration of the results of serological tests, in all my cases, can be summarised thus:

(a) Positive serological findings are the rule in

cases presenting the clinical features of Dementia Paralytica -- that is dementia with or without confusion, and neurological signs.

(b) Positive "fluid" syndromes may be found in cases not conforming clinically to the above definition of Dementia Paralytica, and, in such cases, do not necessarily make the diagnosis.

(c) A diagnosis of Meningo-vascular syphilis is likely to be confirmed, if the mental state is not one of Dementia and/or Confusion, when the blood gives a positive reaction and the c.s.f. a negative reaction to a diagnostic test for syphilis, in the presence of other positive "fluid" tests.

(d) The diagnosis of the form of neurosyphilis cannot be made accurately or dogmatically on the presence of a positive reaction to any test, or group of tests, without giving detailed consideration to the mental and neurological signs and symptoms.

(f) Response to treatment.

Though various treatments had been used throughout the 14 years under review, Tables XVII - XIX (Pages 165 and 166), the main treatments given were, Malaria or Pyrifer or Tryparsamide, singly, or more usually, in combination. By far the best results were obtained with Tryparsamide, and an intercurrent course of Malaria or Pyrifer. The response to treatment of cases presenting mental pictures similar to fundamental reaction-type psychoses, as illustrated in my sequence of cases, is considerably better than in those which could be grouped as General Paralysis. Reference to Table XIV (Page 163), proves that 51% of the former type of case showed some degree of benefit from treatment, as evidenced by those who were able to leave hospital and those in whom life had been prolonged, compared to only 14% of those admitted to be cases of Dementia Paralytica. This result is what one would anticipate, bearing in mind the respective pathologies of the conditions, and it further serves to confirm my belief that the two main divisions to which, on clinical grounds, I have allotted cases, is correct.

SECTION VI.

SURVEY OF LITERATURE.

(a) General.

Many years before syphilis was demonstrated, beyond argument, to be the cause of General Paralysis, various forms of insanity were attributed to syphilis of the brain and intracranial structures. The descriptions of many of these forms of Syphilitic Insanity differed in few respects from the comparable non-syphilitic insanities, and, in fact, often the diagnosis was made on the history of a syphilitic infection, or on the presence of somatic signs of syphilis. It was early appreciated that anti-syphilitic treatment helped such cases towards a remission, but it was also recognised that untreated cases, and many treated cases, tended to early dementia or death from intercurrent causes as a sequel of the syphilis. From Bucknill and Tuke's observation, that all forms of Insanity could be complicated by General Paralysis, one infers, however, that, in the absence of a history of syphilis, or in the absence of its somatic manifestations, many cases were

diagnosed, in their early stages, as ordinary reaction-type psychoses. Though syphilis was not related to General Paralysis by early writers, Fournier described a syphilitic Pseudo-General Paralysis, which he differentiated from "true" General Paralysis, in, among other ways, that the lesion was meningeal rather than cortical. It is interesting, in reading the chapters on Syphilitic Insanity in these old books, how often in the fully developed forms, a detailed differential diagnosis from General Paralysis was made.

Mickle, for instance, mentions that.....

> "As regards syphilis, attention must be given to the history of the case; the co-existence of other manifestations of syphilis; the course of the infection; the indications of local straightly circumscribed lesions or growths; the results of treatment. Also, in syphilis, the absence or less marked degree of the most significant motor signs, as the affection of lips, face, tongue; the rarity of exalted delusions; the onset, rather by indications of somatic than of psychical disorder".

Later, in discussing the early symptoms, he writes,.....

> "While there is much that is similar in the syphilitic cases, yet...."

and then he goes on to stress the early involvement of the cranial nerves as characteristic of syphilitic cases.

In both the conditions when fully developed, he finds little difference, but states that.....

> "...in syphilitic cases, as compared with general paralysis, there is, at first, an obscuration, rather than a destruction of mind".

He quotes various authorities on the Continent to support his points of differentiation, and particularly to support his observations that "gummatous infiltrations" and syphilitic "adhesive meningitis" frequently simulate General Paralysis.

Shaw mentions that General Paralysis may quickly succeed an attack of acute Delirious Mania and quotes Fournier's mental form of cerebral syphilis, of which he described two varieties, the Expansive and Depressive, both of which bear some resemblance to non-organic psychosis. Indeed, the severe form of the Expansive variety is regarded as a true maniacal condition.

Folsom states that the symptoms of the prodromal period of general paralysis.....

> "may be marked by the prominence of almost any of the symptoms of nearly all the mental diseases".

"Acute mania has been known to constitute the prodromal period of general paralysis for a number of years".

"Expansive delusions.....are found, but often not until or near the end. The other symptoms vary within a wide range, so as to simulate almost every form of insanity; and it is quite possible that they include what a more exact pathology will hereafter recognise as several distinct diseases".

He, himself, describes four varities of General Paralysis, including a Melancholic and a Manic, but points out that all four varieties.....

"differ from each other very little in their later and final stages".

He mentions cases of diffuse cerebral syphilis in which the differential diagnosis from general paralysis is impossible. "Syphilitic Insanity" in his opinion includes.....

"only such cases of Mania, Melancholia, and Delusions of persecution of the ordinary type, as depend upon the presence of the syphilitic poison in the system".

Mott considered syphilitic brain disease, which he described separately from General Paralysis, under the following headings:-

a. Basic syphilitic meningitis.

b. Syphilitic diseases of the brain convexity.

c. Syphilitic arteritis.

d. Cerebro-spinal syphilis.

The mental symptoms of Basal Meningitis he considers so variable that.....

> "at one time they may assume the case to be an epileptic, at another a general paralytic, or an imbecile, or the case may be diagnosed as mania or melancholia".....
>
> "A great many cases which died in the Asylum were diagnosed as General Paralysis, and certified as such after death".

Meningo-encephalitis of brain convexity he regarded as very difficult to distinguish from general paralysis though.....

> "neither clinically, nor by macroscopic or microscopic examination of the nervous system could they be looked upon as examples of General Paralysis".

The atrophy of the neurones he considered to be secondary, in contrast to the primary atrophy in general paralysis.

Syphilitic Arteritis, he believed, occurred in many cases sent to asylums, because the presenting picture was mental and.....

> "a diagnosis made referring to the mental symptoms rather than the organic cause of the disease".

The majority of the cases cited by Mott, to illustrate his research, were only diagnosed at post-mortem as syphilitic brain disease. Nearly 20% had been diagnosed clinically as General Paralysis. Others had been diagnosed clinically as Mania, Melancholia, Delusional Insanity, and Epilepsy. He stresses the importance of the early diagnosis of syphilitic brain disease.....

> "on account of its curability, provided the disease is treated before destructive changes have become advanced".

Prior to the introduction of the Wasserman, all these authorities whom I have so far quoted found it difficult to distinguish between Mania, Melancholia, and Delusional states occurring in association with syphilis and General Paralysis, and such conditions uncomplicated by the latter. While recognising the different mental syndromes the fact of a supervening General Paralysis led them, I believe erroneously, to formulate different types of the disease, rather than to recognise the predominant Psychosis being complicated by the General Paralysis or syphilitic process.

(b) Classifications.

Most neurologists and neuropathologists have adopted, for descriptive purposes, a classification of Neurosyphilis into two main divisions:

A. Meningo-vascular or Interstitial.

B. Parenchymatous.

The Interstitial variety may present itself as a local or generalised inflammatory reaction of the meninges; as an endarteritis giving rise to occlusion and softening; or as gummata. In other words, the supporting, nutritive, or enclosing tissues of the nervous system are involved primarily rather than the purely nervous tissue. In parenchymatous neurosyphilis the actual neurones of the brain, and spinal cord, are primarily affected and the pathological process is essentially degenerative, as distinct from the inflammatory process in meningo-vascular neurosyphilis. Stress is, however, laid on the point that this division, or classification, is not sharply defined either pathologically or clinically, and that mixed forms must, and do occur.

Weil classifies the histo-pathological changes into

four groups.....

1. Meningo-encephalitis (Meningo-myelitis).
2. Vascular Syphilis.
3. General Paresis.
4. Tabes Dorsalis.

He asserts that each of these types may occur isolated in its pure form, or in different combinations.

Worster-Drought follows much the same scheme as Mott propounded 50 years ago. He recognises, first of all, the Parenchymatous and the Interstitial varieties, and, thereafter, subdivides in accordance with the part of the nervous system principally involved. He stresses the arbitrary nature of the classification, but recognises its practical usefulness from the clinical, pathological, therpeutic, and prognostic points of view.

Dattner's descriptive classification is more or less in agreement with that of Worster-Drought, with the exception that he places all Asymptomatic Neurosyphilis as Meningo-vascular Neurosyphilis, rather than grouping early cases as meningo-vascular, and late cases as parenchymatous.

It is of interest in this connection to refer to the International Classification of Diseases. We find Neurosyphilis under three headings:-

024 Tabes Dorsalis.

025 General Paralysis of the Insane.
Dementia Paralytica.
Tabetic General Paralysis.
Meningo-encephalitis.

026 Other Syphilis of the Central Nervous System.
Aneurysm and Gumma.
Cerebral Syphilis.
Cerebrospinal Syphilis.
Latent (Early and late).
Meningo-vascular syphilis.
Psychosis with syphilis of Central Nervous system (any type except General Paralysis).

In all classifications of neurosyphilis, therefore, since the beginning of the century, the factors determining the classification are mainly the pathological findings. These findings are, in clear cut cases, not disputed by anyone, but all authorities are agreed that mixed types, or combinations of disease processes, are frequently found. The clinical signs and symptoms in the pure forms of both Parenchymatous and Interstitial Neurosyphilis, are also rarely disputed. As I have shown

above, the primary neuronic degeneration in Cerebral Parenchymatous syphilis results in confusion and dementia, and the neurological changes, in typical cases, are fairly constant. In early uncomplicated Meningo-vascular neurosyphilis one finds, however, considerable variation, dependent upon whether the infection is generalised or localised, and, if the latter, the particular form of the disease and the particular site of it. Neurological signs could be absent or vary widely, but, as the infective process generally begins in the base of the brain, involvement of one or several of the cranial nerves could reasonably be expected. In untreated, or advanced cases, a more constant neurological pattern should be observed. No fixed, or unchanging, mental syndrome can possibly be postulated, however, in early Interstitial syphilis from consideration of the pathological changes, though, in advanced cases, due to secondary neuronic destruction, a picture of confusion and dementia would be anticipated.

Many cases of Interstitial neurosyphilis show no mental changes, though neurological, and serological signs may be marked. Where symptoms of mental disorder, associated

with early signs of Interstitial Neurosyphilis, occur, one would, therefore, be justified in assuming that the psychosis would have developed independently from the syphilis, though the latter may have been an incidental precipitating factor. If this hypothesis is true, one should find from a study of case material, in those cases with evidence of neurosyphilis and a psychosis, that the latter differs in no way from a similar psychosis, uncomplicated by neurosyphilis. I believe that this assumption is true, and I also believe that many such cases of neurosyphilis, associated with a psychosis, are diagnosed as General Paralysis merely from the fact of the presence of psychotic symptoms, with or without dementia.

Dattner's comment in this connection is worth quoting. He writes:

> "If a patient with meningo-vascular syphilis presents psychotic manifestations, even the experts may be misled, and consider him a paretic".

(c) Correlation of Pathological and Clinical Pictures.

Shaw Bolton, in 1903, wrote that.....

"relatively little care has been bestowed on the

correlation of the morbid anatomy and clinical features of the different types of mental alienation".

This opinion holds good to the present day, though with the coming of psycho-surgery, and particularly topectomy, much more may be hoped for in the future. However, no observations so far gained from such operations, have thrown much light on the genesis of the psychoses. From the point of view of this thesis, study of the sites of the syphilitic lesions in Interstitial neurosyphilis does not give any indication of the form the mental symptoms, if any, are likely to take. Conversely and more accurately, the mental picture does not predict the nature of the pathology of the lesion, though, in conjunction with neurological and serological evidence of neuro-syphilis, the presence of a schizophrenic, paranoid, or affective state, would indicate a meningo-vascular, rather than a parenchymatous lesion.

On further referring to the earlier writers, who were dependent for their diagnosis on their clinical judgment alone, we find frequent references to types, both

of Syphilitic Insanity and General Paralysis, which in the early stages, at least, could not be clearly differentiated from their non-specific counterparts.

Mickle, (1886), describes in great detail a Maniacal form of General Paralysis, a Melancholic form, and a form with symptoms of Circular Insanity. The maniacal form, in the early stages, bears a marked resemblance to Acute Mania, or Simple Mania, as Mickle calls it. He more than appreciates the difficulty of differential diagnosis and states that, ...

> "facts indicating General Paralysis are sometimes inconspicuous or absent in mania, which, without solution of continuity, subsequently merges with, or is transformed into, the psychical sphere of General Paralysis; so that it proves itself to have been a Paralytic Mania. On the other hand, facts of General Paralysis ..... are not always entirely unknown in ordinary acute mania".

He contends, that in the absence of somatic signs of General Paralysis, a well founded diagnosis is impossible. Nevertheless, he also records that the Maniacal form of General Paralysis.....

> "is that one which offers, perhaps, the most frequent, protracted, and marked remissions, ... rarely, however, is the recovery permanent".

This type, as described by Mickle, could be illustrative of my contention. Similarly, his melancholic type cannot be distinguished, on the mental plane, from true Melancholia, and he admits that only the presence of somatic signs of syphilis and the progress to eventual dementia, allow of a certain diagnosis. The 'Circular' form is also, according to Mickle, only to be separated from Circular Insanity by.....

> "the history of the case, and, occasionally, the more marked physical signs in the former".

Shaw, though his descriptions are briefer than Mickle's, describes an intermediate stage of General Paralysis,.....

> "when there are mental symptoms without certain diagnostic somatic characteristics".

The mental condition, he states, may resemble Mania, Melancholia, or 'Folie Circulaire', and he quotes Voisin as "fixing the maximum limit of this period at two years" and saying.....

> "if somatic symptoms appear after a longer period of mental aberration than this, we have had to do in the first instance with some form of simple insanity".

From this description I see no reason to question my assumption that such cases were eventually diagnosed as General Paralysis merely because, though recognisable as simple insanities in the early stages, they later showed somatic signs, and presumably terminated in dementia, with paralysis.

Kraepelin, in his lectures on Clinical Psychiatry, makes frequent reference to General Paralysis. He discusses depressive states in this disease, which are no different from Melancholia, except as a "result of physical examination". Similarly, he illustrated a case, which, "as soon as we examinehis physical condition more closely", is found to be General Paralysis rather than Dementia Praecox. Muncie mentions how, under Kraepelin, the percentage of cases of General Paralysis seen at the Heidelberg Clinic reached the 'astounding' figure of 30, and how with the advent of the Wasserman reaction, the figure fell abruptly to 10 per cent. The inference one can draw from Kraepelin's descriptions, and Muncie's figures, is that cases of simple psychoses differ little in the mental picture from similar psychoses complicated with neurosyphilis.

Savage, writing on the relationship between Syphilis and Insanity in Tuke's 'Dictionary of Psychological Medicine', stated that syphilis.....

> "may be present in patients whose insanity does not depend upon it, and we know no form of insanity deserving the name 'Syphilitic Insanity!".

Here again, one must conclude that the writer, an authority on the subject, could not see, except in General Paralysis, with its progressive degeneration, any difference between Insanities associated with neurosyphilis and those Insanities with no evidence, or history, of syphilis.

Among Mott's 62 cases of Brain Syphilis one can readily diagnose Manics, Melancholics, and Paranoid states. Many of his illustrative cases showed, however, no mental abnormality, and yet all cases which came to post-mortem, whether diagnosed as General Paralysis, Epilepsy, Mania, Melancholia, or Paranoid state, were found to be suffering primarily from an Interstitial form of neurosyphilis.

In another paper on "The Etiology and pathology of

General Paralysis", Mott mentions that syphilitic meningo-encephalitis can give rise to secondary destructive changes in the neurones and so complicate the picture.

H.W.Lewis wrote, in an article on Syphilis in General Paralysis, that,.....

> "from time to time one sees cases of Mania, who after a short stay in the asylum, obtain their discharge as recovered, only to return at a later date with well marked symptoms of General Paralysis".

This is an occurence that has been noted by several authors, and which was found in not a few instances among the cases I am reviewing. The converse was equally true, and a few cases who had been treated as General Paralytics, and discharged as recovered, were readmitted some years later, showing negative, or almost negative, serological findings, no deterioration in neurological signs, but with identical mental symptoms. These observations can but confirm the fact that the original diagnosis was wrong, and that a diagnosis of the fundamental psychosis with neurosyphilis would have been more exact.

In the course of a paper on 'The Clinical aspects of Syphilis of the Nervous System', Head and Fearnsides make

occasional mention of the mental picture, and one finds such references as,.....

"....occasionally the condition may resemble dementia praecox".....

"....occasionally this form of cerebral syphilis evokes in young men a condition indistinguishable, at first sight, from dementia praecox. The inhibition of mental processes, want of emotional expression, and negativism, that go to form the characteristic picture of this disease, may be present, but the increased cell content of the c.s.f., and the remarkable improvement with antisyphilitic remedies, show that it belongs to the acute syphilitic dementias".....

"....there is not a symptom nor a sign in Dementia Paralytica which cannot be present in a case of subacute meningo-vascular syphilis" ..... "By long continued observation and by watching the effect of treatment, not only on the patient, but on the Wasserman reaction in the cerebrospinal fluid, it is possible in many cases to separate these two conditions of such different prognostic import".

These quotations speak for themselves in support of my contention that many cases of Neurosyphilis are lumped together with General Paresis, or separated from it, merely because the mental picture is associated with neurological signs, or serological evidence of syphilis. The presenting mental picture takes a subordinate place in the field of diagnosis.

It will now be seen that a study of the literature

up to the introduction of the Wasserman diagnostic reaction, shows that, although the essential pathology of Dementia Paralytica was universally accepted, -- a primary neuronic destruction -- and although the picture of the mental sequelae of the disease was undisputed -- "confusion is the distinguishing characteristic of the first stage ... yet, dementia is the mental groundwork" (Mickle) -- various 'aberrant' types of the disease were described, which, in the early stages, at least, were indistinguishable from simple insanities, and were only attributed to the effects of General Paralysis, and later of syphilis, by their tendency to remission, with or without treatment. These psychoses, in my opinion, could all have been apparent in the absence of a syphilitic infection.

In the past thirty years many advances in the treatment of Neurosyphilis have been introduced, and many investigators have recorded the results of their particular methods. The majority of these papers, leave one to presume that a diagnosis of General Paralysis, or Dementia Paralytica, was beyond dispute, but with few exceptions the writers merely state that serological

findings confirmed the diagnosis, and they do not detail the mental syndromes. The results of treatment in such instances show remission rates varying from 5% to 67% (Dattner), and such a wide variation can only be attributed to the inclusion, in many investigations, of cases which were probably meningo-vascular rather than parenchymatous neurosyphilis. That such an error in diagnosis can occur is amply demonstrated by both pathologists and neurologists. I have already referred to Mott's series of post-mortems on cases of syphilitic brain disease, in which he found that nearly 20% of cases had been diagnosed clinically as General Paralysis. More recently Biggart, in his 'Pathology of the Nervous System', has bluntly recorded that in about 20% of cases, clinically diagnosed as G.P.I., which he post-mortemed, the diagnosis was wrong. If, in cases progressing to death, such a large error in diagnosis is possible, I feel that the error among remissions, and especially the reputedly "recovered" cases, must be much greater. Reference to the neurologists also indicates that an error in diagnosis does occur. I have already quoted from a paper by Head and Fearnsides to show that in

certain cases it was only the effects of treatment which established their final diagnosis. Hildred Carlill, in the Lancet in 1918, stated that many of his cases showed physical and clinical improvement with treatment, but qualified this by candidly admitting.....

> "No doubt many of these cases suffered from meningo-vascular rather than from syphilis centralis, and so, consequently, reacted better to treatment".

Worster-Drought states on more than one occasion in his book on Neurosyphilis, that most, if not all, of the cases of General Paralysis reported as cured by ordinary anti-syphilitic measures, have almost certainly been cases of interstitial syphilis. It will be noted that these neurologists differentiate parenchymatous from interstitial syphilis by the effects of treatment, though one presumes that the clinical picture led to the original diagnosis. It follows that, though certain neurological signs can be typical of General Paralysis, other conditions associated with syphilis of the brain, such as meningo-vascular syphilis, can produce similar signs, and complicate the picture of a simple psychosis.

In November 1928, Brander, in opening a Royal Medico-Psychological Association discussion on General Paralysis, related how, in a series of 166 cases, the diagnosis was arrived at on clinical grounds and verified, in all cases, post-mortem. During the same period, 7 cases had had another diagnosis, which was altered to General Paralysis, on the strength of the laboratory findings. Three of these cases died and the diagnosis was confirmed. A fourth case remitted and was discharged two years later. A fifth continued unchanged for 18 years. The sixth case had previous attacks of Mania-melancholia, and had had two remissions since being regraded as a General Paralytic. The seventh had a diagnosis altered from Dementia Praecox, but eighteen years later he too was alive and working usefully. Brander's contention was that in four of these cases the progress was so different from the other 169 that the diagnosis of General Paralysis, in their case, was wrong, despite the serological reactions.

Professor Robertson, at the same clinical meeting, said.....

> "The factor which differentiated General Paralysis from any other syphilitic condition was the test of treatment".

He believed that serological methods had made the diagnosis more accurate by including many earlier types which responded well to treatment. Soutar, though not deprecating the value of treatment, thought it wrong to assume General Paralysis merely on the presence of serological reactions.....

> "They might be suffering from any other form of psychosis..... Might be an ordinary Melancholia or a variety of Delusionl insanity".

A review in the Journal of Mental Science of a paper on "General Paralysis and Schizophrenia" by Claude, assigns to the author the opinion that General Paralysis could co-exist with Schizophrenia, of the Catatonic and Paranoid types.

Stewart, in comparing the colloidal benzoin test with the Lange, said that the former had only failed in one case, that of a melancholic who twelve months later gave a positive reaction. "At the second test, however, the clinical condition had changed to one of Melancholic General Paralysis".

Gordon has stated that in the records there are some cases pointing to the co-existence of manic-depressive states and cerebral syphilis. In regard to Dementia Praecox he wrote, ...

> "It seems, therefore, logical to contend that syphilis is capable of creating a syndrome resembling that of Dementia Praecox. On the other hand, the deviation in the typical manifestations, and in the course of the infection, leads one logically to admit another presumption, namely that the persons thus affected are potentially praecox men, who would have developed the disease in spite of syphilis, but in whom the syphilitic infection introduced certain modifications".

Tennent, in discussing response to treatment, stated that.....

> "the clinical form offering the greatest likelihood of success in treatment, is the manic".

The euphoric type, which he closely links with the manic type, was in his experience the next most favourable. Other writers on the subject, whom he quotes, held similar views. Of five of his own cases, who presented symptoms for less than a month, and who showed good remissions with treatment, four were manics. Other investigators mention Melancholia and Hypochondriacal

types as varieties in which the outlook, with treatment, was good. It is common experience, however, that Manic-depressives frequently show spontaneous remissions, and so with treatment, serological improvement could coincide with such a remission. One is reminded here of Ostler's statement that.....

> "prolonged remissions, which are not uncommon, (in General Paralysis) are often erroneously attributed to the action of remedies".

On the other hand serological reactions in themselves are no guarantee of clinical improvement, as many cases, clinically unimproved, do eventually show negative serological findings.

Hutton stresses that the co-existence of mental symptoms and of positive reactions in blood and c.s.f., is not sufficient evidence on which to base a diagnosis of General Paralysis. She points out that the c.s.f. becomes positive during the secondary stage of syphilis and remains so throughout the latent period.....

> "During this time the patient may exhibit some other form of mental disorder, such as Schizophrenia, Cyclothymia, or a Toxic-confusional state. The correct diagnosis in cases of this sort will be that of the manifest psychosis and latent asymptomatic syphilis, and both prognosis and treatment must be based on recognition of this".

Dr Hutton's reference to asymptomatic neurosyphilis raises a question which I feel has a distinct bearing on the subject of my dissertation, and one upon which I must expand.

Latent or Asymptomatic Neurosyphilis has been defined as the presence of pathological changes in the cerebrospinal fluid in the absence of symptoms, or clinical signs, of disease of the nervous system. Worster-Drought recognises two varieties - an early and a late. The early asymptomatic form is found in the first few months of infection, and coincidentally with the secondary manifestations of syphilis. It is, he believes, the result of a mild, though asymptomatic, meningitis, which responds favourably to ordinary antisyphilitic treatment. The late form of asymptomatic neurosyphilitis is found, generally accidentally, many years after the primary infection. Worster-Drought believes that this variety of asymptomatic neurosyphilis probably represents a form of parenchymatous neurosyphilis, from the serological changes, the resistence to ordinary antisyphilitic measures, and the fact that some cases terminated in General Paralysis. In the course of Dattner's study, he does not appear to

place the same significance upon early asymptomatic neurosyphilis as does Worster-Drought. From a wide survey of the literature he concludes that, though the percentage of syphilitics showing positive fluid syndromes may vary between 20% and 50% two years after infection.....

> "there is a marked tendency to spontaneous elimination of the invading agent in the early years of syphilitic involvement of the central nervous system" .... "We do not have to pay the same attention to spinal fluid changes within the first years of infection as to those present in the late period, for there is still a possibility that they may disappear spontaneously".

He stresses, however, that it is extremely rare for patients with persistently positive cerebrospinal fluid syndromes to reach a great age without showing signs of clinical neurosyphilis. Supporting evidence of this is given by Moore and Hopkins, quoted by Dattner, who showed that the percentage of pathological spinal fluids in Asymptomatic Neurosyphilis is less in the late cases than in the early. This is "due to the fact that by this time a number of cases have developed frank clinical neurosyphilis".

The significance, to my mind, of such a high proportion of syphilitics with positive serological findings within a

short time of infection, lies in the possibility that, if these patients develop an intercurrent psychosis, manifestly schizophrenic, manic-depressive, or paranoid, the mere finding of spinal fluid reactions of a positive nature, could tend, and almost certainly does, to lead to an erroneous diagnosis of General Paralysis.

With regard to late asymptomatic neurosyphilis, Dattner, like Worster-Drought, believes that the positive cerebrospinal fluid findings indicate an active syphilitic process. He considers spontaneous reversal of such findings rare in this late form. Unlike Worster-Drought, however, he states that such late forms of asymptomatic neurosyphilis may later show meningo-vascular signs and symptoms, or those associated with General Paralysis. In a subsequent chapter of his book, Dattner, seeks to establish that asymptomatic neurosyphilis and meningovascular neurosyphilis should be dealt with under the one heading.....

> "...since both are caused by identically the same process, looked upon at one time from the pathologic-anatomic point of view, at another from the clinical. The discriminating factor is the appearance of objective clinical signs and symptoms".. ... "As long as the process has not impinged on structures that are essential for the proper functioning of the nervous system, or has not progressed too far, we are dealing with asymptomatic neurosyphilis".

Whichever view is held, however, as to the type of neurosyphilis into which the late asymptomatic variety finally develops, the possibility of the patient showing clinical evidence of a psychosis, unrelated to the syphilitic process, must be far from remote. It must be, at least, in the same proportion as psychoses affect the non-syphilitic population. There is little doubt in my mind that such cases would, in most circumstances, be regarded as General Paralytics. If Dattner's view is the correct one, those cases with a manifest psychosis and neurosyphilis would have a much more favourable prognosis, and, if erroneously diagnosed as General Paralytics, would give a false impression of the curative powers of modern therapies in Dementia Paralytica.

Two former colleagues have told me that each had treated a clinically undisputable case of Melancholia with Electric Convulsion Therapy, only to find, while treatment was well under way, that the cerebrospinal fluid showed all the positive findings associated with General Paralysis. No evidence of neurosyphilis, other than a positive blood serum, had been elicited on admission. The interesting point is that both cases showed rapid and

complete mental remissions with E.C.T., and before being given malaria and tryparsamide. Subsequent treatment of the neurosyphilis produced beneficial results in the c.s.f. Each of these cases was undoubtedly a psychosis with asymptomatic neurosyphilis. If treatment with E.C.T. had been posponed until the cerebrospinal fluid findings had become available, I have little doubt, that in both cases, the diagnosis would have been altered to one of General Paralysis, and that treatment with malaria and tryparsamide would have been the only one given. Any improvement or mental remission would have been attributed to the effects of the malaria and tryparsamide, and both cases would have gone to swell the numbers of Dementia Paralytica cases who had recovered.

Nicol and Hutton mention similar cases whom they found to be suffering from Schizophrenia, Manic-depressive insanity, or some chronic Delusional state.....

> "They have been discharged, but in several instances have relapsed, true to the type of their mental disorder".

It is a well recognised fact that late forms of meningo-vascular syphilis may be indistinguishable from

those of a parenchymatous nature and Dattner reminds us that mistakes in diagnosis, classifying Meningo-vascular neurosyphilis as Dementia Paralytica, were strongly suspected, on the part of the Vienna Clinic, when the first reports of therapeutic successes in malaria-treated cases were published. He contends that mistakes of this kind are unavoidable....

> "since in borderline cases even the pathologists fail to differentiate between General Paralysis and Meningo-vascular syphilis".

In an article on 'The Clinical Aspects of General Paralysis', Nicol and Hutton wrote,.....

> "It was at first thought that diagnosis would be made easier - (with Laboratory aids) - but, on the contrary, reliance on the serological findings has led to confusion and wrong diagnosis, with consequent fallacious statistical results. While we agree that the true general paralytic, before treatment, must exhibit a positive Wasserman of the cerebrospinal fluid, with increased cell content and protein, and, in most cases, a typical paretic curve, we must not lose sight of the reverse, and that is that a positive cerebrospinal fluid does not necessarily label a case as a general paralytic. In other words, we meet with three clinical varieties, in which the serological findings are positive:
>
> (1) The true general paralytic, who should be diagnosed without the aid of laboratory findings, but in whom the Wasserman affords merely confirmatory evidence.

(2) Those doubtful cases in which there may be one or two vague mental symptoms or clinical signs, possibly suggestive of General Paralysis, and in which the presence of a positive result (in c.s.f.) should indicate the possibility of General Paralysis and the advisability of therapeutic measures.

(3) Those cases in which, in the course of routine examination, a positive serum is discovered, so demanding a lumbar puncture, yet in spite of positive serological findings they can in no way be regarded as suffering from general paralysis".

These three clinical varieties, defined by Nicol and Hutton, favour my contention that Dementia Paralytica is a distinct entity, and that other psychoses, associated with positive serological findings, and in some cases neurological signs, are, but should not be, classified as General Paralysis.

It is not denied that many cases of meningo-vascular syphilis terminate in a dementia as profound as occurs in the cerebral parenchymatous form, and that, at post-mortem, wasting, indicating neuronic destruction, may be gross. Even plasma cells, at one time considered as diagnostic for General Paralysis, may be found in cases of meningo-vascular syphilis. The important distinction lies in the fact that, potentially, cases of meningo-vascular syphilis present a better prospect with treatment. The more advanced a case is, however, the less is the possiblity of cure, or even arrest, of the disease process. Dattner puts it in

another way, ...

> "As long as the destructive process is in its initial stage and little damage has been inflicted upon the parenchymatous tissues, it - (the reversal of the psychic state of the patient to his former standard) - may still be possible. But this cannot be expected in patients who come under our care when they are already deteriorated to a marked degree .... It is beyond the clinician's control to restore tissues already irreparably damaged".

This is a view in keeping with the earliest opinions of neuro-pathologists such as Mott, Shaw Bolton and Watson, and generally expressed by authorities at the present time. There is little doubt but that many cases of meningo-vascular syphilis are treated for the first time, when the disease is too advanced, the secondary neuronic destruction too diffuse, and the consequent dementia too far established, for more than an arrest of the syphilitic process to be obtained. With the resolution of the inflammatory process, however, as distinct from the degenerative, life can be prolonged for a few years, though the most that can be expected in the way of social rehabilitation, would be simple routine work under supervision in hospital. Many cases of this type are to be seen in mental hospitals today, and, in my own experience, few have a diagnosis other than General Paralysis.

It is frequently stated that serological findings can differentiate between cases of interstitial and parenchymatous neurosyphilis. Even Dattner, however, states that.....

> "in many cases it is extremely difficult, on serological grounds, to differentiate G.P.I. and Meningo-vascular syphilis".

His survey of the literature on the serology of neurosyphilis is probably the most comprehensive in existence, and yet, a study of his work cannot fail to leave the impression, that there is no especial group of serological reactions and findings, which is pathognomonic of any particular variety of neurosyphilis. We have already seen the view expressed that early Asymptomatic or Latent neurosyphilis is the result of a mild meningeal infection. Yet many investigators have recorded, in cases of early asymptomatic neurosyphilis, positive Wasserman reactions, increased cell counts, increased globulin reactions, and not infrequently 'paretic' Lange curves. The late form of Latent neurosyphilis, Dattner contends, is concomitant with Meningo-vascular neurosyphilis, and yet Worster-Drought states that the Lange curve is invariably 'paretic'.

A positive Wasserman reaction is stated to be found in all cases of untreated General Paralysis, but a similar

finding is by no means infrequent in Meningo-vascular syphilis. This latter result is explained by the fact that, in meningo-vascular conditions, parenchymatous tissue is frequently involved to some extent. The combination of a positive blood Wasserman and a negative cerebrospinal fluid Wasserman, is considered as indicative of a Meningo-vascular infection both by Dattner and Worster-Drought, and judging from my own experience this is more than feasible, as more than 40% of cases presenting this phenomena in my series of cases were improved with treatment.

Much stress has been laid on the Lange Colloidal Gold reaction as a diagnostic indicator, and frequently the presence of a 'paretic' curve - that is, precipitation in the highest concentration, or the first zone - is the finding on which a diagnosis of General Paralysis is made. But, though this curve may invariably be demonstrated in undisputed cases of General Paralysis, it also occurs, and not infrequently, in cases of Tabes Dorsalis, Tabo-paresis, Meningo-vascular syphilis, "Neuro-recurrences", Asymptomatic syphilis, and even in cases of non-syphilitic infection of the nervous system.

From this, one is entitled to state that, if a diagnosis has been made in cases presenting a mental picture of Mania, Melancholia, Schizophrenia, and so on, merely on the demonstration of a 'paretic' Lange curve, -- as so frequently does happen -- then the diagnosis of Dementia Paralytica in many cases could be unwarranted.

Pleocytosis offers no reliable guide to the form of neurosyphilis. In meningo-vascular cases the increase in the number of cells may be slight, (Worster-Drought), while in General Paralysis the increase can be considerable. It may be appropriate at this point to mention that the routine cell count at Rainhill was abandoned by Watson who stated that.....

> "it did not compensate for the time and labour involved in the examination of a large number of cases".

The presence of an increase in Globulin - a usual diagnostic test - though to a high degree characteristic of syphilis, is, according to Dattner, by no means specific for it, and "may be positive in many different neuropsychiatric disorders".. Quantitative tests for globulin are all very complex, or require considerable amounts of cerebrospinal fluid, and all lack accuracy. Thus,

though in conjunction with other positive findings, an estimation of globulin excess, may be valuable, in itself it cannot be used as a reliable indicator of the type of syphilitic process in the nervous system of any given patient.

Finally, I may be permitted to reiterate Dattner's remarks on the subject of the diagnostic value of cerebrospinal fluid reactions as a whole. While granting that in general, typical 'fluid syndrome' are found in neurosyphilis, he emphasises that.....

> "There is not a single test that can be considered as exclusively characteristic of a specific type of neurosyphilis".

Bearing this conclusion in mind, it is apparent that positive cerebrospinal tests cannot be categorically stated to differentiate, for example, between meningo-vascular and parenchymatous neurosyphilis. Further, cases with positive fluids, on the average typical of General Paralysis, associated with atypical mental symptoms and signs, cannot justifiably be finally diagnosed as General Paralysis on the mere presence of these findings, as many other clinical types could give similar mental and serological pictures.

Thus, in cases where clinical examination and assessment would indicate a diagnosis of a Psychosis with Neurosyphilis, such a diagnosis is justified even in the presence of positive serological findings. In other words, laboratory tests do not confute the possibility, or practicability, of my contention that ordinary psychoses, associated with evidence of neurosyphilis, are diagnosed as General Paralysis.

I have now demonstrated the reasons that have led me to separate these 270 cases in my series from those that I have already proved to be cases of Dementia Paralytica. I have considered the question from the mental state, the neurological findings, the serological and pathological changes, and I have sought by lengthy reference to the literature to support my own conclusions. I believe that in so doing, I have succeeded in establishing the second objective of my thesis, which may now be restated as, ...

(2) Fundamental reaction-type psychoses do occur in patients suffering from neurosyphilis and are frequently erroneously or misguidedly diagnosed as Dementia Paralytica, merely on the presence of certain changes in the character of the cerebro-

spinal fluid, on the response to treatment, or on the tendency of untreated or inadequately treated cases to dement. These cases are primarily meningo-vascular syphilitics and the syphilis may or may not be a precipitating agent in the particular form of mental disorder exhibited. The process does extend to the cerebral cortex, especially if treatment is inadequate, and by so doing gives rise, secondarily, to a clinical condition of dementia, indistinguishable from Dementia Paralytica.

SECTION VII.

PROGNOSIS

One hesitates, from experience, to prognosticate in any case of neurosyphilis, as clinical signs and symptoms may vary in degree, from mild to severe, and yet not indicate the possible response to treatment. Mild cases may progress to dementia and death, despite vigorous treatment, whereas severe cases may respond remarkably to normal routine medication. I have shown that serological examination also offers little help in this direction, though certain combinations of findings do suggest a better prospect than others.

From earliest times the prognosis has been considered to be poor in General Paralysis, and I have shown how, in those cases which I have classified as examples of this disorder, even with modern therapy the outlook is grim. Those few cases in which the disease process is arrested, do not escape without some residual impairment of intellectual function.

When one considers the nature of the pathology of the condition - a primary diffuse neuronic destruction,

particularly affecting the frontal cortex - the result of treatment can occasion no surprise. Beyond treating the disease in its prodromal stage, no possiblity of preventing serious damage is possible. Unfortunately it is rarely that cases present themselves at this stage for treatment, and, on the contrary, when they do seek treatment, so much of the neuronic element has been destroyed that it is beyond the physician's power to restore the lost function.

The prognosis in Syphilitic Insanities, on the other hand, has always been regarded much more optimistically. Even during last century when the treatments available, compared with modern methods, were very limited, most authorities have recorded considerable success with such cases. Fournier, who, as I have previously noted, was the first to describe syphilitic Pseudo-general Paralysis, differentiated the condition from "true" General Paralysis on, among other grounds, the possibility of treatment having a curative effect.

In the years subsequent to Mott's researches all authorities have indicated agreement with his dictum, that

it was important to differentiate between primary Parenchymatous neurosyphilis and Interstitial, or Meningo-vascular neurosyphilis from the fact of the much more favourable response to treatment in the latter condition. Few, if any, physicians these days would disagree with this opinion, and there is also general agreement that the reason for this more favourable prognosis lies in the fact that the inflammatory process in Interstitial neurosyphilis can be attacked much more rigorously with antisyphilitic remedies via the blood stream.

I have already indicated that trivalent arsenical compounds, by their inability to penetrate the blood - cerebrospinal fluid barrier, have little or no effect upon parenchymatous neurosyphilis, and that pentavalent arsenicals, such as tryparsamide, though able to help in the arrest of the disease process, are the only organic drugs available for this purpose. Most authorities tend to administer tryparsamide with caution, as it is believed to cause or accelerate optic atrophy, but it is my own view that the use of the drug is justified, even in these days of penicillin, and that the dangers attributed to it

are over emphasised. In this connection it is interesting to note Pearce's investigation in the use of the drug in Trypanosomiasis, where the total dosage per course of treatment is generally much larger than that advocated in General Paralysis (40 to 50 grammes in Trypanosomiasis compared to 24 to 36 grammes in Neurosyphilis). She states, after extensively reviewing the literature, that.....

> "The consensus of opinion is that..... complications may be largely avoided by employing a system of small or medium sized doses, or of graduated doses given at intervals of not oftener than once a week".

She does not regard visual complications as constituting any serious objection to the use of the drug, and quotes the following summary of cases reviewed in the literature in support of her opinion:-

Total number of patients.....	1658
Number of visual disturbances.....	82
Incidence of visual disturbances.....	5·0%
Incidence of transitory disturbances..	3·2%
Incidence of permanent disturbances...	1·8%

In my series of cases, as already mentioned, there were 16 cases of optic atrophy - 3% of admissions. In only 7 cases was tryparsamide given as part of the treatment, and, therefore in only 1·3% of cases could it have influenced the atrophying process - a figure which approximates closely to Pearce's.

Despite the excellent effect of tryparsamide, combined with other forms of therapy, in Dementia Paralytica, the percentage of cases showing improvement is much less than in Meningo-vascular neurosyphilis, and this is undoubtedly due to the fact that the trivalent arsenicals, combined with Bismuth preparations, can be applied in infinitely greater concentration to the diseased tissues in the latter diseases.

It follows, therefore, that if, as I believe I have proved, more than 50% of cases diagnosed as General Paralysis, were in actual fact, cases of Meningo-vascular syphilis with an inter- or concurrent psychosis, the treatment administered was, in these cases, not adequate. Few cases, for example, were given trivalent arsenic and Bismuth (Table XIX - Page 166), and it is not inconceivable that, if more cases had been vigorously treated with these drugs, the percentage of improvements would have been much higher.

Having been diagnosed, however, as Dementia Paralytica, the treatment of choice in that condition was used, with the result that the inflammatory process typical of

Meningo-vascular neurosyphilis, was more slowly attacked, and secondary neuronic degeneration not minimised.

It follows, therefore, that if a more accurate clinical diagnosis of the pathological process were possible, more appropriate and beneficial treatment could be instituted. My investigations led me, as I have attempted to prove, to the conclusion that a more precise diagnosis can be reached by adequate clinical assessment of the mental state, and by that alone. To do so would enhance the prognosis of mental disorders associated with neurosyphilis, by permitting the neurosyphilis to be rigorously treated, and by leaving the opportunity for the concurrent psychosis to be treated independently by appropriate therapeutic methods. I feel that I can now re-state the third, and final, objective of my thesis...

(3) It would be advantageous to differentiate between Dementia Paralytica, as defined in my first objective (Page 65), and Insanity with Neurosyphilis, because the principles of treatment of the neurosyphilis are vastly different in the two conditions, and, in addition, methods

appropriate to the treatment of the intercurrent, or concurrent, psychosis, in the latter, could be, where necessary, invoked.

SUMMARY AND CONCLUSIONS.

1. An attempt has been made to demonstrate, by investigating a series of 539 cases, diagnosed, at one stage or another during their stay in hospital, as cases of General Paralysis, that by careful assessment of the mental state a more accurate diagnosis could be made, and that more than half the cases analysed should have been regarded as simple reaction-type psychoses with neurosyphilis, rather than Dementia Paralytica.

2. A review of the literature since the first case of General Paralysis was described, has shown that in the years prior to the introduction of laboratory diagnostic tests for syphilis, many cases of simple mental disorder were believed to be complicated by General Paralysis, a belief which supports my conclusions.

3. Since the introduction of diagnostic tests for syphilis, the mental state has tended to become a subordinate factor in the diagnosis, and the results of laboratory examinations have come to be the factors which determine the diagnosis.

4. I have shown that, both from a study of my cases, and of the literature on the subject, such dependency on serological tests is not justified, as there is no single test or group of tests which can be considered, per se, to be infallible for any variety of neurosyphilis.

5. On the contrary, serological tests can, at the best, merely confirm a diagnosis reached by clinical assessment of each case, as positive reactions have been recorded in non-syphilitic cases.

6. Examination of the cerebrospinal fluid in confirmed cases, at intervals following treatment, can indicate, however, the response or otherwise, of the disease process to the action of the various remedies. The tests most useful in this connection are the Sigma Reaction and the Lange Colloidal Gold Test.

7. The pathologies of the different forms of neurosyphilis are distinct in the early stages. General Paralysis is a parenchymatous disease, and is evidenced by a primary degeneration of neurones, while Interstitial Neurosyphilis is principally a disease of the arteries and meninges, and only secondarily affects the neuronic elements.

8. In advanced cases of neurosyphilis it is frequently impossible macroscopically, to distinguish between the cerebral appearances in Meningo-vascular conditions and General Paralysis, as the primary neuronic destruction in the latter is evidenced by cortical wasting, which can be equalled by the secondary degeneration of nerve cells in the former.

9. Even microscopically a differention is often extremely difficult because 'mixed' types of infection are not infrequent, and parenchymatous destruction may occur concurrently with degenerative processes in the blood vessels and meninges, and present no indication as to the part originally infected.

10. From the nature of the histological changes it is apparent that the effect of treatment should be much more beneficial in these forms of neurosyphilis in which the spirochaete can be attacked most vigorously. I have shown that clinically this presumption is true, because in those cases where the condition was considered to be meningo-vascular syphilis the improvement rate was considerably greater than in parenchymatous cases.

11. A corollary to this conclusion can be stated. In General Paralysis, which is essentially a disease of the nerve cell, the prognosis is poor because the treatments available are fewer than in other neurosyphilitic conditions, and, at the best, any remedy can only halt the disease process, and cannot cause regeneration of destroyed nerve elements, or thereby restore function. In meningo-vascular conditions, on the other hand, the inflammatory process can be cured by many drugs and methods of treatment, and if these treatments are instituted before the secondary neuronic destruction becomes diffuse, restoration of function will take place.

12. Syphilis of the nervous system, or intracranial structures, as evidenced by neurological signs, cannot be diagnosed as to type, from such knowledge alone. Though involvement of the cranial nerves is more usual in meningo-vascular conditions, there are no signs, with the possible exception of optic atrophy, which cannot occur in General Paralysis.

13. The effect of treatment on nervous tissue, as indicated by neurological improvement, is variable, but

there is rarely, if ever, any improvement in the signs indicative of damage to the nerves associated with the function of sight, and movements of the pupil and eyeball.

14. Consideration of the serological, neurological, and pathological findings in 539 cases of neurosyphilis permitted no dogmatic conclusions, but estimation of the associated mental disorder indicated the possibility of a clinical differentation between Parenchymatous and Interstitial neurosyphilis.

15. It was possible to separate all but 19 cases into catagories, according to the predominant features of the psychiatric picture. In some Dementia was the prevailing syndrome; in others Confusion; whilst in many the picture was of Mania, Melancholia, Schizophrenia or Paranoid State.

16. Those cases in which Dementia or Confusion was outstanding have been shown to have been, beyond any doubt, cases of Dementia Paralytica.

17. The remaining cases have likewise been proved to have been primarily simple reaction-type psychoses complicated by neurosyphilis, which ultimately tended to obliterate the features of the fundamental disorder.

18. The error in clinical diagnosis has been shown to be approximately 20% in cases which proceed to death, by reference to the work of a pathologist prior to the introduction of serological diagnostic aids, and also to the work of a pathologist nearly 40 years later.

19. When the much more favourable response to treatment of Interstitial Neurosyphilis is borne in mind, the possible error in clinical diagnosis among 'recovered' cases of General Paralysis is likely to be considerably in excess of 20%.

20. In the cases investigated, only 29% or the 250 judged to be General Paralysis showed any arrest of the disease with treatment, compared with 47% of those cases considered to be simple reaction-type psychoses with neurosyphilis.

21. Treatments specific in Meningo-vascular syphilis -- bismuth and trivalent arsenicals -- had little effect on General Paralysis, in which pyrexial treatment -- malaria or pyrifer -- combined with pentavalent arsenic, such as tryparsamide, was the method of choice.

22. Where cases of Meningo-vascular syphilis are diagnosed as General Paralysis, and treated accordingly, the effect of treatment, though possibly beneficial, is not so effective as would be that for the actual disease.

23. Though the place of Penicillin in the treatment of Neurosyphilis is not yet firmly established, my experience, and the consensus of opinion, would appear to show that in General Paralysis, tryparsamide, and occasionally pyrexial therapy are also required, while in Meningo-vascular syphilis arsenicals and bismuth cannot be ommitted, if maximum benefit is to be obtained.

24. From consideration of all aspects of the subject, Dementia Paralytica has been defined as a disease, especially affecting the nerve elements in the frontal areas of the cerebral cortex, due to the action of the

Spirochaeta Pallida, or its toxins, and evidenced clinically by a rapidly progressive dementia, which may be preceded by a state of ocnfusion, associated with extreme restlessness, emotional lability or expansive exaltation. It is primarily a degenerative disease of the neurones, and as such, cure is not possible, though arrest of the disease process, by treatment, can prolong life, and even permit of some social rehabilitation.

25. In a similar fashion it has been shown that Fundamental reaction-type psychoses do occur in patients suffering from neurosyphilis, and that they are frequently erroneously or misguidedly diagnosed as Dementia Paralytica, merely on the presence of certain changes in the character of the cerebrospinal fluid, on the response to treatment, or on the tendency of untreated, or inadequately treated cases to dement. These cases are primarily meningo-vascular syphilitics and the syphilis may or may not be a precipitating agent in the particular form of mental disorder exhibited. The process does extend to the cerebral cortex, especially if treatment is inadequate, and by so doing gives rise, secondarily, to a clinical condition of dementia, indistinguishable from Dementia Paralytica.

26. Finally, I have shown that it would be advantageous to differentiate between Dementia Paralytica as defined above and Insanity with Neurosyphilis, because the prinicples of treatment of the neurosyphilis are vastly different in the two conditions, and, in addition, methods appropriate to the treatment of the intercurrent, or concurrent, psychosis, in the latter, could be, where necessary, invoked.

REFERENCES.

of Authors quoted in the text to whose works reference has been made.

Adams, Burton Warren - The Spectre of Neurosyphilis- Urologic and Cutaneous review - January 1941.

Bamford, C.B. - The Treatment of General Paralysis - Journal of Mental Science - July 1928.

Bianchi, L. - Brain (London) 1895.

_____ " " Textbook of Psychiatry - Translated by J.H.Macdonald - 1906.

_____ " " The Mechanism of the Brain - Translated by J.H.Macdonald - E & S Livingstone (Edinburgh) 1922.

Biggart, J.H. - Pathology of the Nervous System - E & S Livingstone (Edinburgh) 1936.

Brain & Strauss - Recent Advances in Neurology and Neuro-psychiatry - fifth edition (1945) - J & A Churchill (London)

Brander, J. - The diagnosis of General Paralysis of the Insane as a clinical and pathological entity. - Journal of Mental Science - October 1928.

_____ " " Discussion on General Paralysis - Journal of Mental Science - January 1929.

Bolton, J.Shaw - Functions of the Frontal Lobes - Brain (London) 1903.

_____ Amentia and Dementia - Archives of Neurology Vol. ii.

Bucknill & Tuke, D.Hack - Psychological Medicine - 4th Edition (1879) - J & A Churchill (London).

Campbell, A.W. - Neuro-muscular changes in General Paralysis - Journal of Mental Science - April 1894.

Carlill, Hildred - Diagnosis and Treatment of Syphilis of the Central Nervous System - The Lancet, February 16th 1918.

Claude, H. - General Paralysis and Schizophrenia - Journal of Mental Science - July 1928.

Clouston, T.S. - Clinical Lectures on Mental Diseases - Sixth Edition (1904) - J & A Churchill (London).

Cobb, S. - Borderlands of Psychiatry (1943).

Dattner, B. - The Management of Neurosyphilis (1944).

Esquirol, M. - Observations on Delusions of the Insane - Translated by William Liddell (1833).

Fildes, P. & Mackintosh, J. - Parasyphilis of the Nervous system - Brain, July 1913.

_____ Syphilis and Parasyphilis - Brain, September 1914.

Folsom, C.F. - Mental Diseases (1886).

Freeman, W., Watts, J.W., & Lyerley, J.G. - Psychosurgery, (1942).

Gordon, A. - Psychoses other than Paretic Dementia in syphilitic indivduals - Urologic and Cutaneous Review - January 1941.

Haslam, John - Observations on madness and melancholy - 2nd edition, London (1809).

Haskins, J.LeRoy. - The Psychiatrist and Neurosyphilis - Urologic and Cutaneous Review (1941).

Head, H., & Fearnsides, E.G. - The Clinical Aspects of syphilis of the nervous system - Brain, September 1914.

Harman, M., & Rosenblum, M.P. - Acute General Paralysis - American Journal of Psychiatry (1940).

Harrison, G.F., & Nussbaum, I.R. - Personal Communication on Psychosis with neurosyphilis

Henderson, D.K., & Gillespie, R.D. - A Text-book of Psychiatry - Oxford Medical Publications - 6th edition (1946).

Hutton, E.L. - Recent Advances in the Aetiology and Treatment of Neurosyphilis - Journal of Mental Science - January 1941.

International Statistical Classification of Diseases, Injuries, and Causes of Death (Vol. I) - His Majesty's Stationery Office (1949).

Kraepelin, E. - Lectures on Clinical Psychiatry - Translated by T.Johnstone (1904)

_____ - Manic-Depressive Insanity and Paranoia - Translated by R.H.Barclay.

Lugaro, E. - Modern Problems in Psychiatry - Translated by D.Orr and R.G.Rows (Manchester) (1909).

Lewis, H.W. - Syphilis in General Paralysis of the Insane - Archives of Neurology, Vol. 1, 1899.

Maudsley, H. - Pathology of Mind (1879).

Meagher, E.T. - General Paralysis and its treatment by induced Malaria - Special report of Board of Control (England & Wales) 1929.

Mickle, W.Julius - "General Paralysis of the Insane" 1886

_____ - Section on "General Paralysis" in Tuke's Dictionary of Psychological Medicine (1892)

Mott, F.W. - Archives of Neurology, Vol. I and II.

_____ - Syphilis of the Nervous System, Vol. IV (1910)

Muncie, W. - Psychology and Psychiatry (1939).

Moore, J.E., & Hopkins, H.H. - Asymptomatic Neurosyphilis - Journal of the American Medical Association (1930).

Nicol, W.D., & Hutton, E.L. - Some clinical aspects of General Paralysis - Journal of Mental Science - October 1935.

_____ - Neurosyphilis and its treatment - Journal of Mental Science, January 1944.

Nicole, J.Ernest - Malaria in Neurosyphilis - Journal of Mental Science -- July-October 1943.

Ogilvie, Robertson F. - Pathological Histology - E & S Livingstone (Edingburgh) (1940).

Ostler, Wm., & McCrae, Thos. - Principles and Practice of Medicine (10th Edition) - D.Appleton & Co., London (1925).

Pearce, L. - The treatment of Human Trypanosomiasis with tryparsamide - Monograph No.23 of the Rockefeller Institute for Medical Research - August 1930.

Pritchard, J.C. - A treatise on Insanity (1835).

Reeve, E.F. - Diagnosis of General Paralysis - Journal of Mental Science - April 1928.

Robertson, G.M. - Discussion on General Paralysis - Journal of Mental Science - April 1928.

Rylander, R. - Personality changes after operation on the frontal lobes (Oxford University Press) (1939)

Savage, G.H. - Relationship between syphilis and Insanity - Tuke's Dictionary of Psychological Medicine (1892

Shaw, James. - Epitome of Mental Diseases - John Wright & Co. (Bristol) (1897).

Sigma Reaction - The Sigma and Wasserman Reactions compared - Medical Research Council - Special Report No.78 (1923).

Soutar, J.G. - Discussion on General Paralysis - Journal of Mental Science, January 1929.

Smyth, J.F. - The relation of the Spirochaeta Pallida to the pathological changes of Dementia Paralytica - Journal of Mental Science, October 1928.

———— — — Discussion on General Paralysis - Journal of Mental Science, January 1929.

Stewart, F.H. - Investigation into the prolonged treatment of General Paralysis with Tryparsamide - Journal of Mental Science, January 1930.

Watson, G.S. - Archives of Neurology, Vol. ii.

———— — — Unpublished conclusions.

———— — — Diagnosis of G.P.I. - Journal of Mental Science, April 1928.

Weil, A. - Text-book of Neuropathology - Heinemann (London) (1946).

Worster-Drought, C. - Neurosyphilis - John Bale & Sons (London) (1940).

APPENDIX.

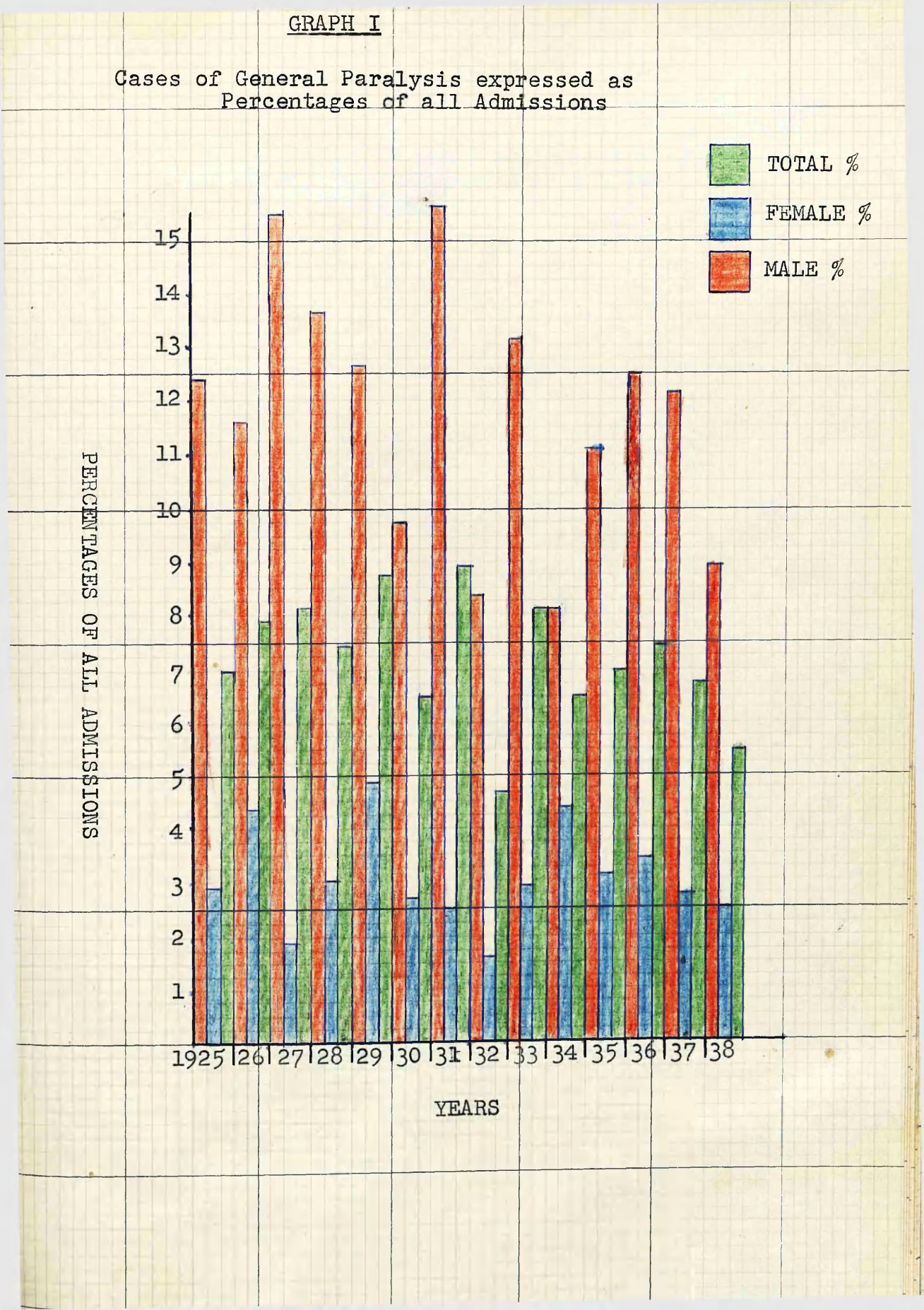
TABLE I

Shows all admissions, and cases diagnosed as General Paralysis, each year from 1925-1938. Also the percentage of General Paralysis during the same period.

	MALE			FEMALE			TOTAL		
YEAR	All Cases	G.P.I.	%	All Cases	G.P.I.	%	All Cases	G.P.I.	%
1925	331	42	12·4	336	10	2·9	667	52	7·0
1926	310	36	11·6	340	15	4·4	650	51	7·8
1927	337	52	15·5	378	7	1·9	715	59	8·2
1928	235	32	13·6	332	10	3·0	567	42	7·4
1929	316	40	12·6	311	15	4·8	627	55	8·7
1930	254	25	9·8	230	6	2·6	484	31	6·4
1931	230	36	15·7	238	6	2·5	468	42	8·9
1932	205	17	8·3	243	4	1·6	448	21	4·7
1933	242	32	13·2	241	7	2·9	483	39	8·1
1934	271	22	8·1	224	10	4·3	495	32	6·5
1935	234	26	11·1	254	8	3·1	488	34	6·9
1936	172	22	12·5	232	8	3·4	404	30	7·4
1937	166	20	12·1	223	6	2·7	389	26	6·7
1938	212	19	8·9	238	6	2·5	450	25	5·6
MEAN	251	30	11·9	273	8	2·9	524	39	7·4

GRAPH I

Cases of General Paralysis expressed as Percentages of all Admissions



GRAPH II

Annual percentage of cases admitted during the period who were diagnosed as General Paralysis.

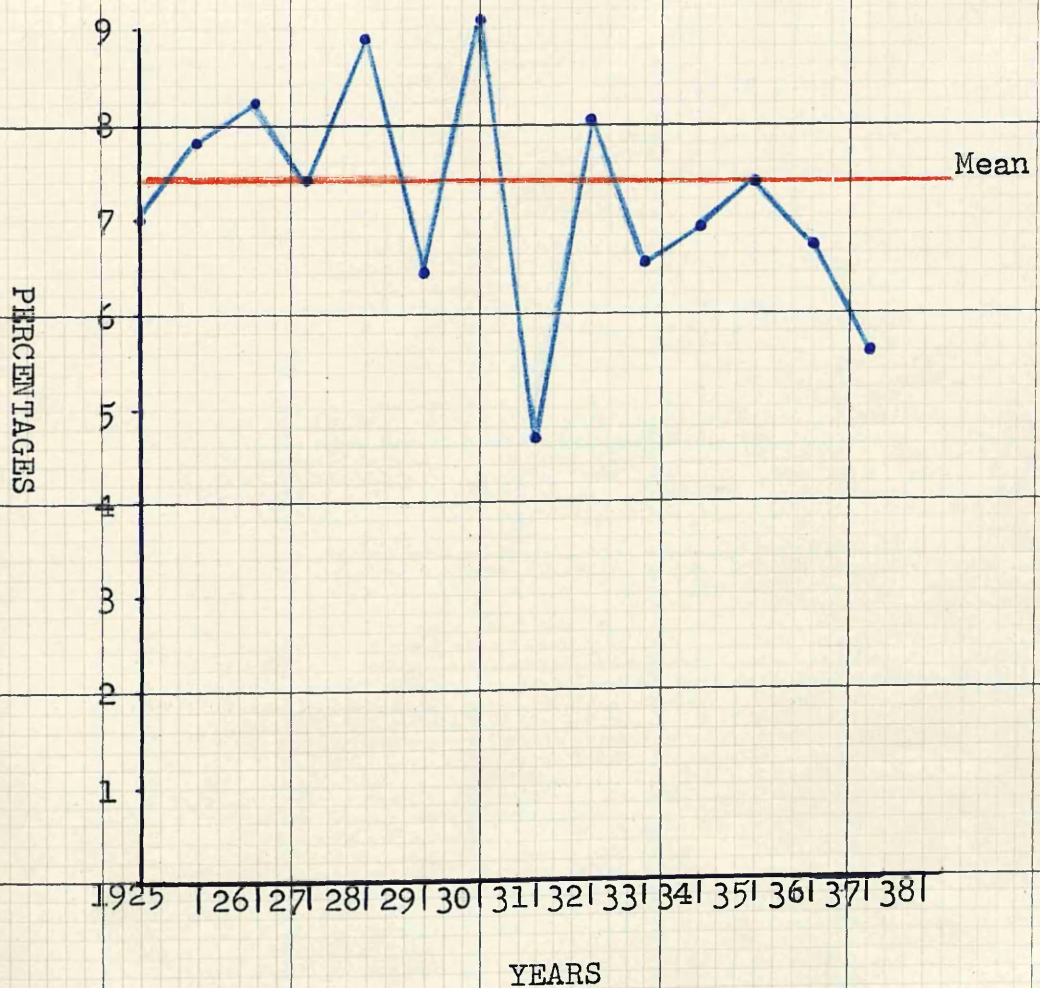


TABLE II

Admissions, discharges, and deaths, in patients who had been diagnosed as General Paralytics.

	Admissions			Discharges			Deaths		
YEAR	M.	F.	Total	M.	F.	Total	M.	F.	Total
1925	42	10	52	6	2	8	31	5	36
1926	36	15	51	7	1	8	32	7	39
1927	52	7	59	7	1	8	37	4	41
1928	32	10	42	12	7	19	18	5	23
1929	40	15	55	16	6	22	19	4	23
1930	25	6	31	10	7	17	10	4	14
1931	36	6	42	12	4	16	16	3	19
1932	17	4	21	6	1	7	15	2	17
1933	32	7	39	7	1	8	18	5	23
1934	22	10	32	2	2	4	25	4	29
1935	26	8	34	7	2	9	14	8	22
1936	22	8	30	10	2	12	9	6	15
1937	20	6	26	5	5	10	10	6	16
1938	19	6	25	5	-	5	17	-	17
TOTAL	421	118	539	112	41	153	271	63	334

GRAPH III

Admissions compared with discharges and deaths, among cases diagnosed as General Paralysis, each year from 1925-38. The steady decline in the numbers of cases admitted should be compared with the percentages of all admissions in Graph II.

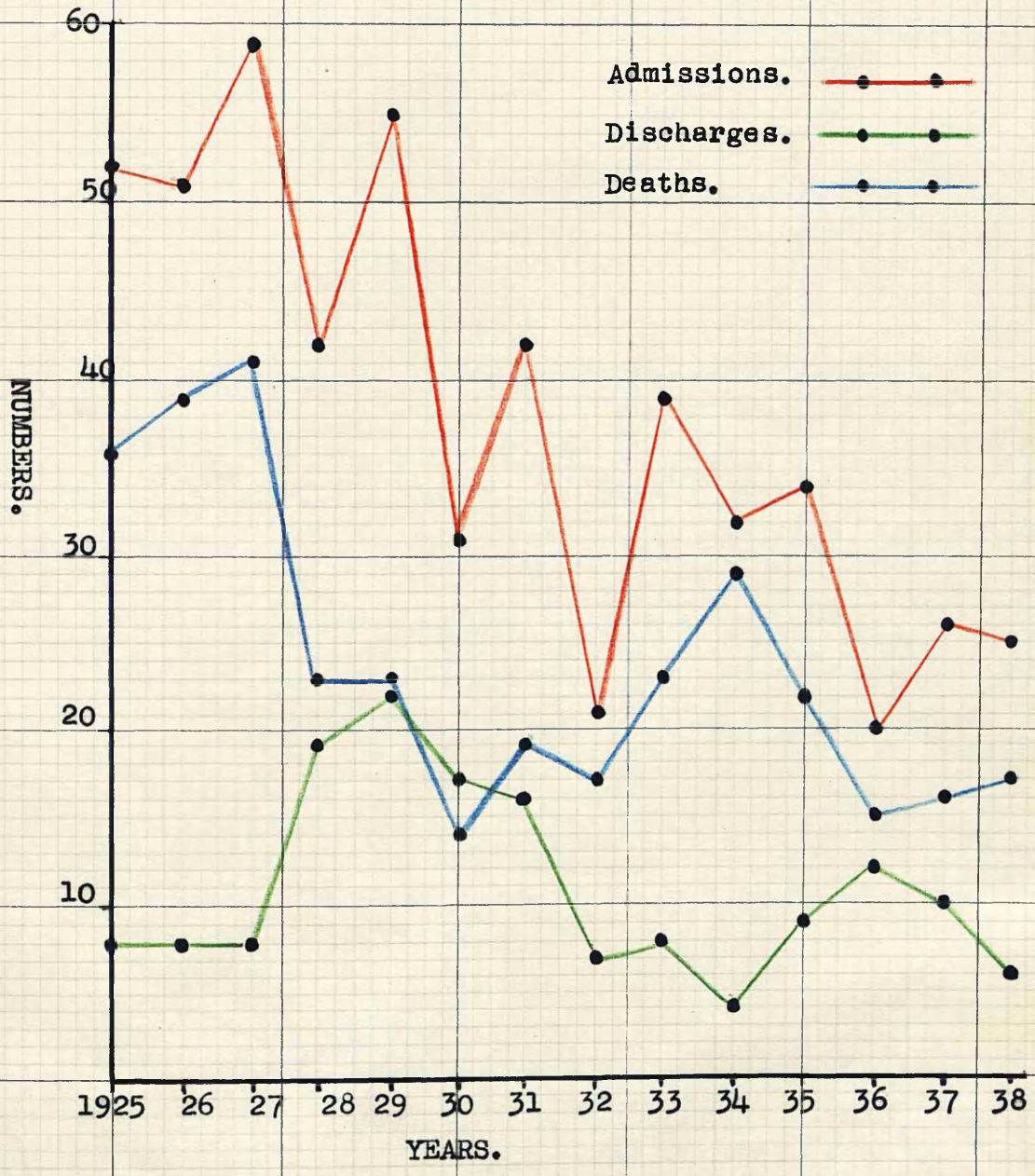


TABLE III

The number of patients admitted and whether they died, were discharged, or remained in hospital.

	Admitted	Discharged	Deaths	In Hospital	Total Improved
Males	421	112	271	38	150
Females	118	41	63	14	55
Totals	539	153	334	52	205

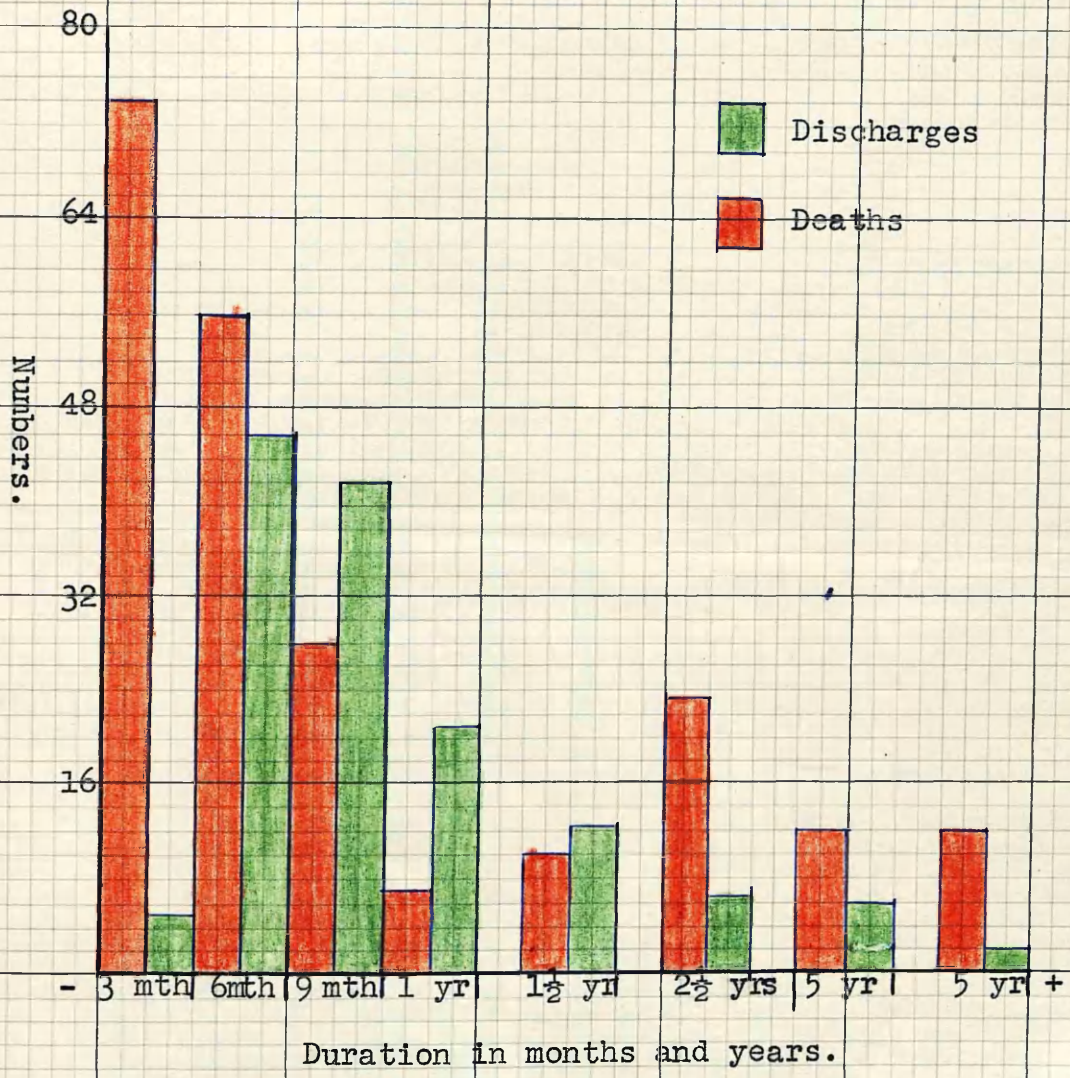
TABLE IV

The above expressed in Percentages.

	Admitted	Discharged	Deaths	In Hospital	Total Improved
Males	78%	27%	64%	9%	36%
Females	28%	35%	53%	12%	47%
Totals	100%	28%	62%	10%	38%

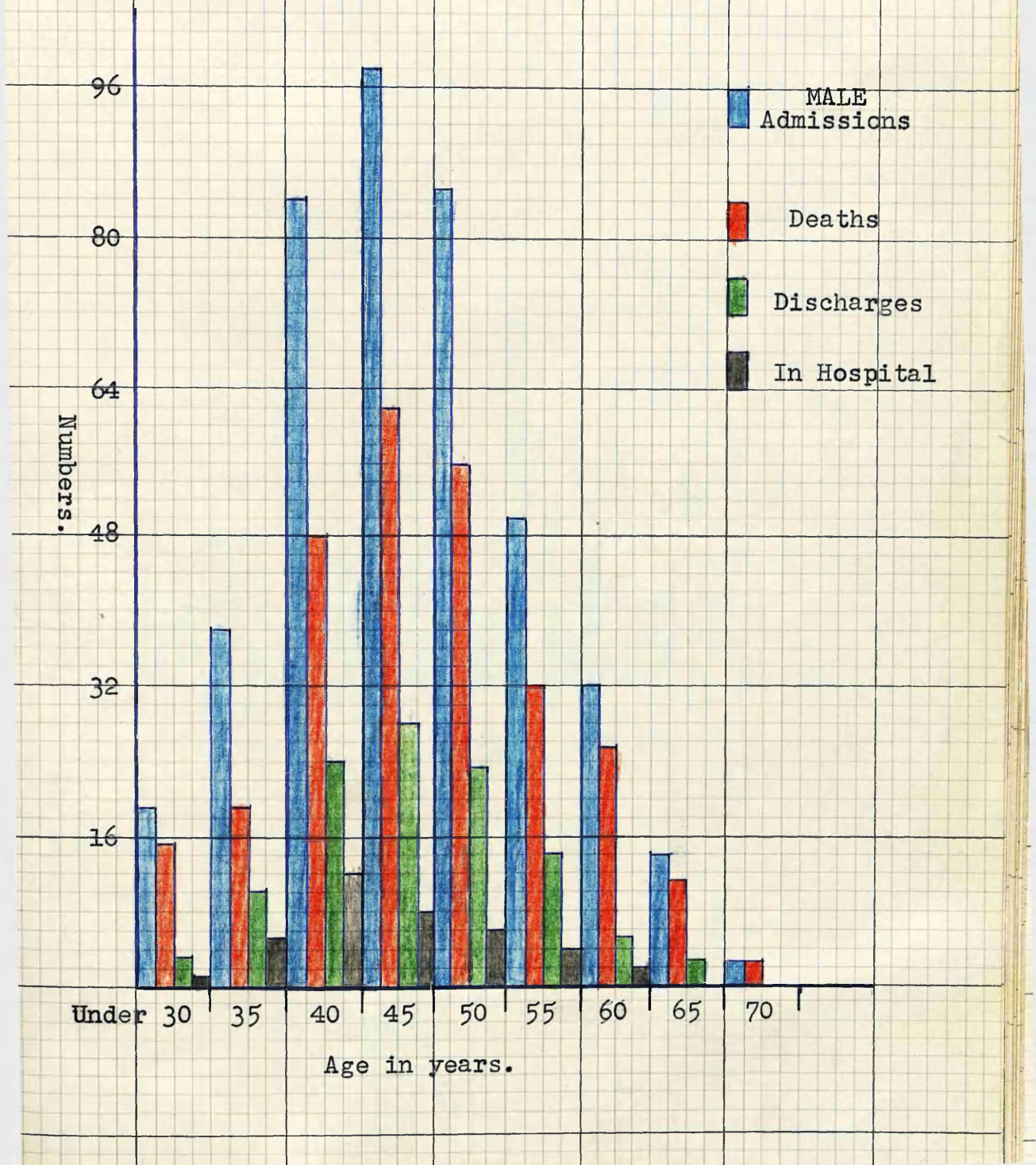
GRAPH IV

Duration of Residence in Hospital prior to death or discharge of those patients who received some form of antisyphilitic treatment.



GRAPH V

Illustrating age groups, on admission, of all Males and whether they died, were discharged, or remained in hospital.



GRAPH VI

Illustrating age groups, on admission, of all female patients, and whether they died were discharged, or remained in Hospital.

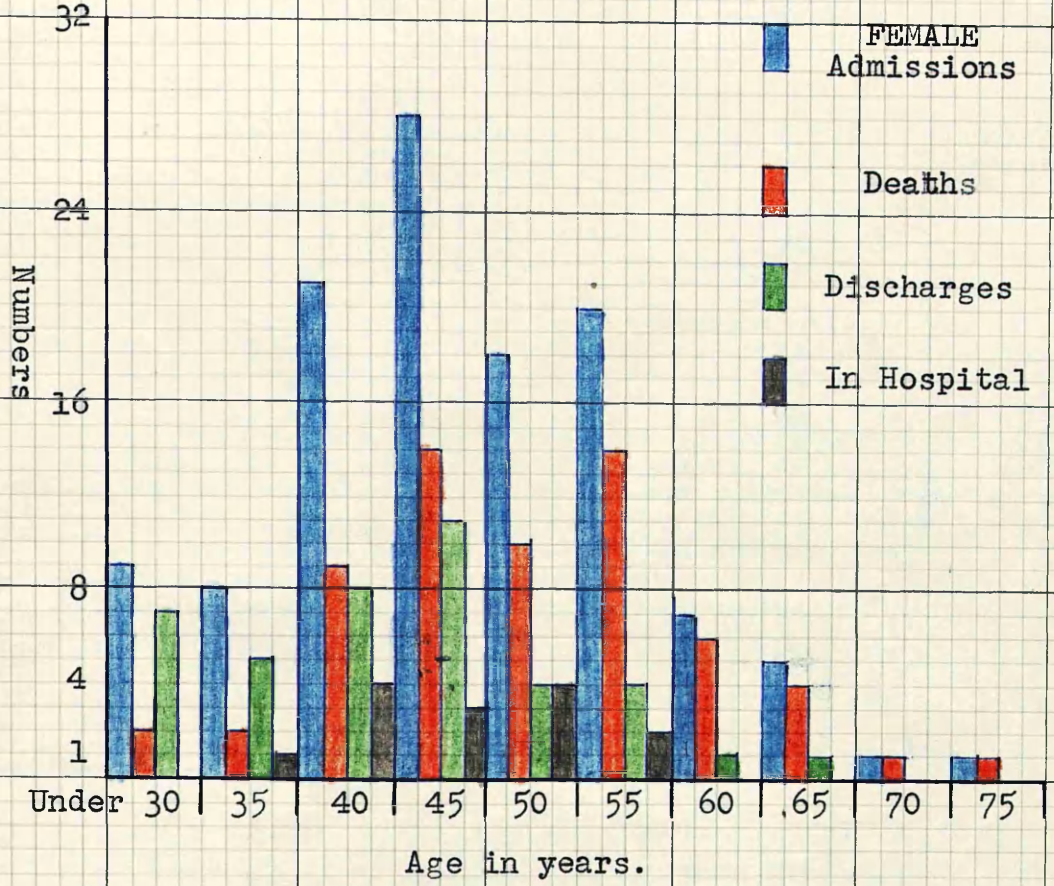


TABLE V.

Gives mental condition on admission of all patients, and whether dead, discharged, or remaining in Hospital.

	DEATHS		DISCHARGES		IN HOSPITAL		TOTAL		COMBINED TOTAL.
	M	F	M	F	M	F	M	F	
1. DEMENTIA	49	8	11	0	6	1	66	9	75
2. CONFUSION	101	18	32	12	6	6	139	36	175
With Restlessness	60	17	18	10	4	5	82	32	114
With Emotional Lability	11	0	2	0	0	1	13	1	14
With Exaltation	30	1	12	2	2	0	44	3	47
3. Manic-depressive.	42	23	27	17	2	4	71	44	115
MANIA.	16	12	8	9	2	3	26	24	50
MELANCHOLIA	26	11	19	8	0	1	45	20	65
4. Schizophrenia	31	12	10	10	9	0	50	22	72
5. Paranoid States.	36	1	27	1	15	3	78	5	83
6. Unclassifiable	12	1	5	1	0	0	17	2	19
TOTALS	271	63	112	41	38	14	421	118	539

TABLE VI

Gives total of the two main sub-divisions according as whether dead, discharged, or in Hospital.

	DEATHS		DISCHARGES		IN HOSPITAL		TOTAL		COMBINED TOTAL.
	M	F	M	F	M	F	M	F	
1. DEMENTIA	49	8	11	0	6	1	66	9	75
2. CONFUSION	101	18	32	12	6	6	139	36	175
TOTAL	150	26	43	12	12	7	205	45	250

TABLE VII

3. MANIC DEPRESSIVE	42	23	27	17	2	4	71	44	115
4. SCHIZOPHRENIA	31	12	10	10	9	0	50	12	72
5. Paranoid States.	36	1	27	1	15	3	78	5	83
TOTAL	109	36	64	28	26	7	199	71	270

TABLE VIII

Numbers and percentage improvement in each group, showing that the mental state can give some indication of prognosis.

GROUP	TOTAL CASES	IMPROVED	o/o
1. DEMENTED.	75	18	24%
2. CONFUSIONAL	175	56	32%
3a. MANIA.	50	22	44%
3b. MELANCHOLIA.	65	28	43%
4. SCHIZOPHRENIA.	72	29	40%
5. PARANOID.	83	46	55%

TABLE IX

Showing severity of neurological signs on admission of all patients, and whether they died, were discharged, or remained in hospital.

	DEATHS		DISCHARGES		IN HOSP.		Total		Total
	M	F	M	F	M	F	M	F	
1. MARKED SIGNS.	138	31	62	17	16	4	216	52	268
2. SLIGHT.	79	21	37	12	12	7	128	40	168
3. NO SIGNS.	48	13	15	11	13	3	76	27	103
TOTALS	265	65	114	40	41	14	420	119	539

TABLE X

Showing incidents of commoner neurological signs, on admission, in all patients, and classified in accordance with eventual disposal.

	DEATHS		DISCHARGES		IN HOSPITAL		TOTAL	
	M	F	M	F	M	F	M	F
1. Pupillary changes & Cranial Nerves.	151	31	70	20	22	4	243	55
2. Deep reflexes increased.	89	24	50	10	10	5	149	39
3. Deep reflexes absent.	66	14	20	11	10	5	96	30
4. Speech disorders	56	10	31	1	6	1	93	12
5. No Signs.	48	13	15	11	13	3	76	27

TABLE XI

Incidence of main neurological signs on admission, in those patients exhibiting mental states of Mania, Melancholia, Schizophrenia, and Paranoia.

	MALES	FEMALES	TOTAL
1. Pupillary Changes.	63	27	90
2. Other Cranial nerves.	15	6	21
3. Speech disorders.	19	3	22
4. Exaggerated Reflexes.	49	18	67
5. Diminished Reflexes.	26	13	39
6. No signs.	58	16	74

TABLE XII

Mental states on admission of all patients with no neurological signs, and whether dead, discharged, or remaining in Hospital.

	DEATHS		DISCHARGES		IN HOSPITAL.		TOTAL		COMBINED TOTAL
	M	F	M	F	M	F	M	F	
1. DEMENTIA	4	1	2	-	-	-	6	1	7
2. CONFUSION	13	6	1	-	-	1	14	7	21
(a) With Restlessness	8	5	-	-	-	1	8	6	14
(b) With Emotional Lab.	1	1	-	-	-	-	1	1	2
(c) With Exaltation.	4	-	1	-	-	-	5	-	5
TOTAL 1 & 2	17	7	3	-	-	1	20	8	28
3. Manic-Depressive	15	4	6	6	2	1	23	11	34
(a) Mania.	10	3	5	3	1	1	16	7	23
(b) Melancholia	5	1	1	3	1	-	7	4	11
4. Schizophren.	13	1	6	4	4	1	23	6	29
5. Paranoid.	3	-	-	1	7	-	10	1	11
TOTAL. 3. 4. & 5.	31	5	12	11	13	2	56	18	74
6. Unclassifiable	-	1	-	-	-	-	-	1	1
GRAND TOTAL	48	13	15	11	13	3	76	27	103

TABLE XIII

Showing numbers and percentages of total patients with no neurological signs, who presented mental states of (1) Confusion-Dementia, and (2) of Mania-Melancholia-Schizophrenia and Paranoia.

	M	F	TOTAL	PERCENTAGE OF TOTAL CASES	PERCENTAGE OF GROUP CASES.
1. DEMENTIA ETC	20	8	28	5%	11%
2. MANIA ETC.	56	18	74	14%	27%
TOTAL.	76	26	102	19%	-----

TABLE XIV

Showing effect of treatment on patients with no neurological signs according to mental state, and compared with response of all patients.

	M	F	TOTAL	PERCENTAGE IMPROVED. With no Signs	of all Cases.
1. DEMENTIA ETC	3	1	4	14%	29%
2. MANIA ETC.	25	13	38	51%	46%
TOTALS.	28	14	42	41%	38%

TABLE XV

Showing comparison of the strength of the Sigma reaction in the blood and c.s.f, and whether the patients died, were discharged, or remained in Hospital.

SIGMA REACTIONS.	DISCHARGES M	DISCHARGES F	DEATHS M	DEATHS F	IN HOSPITAL M	IN HOSPITAL F	TOTAL
c.s.f. less than blood.	65	22	143	44	23	8	305
c.s.f. = blood.	18	9	43	7	8	4	89
c.s.f. greater than blood.	24	6	56	9	5	1	101
c.s.f. & blood negative.	3	1	10	4	3	1	22
						TOTAL PATIENTS.	517

TABLE XVI

Showing strength of the Sigma reaction in the cerebrospinal fluid in all cases.

REACTION	UNITS	DISCHARGES M	DISCHARGES F	DEATHS M	DEATHS F	IN HOSPTTAL M	IN HOSPTTAL F	TOTAL
NEGATIVE	0.0 -0.9	10	5	39	6	9	1	70
WEAK	1.0 -1.5	19	10	27	13	2	4	75
WEAK +	1.6 -4.0	31	9	68	16	8	-	132
STRONG -	4.1 -10.0	34	9	76	16	12	3	150
STRONG	10.1 -31.0	16	4	45	11	4	6	86
STRONG +	over 31.0	-	-	4	-	-	-	4

TABLE XVII

Showing response to various treatments.

	Malaria or Pyrifer	Mal. or Pyr. and Tryparsamide	Trypars.	Other Treatment	No Treatment	Total
DEATHS	81	55	51	35	112	334
REMISSIONS	25	86	6	23	13 x	153
IN HOSPITAL	8	28	2	14	-	52
TOTAL	114	169	59	72	125	539

x Includes 5 cases transferred and 4 discharged to the care of friends.

TABLE XVIII

Results in TableXVII expressed as percentages.

	Malaria or Pyrifer	Mal. or Pyr. and Tryparsamide.	Trypars.	Other Treatment.	No Treatment.
DEATHS	71.1%	32.5%	86.4%	49.3%	89.6%
REMISSIONS	21.9%	50.9%	10.2%	30.9%	11.4%
IN HOSPITAL	7.0%	16.6%	3.4%	19.8%	-
TOTAL	100%	100%	100%	100%	100%

TABLE XVIII A.

Showing percentage deaths compared to percentage improved - that is, those discharged plus those in Hospital.

	Mal. or Pyr.	M or P + Tryp.	Trypars.	Other Treatment.	No Treatment.
DEATHS	71.1%	32.5%	86.4%	49.3%	89.6%
IMPROVED	28.9%	67.5%	13.6%	50.7%	11.4%

TABLE XIX

Giving in detail the other treatments included in Tables XVII, XVIII, XVIII A.

TREATMENT.	DEATHS	DISCHARGES	IN HOSPITAL	TOTAL
1. Malaria & Sulphosin.	1	1	0	2
2. Malaria & Diathermy.	1	1	0	2
3. Malaria & Rubyl.	1	1	3	5
4. Mal. & Sulphosin &Tryparsamide.	5	1	1	7
5. Mal&Rubyl & Tryparsamide.	0	2	1	3
6. Mal.&Tryparsamide. Neokhars.& Bismuth.	1	0	3	4
7. Pyrifer & Neokharsivan.	1	1	0	2
8. Pyrifer & Neokarsivan&Bismuth.	11	9	6	26
9. Pyrifer &Trypars. Neokhars.& Bismuth.	1	5	0	6
10. Diathermy.	2	0	0	2
11. Diathermy & Tryparsamide.	4	2	0	6
12. Tryparsamide & Sulphosin.	2	0	0	2
13. Neokharsivan.	3	0	0	3
14. Crisalbine.	2	0	0	2
TOTALS.	35	23	14	72