A STUDY OF SELECTED CASES OF NERVOUS DISEASES WITH SPECIAL REFERENCE TO DISSEMINATED SCLEROSIS AND SYPHILIS AND THE VALUE OF THE COLLOIDAL GOLD REACTION AS AN AID TO EARLY DIAGNOSIS,

by

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The following research was undertaken on behalf of the Medical Research Council and its primary object was to attempt an investigation into the aetiology of disseminated sclerosis. It was recognized at the outset that the morbid histology of the disease had been studied in great detail, notably by Dawson,(1) that opportunities of obtaining pathological material were likely rarely to arise and that the chief hope of future advance in the investigation of this disease would appear to lie rather along bacteriological, serological and experimental lines. With this object in view, it appeared desirable closely to co-relate clinical observations with laboratory work, special attention being devoted to the examination of the cerebro-spinal fluid in every case. It was decided to investigate, by way of control, the widest possible series of cases of other diseases of the nervous system and to adopt as a routine the application of the Wassermann reaction and the colloidal gold reaction of Lange. It was hoped by this means that in addition to furthering the primary object of the research, useful observations might be made on the incidence of/

of syphilis in diseases of the nervous system generally, on the value of the Wassermann reaction to the clinician more especially as regards diagnosis and treatment, and on the conclusions that might be drawn from the results obtained in the routine application of the colloidal gold reaction to the cerebro-spinal fluid, a subject upon which relatively little work has so far been published. In addition it was decided to carry out on a large scale experimental inoculation of animals with blood and cerebro-spinal fluid of patients suffering from disseminated sclerosis in varying stages of the disease. This experi-:mental work which is being carried out in co-operation with Dr.John Blacklock, Assistant to Prof.Muir, is not referred to in this paper, the results of the clinical and serological portions of the investigation alone being here considered. The Wassermann reactions were performed in Prof.C.H.Browning's Laboratory by his assistant Dr.Ernest M.Dunlop.

Two hundred cases of nervous diseases were examined and they comprised, in addition to disseminated sclerosis, central and meningo-vascular syphilis, idiopathic and Jacksonian epilepsy, cerebral neoplasm, lethargic encephal-:itis, cerebro-spinal meningitis, herpes zoster, acute myelitis, exophthalmic goitre, amyotrophic lateral sclerosis, peripheral/

peripheral neuritis, hysteria, neurasthenia., the 'D.A.H.' syndrome, myokymia, anorexia nervosa and delusional insanity.

A summary of the clinical observations was recorded by the card index system. In every case the cerebro-spinal fluid was withdrawn by lumbar puncture and examined, and in selected cases, more especially when treatment was being carried out, subsequent examinations of the cerebro-spinal fluid were made at frequent intervals.

The routine adopted in the examination of the cerebro-spinal fluid comprised (1) The enumeration of cells, (2) Tests for protein content, (3) The Wassermann reaction, (4) The colloidal gold reaction, (5) Dark ground illumination. This method was employed in every case of disseminated sclerosis and in the majority of the cases of neurosyphilis, (6) Cultural investigation was carried out in cases of meningitis.

TECHNIQUE OF LUMBAR PUNCTURE. Needles of the Barker type were found to be unsuitable on account of their size for carrying out a large series of lumbar punctures and the best results were obtained with steel needles 8 c.m. in length and of size 10. calibre. It is desirable that the needle should fit a standard record syringe. The needle is sterilized by boiling in the routine fashion, and, before use, it is washed with sterile water to remove any traces of alkali which might interfere with the accuracy of the

Wassermann/

Wassermann reaction. After use, the needle is washed with ether and dehydrated with absolute alcohol. It is then smeared with vaseline to prevent rust. In addition to these precautions it is advisable to discard a needle after it has been used for about a dozen punctures as the risk of breakage is thereby diminished and the cost of replacement is trifling. The syringe is kept in a 10% solution of lysol in alcohol and, before use, is thoroughly washed out with sterile water. This method ensures asepsis and gives satisfactory results: the alternative method of boiling the syringe frequently entails loss from breakage in spite of every precaution being taken.

During the operation of thecal puncture the patient is placed preferably in the sitting posture with the back bent so as to produce a maximum convexity of the lumbar region, the laminae being thus separated to their widest extent. Should the patient's condition not permit of the assumption of the sitting posture he is placed in the left lateral position with the knees and shoulders approximated. The skin of the back is sterilized with spirit, tincture of iodine or picric acid solution and the operator's hands are also sterilized. It is rarely necessary to wear rubber gloves except in cases where the fluid is likely to be required for purposes of culture or inoculation. The position of the intercristal line is located and may be marked with a blue dermatograph pencil prior to the sterilization of the skin or a swab dipped in tincture of iodine and held in a pair of Spencer Wells forceps may/

may be employed for this purpose. The space immediately below the intercristal line is usually selected; this lies between the fourth and fifth laminae.

For success in lumbar puncture the exact location of the point at which the needle is to be inserted is all-important. This is most accurately ascertained by palpa-:tion with the left forefinger, the elastic 'give' of the in-:terspinous ligament being thus recognized. The needle with the stilette in situ is now inserted, the operator using his right hand for this purpose. With the fingers of the left hand he should support the shaft of the needle at a point not greater than one inch from the patient's skin. This method greatly diminishes the risk of breakage. If needles of fine calibre and with a very sharp point be employed, no anaesthetic general or local is required in ordinary cases. Ether anaesthesia is occasionally indicated in cases of meningitis or other severe illness. Local anaesthesia induced by freezing of the skin with an ethyl-chloride spray causes the patient as much pain and discomfort as lumbar puncture itself and owing to the hardening of the tissues increases the difficulty of accurately locating the position of the interspace through which it is desired to enter. When carried out with the above precautions lumbar puncture would appear to be a practically/

practically painless operation. Occasionally one of the roots of the cauda equina is touched by the needle and the patient complains of a shooting pain passing down one leg. This is of no significance. When the needle has penetrated the arachnoid sac the stilette is withdrawn and the fluid is collected in two test tubes, the first few drops being discarded. In cases where it is of special importance to avoid the chances of contamination of the fluid the following procedure may be adopted. The stilette is withdrawn and the end of a fine rubber tube is fitted over the handle of the needle. The stilette is then introduced through the rubber tube into the shaft of the needle. When the needle has entered the arachnoidal sac the stilette is withdrawn and the fluid collected in a test tube by means of the rubber tubing. On completion of the operation the needle is withdrawn and the wound of entrance sealed with a collodion dressing.

When lumbar puncture is performed under a general anaesthetic the flow of cerebro-spinal fluid is increased. This is attributed by Boyd (2) to the rise in the CO_2 content of the blood, Dixon and Halliburton having shown that increase of CO_2 would appear to act as a 'lymphagogue', the cerebro-spinal fluid being thus used as a channel for its excretion.

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It is desirable to collect the fluid in two tubes which have been previously prepared by the technique later to be described for the preparation of glass ware used in the colloidal gold reaction. The fluid contained in the first tube may be employed for the carrying out of the Wassermann reaction while that in the second tube, which is less likely to be contaminated with blood, is used for cell count, dark ground illumination, protein tests and colloidal gold reaction.

The normal rate of flow of cerebro-spinal fluid from the needle is sixty drops per minute and this represents a pressure of 20 to 25 c.m. of water when the patient is in the sitting posture.(2) When the rate of flow is slow it may be accelerated by asking the patient to breathe deeply. In certain diseases, especially intracranial neoplasm and meningitis, the pressure of the cerebro-spinal fluid is increased with consequent acceleration of flow and in the cases investigated in the course of this research the maximum increase noted was in patients suffering from uraemic coma and in cases of status epilepticus due to Jacksonian epilepsy. Occasionally in certain patients the rate of flow was greatly diminished and when these cases were subsequently re-punctured, the same phenomenon was observed. In two cases apparently 'dry' canals were encountered, lumbar/

lumbar puncture being repeated on seven occasions without any fluid being obtained. The minimum amount of fluid required for Wassermann reaction, dark ground illumination, protein tests and colloidal gold reaction is about 8 c.c. If the fluid be required for inoculation purposes, it may be necessary to withdraw larger amounts. It is undesirable to remove more than 15 c.c. except in cases where the pressure is greatly increased.

Effects of lumbar puncture. In the course of upwards of 500 lumbar punctures, no serious after-effects have been observed. Severe headache was complained of in some cases and this would seem chiefly to occur when a relatively large amount of fluid is withdrawn. MacRobert (3) has suggested that the headache following lumbar puncture may be due to the non-closure of the puncture hole in the arachnoid resulting in prolonged epidural leaking. If this theory be correct it would appear probable that in cases where the spinal needle has been accidentally broken off during puncture, epidural leaking would be likely to occur. I have personally seen three such cases, one of which occurring in this series, will be subsequently referred to. None of these patients complained of severe headache though in one the loss of cerebro-spinal fluid was very considerable and the needle had subsequently to be removed by surgical interference./

interference. The mild headache which frequently follows lumbar puncture yields rapidly to the administration of Aspirin and the previous administration of this drug in doses of gr.15 will usually prevent its onset.

Risks of lumbar puncture. In one case in this series the needle broke off while in the thecal canal and the distal portion remained in the tissues. No ill-effect was noted and the patient was unaware of its presence until informed some days later. Such an accident is presumably due to a flaw in the needle and it is difficult to see how it may be avoided beyond strict observance of the precautions already recommended for the preparation and care of needles used for spinal puncture (vid.sup.) The possible risks of lumbar puncture have been urged by Webster (4) who records a series of experimental investigations in the part played by lumbar puncture in precipitating meningitis in animals rendered artificially septicaemic. He argues that lumbar puncture in the presence of a septicaemia may operate in two ways to promote infection of the meninges -

(1) by impairing the integrity of the choroid plexus and meningeal lymphatics,

(2) by extravasation of blood which itself may be infective within the cerebro-spinal space.

In actual practice, such dangers would appear to be theoretical rather than real. I have frequently employed lumbar/

lumbar puncture as a means of controlling otherwise intract-:able delirium and insomnia in cases of lobar pneumonia with almost invariably beneficial results and in no case has any sign of meningitis developed. In view, however, of the theoretical risks involved, it is advisable in pneumonia and similar diseases to resort to lumbar puncture only in cases where all other treatment has failed and where the delirium is actually threatening life.

With reference to the above recorded observations of Webster it is of interest to note that Horrick and Dannenberg have described reaction on the part of the leptomeninges to the infective agents or toxins of a large number of miscella-:neous acute diseases not ordinarily causing true meningitis. Such reaction was shown by increased pressure, pleocytosis and heightened globulin content. The diseases comprised in their series were lobar pneumonia, broncho-pneumonia, influenza, tonsillitis, scarlet fever, measles, variola, herpes zoster, parotitis, typhoid fever, sepsis, arthritis, pleurisy, migraine, reaction to typhoid inoculation and others. The cerebro-spinal fluid showed variation from normal in about one third of the cases studied. Most but by no means all of the patients with subarachnoid reaction showed clinical meningismus (meningitis serose Dupré). On the other hand many examples of meningismus were without pronounced changes in the cerebro-spinal fluid.

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It would therefore appear desirable to exercise caution in carrying out lumbar puncture in cases of acute infectious diseases where a septicaemic condition may be present. In chronic nervous diseases lumbar puncture is a perfectly safe and almost painless operation. It may be performed on out-patients if facilities are available for them to rest in the recumbent position for a few hours. In ordinary cases there is no need for such patients to be admitted to Hospital overnight, a fact which widens the scope of application of this method of investigation.

The value of the examination of the cerebro-spinal fluid as an aid to diagnosis is widely known and emphasis of its importance in this respect is one of the chief results obtained from this research, but the therapeutical advantages of lumbar puncture would appear to be insufficiently appreciated. Reference has already been made to its effect in controlling the delirium of patients in pneumonia. This line of treatment I carried out during the pandemic of influenza in 1918, with, almost invariably beneficial results.

In various other conditions where there are clear indications of increased cerebro-spinal pressure lumbar puncture would appear to be strongly indicated - the resulting diminution in pressure usually producing a rapid improvement in the patient's symptoms.

The/

The following cases will serve as examples:-

A CASE OF URAEMIC COMA TREATED BY LUMBAR PUNCTURE.

Case 136. J.C. Male: aet.15. was admitted to hospital 26/9/20 in a condition of coma. For four days prior to admission he had suffered from severe headache and vomiting. During his first day in hospital he was in a condition varying between coma and epileptiform seizures. The systolic blood pressure was 190 m.m. mercury. The urinary output was 15 oz.- the urine contained albumen and blood and the centrifugalised deposit contained cellular, granular and hyaline casts. On examination of the fundi no abnormality was detected. Purga-:tion, hot packs and finally the administration of pilocarpine failed to relieve his condition. Lumbar puncture was performed under chloroform anaesthesia. The cerebro-spinal fluid was under greatly increased pressure. 20 c.c. of fluid were removed. No abnormality in respect of cell count, Wassermann Reaction, colloidal gold reaction or protein content was detected in the fluid. Subsequent to the puncture the patient's condition rapidly improved and by the following morning he was quite sensible and his urinary output greatly increased. No relapse occurred prior to his discharge from hospital.

A CASE OF PNEUMOCOCCAL MENINGITIS TREATED BY REPEATED LUMBAR PUNCTURE AND FOLLOWED BY RECOVERY.

Case 137. R.B. aet.24. Admitted 9/9/20. On admission patient looked very ill and complained of intense frontal headache. There was slight rigidity of the muscles of the neck and some retraction of the abdomen. Kernig's sign was not elicited. There was well marked tâche cérébrale: the knee jerks were present: the plantar reflexes flexor: pupils were equal and contracted and did not dilate under atropine. There was dulness to percussion at the apex of the right lung and over this area the respiratory murmur was bronchial in character. No adventitious sounds were detected. The percussion note at the left base was slightly impaired. No abnormality was detected in the heart. The urine contained a faint trace of albumen. The blood picture showed a well marked anaemia of the secondary type. There was a leucocytosis of 22,000 per c.m.m.

Lumbar puncture was performed 11/9/20. The cerebro-spinal fluid was under very great pressure. 15 c.c. were withdrawn and examined. The cell count was 8: a differential count showed the presence of large and small lymphocytes. No pus cells were found in the centrifugalised deposit. Films were stained/

stained for tubercle bacillus and meningococcus, with negative results: two cultures for the latter showed no growth in 40 hours. The Wassermann and colloidal gold reactions (the latter of which will be described later) were negative. The lumbar puncture was followed by great improvement in his condition and in 48 hours he had apparently recovered. On 20/9/20 he was allowed up and was apparently convaleacent. On 29/9/20 a second puncture was performed, the cerebro-spinal fluid picture was unaltered except that the pressure was only slightly in excess of normal and the cell count was 23 per c.mm. On 2/10/20 the patient complained of very severe headache of sudden onset and became rapidly semicomatose. Lumbar puncture was performed the same day. The cerebro-spinal fluid did not flow through the needle and had to be drawn off with a 20 c.c. record syringe. The fluid so obtained was turbid and blood-stained. Pneumococci were present in a stained film. 25 c.c. of fluid were withdrawn. This was followed by an almost complete remission of his meningeal symptoms. Four days later he complained of a mild recurrence of headache. Lumbar puncture was again performed and 10 c.c. of fluid withdrawn, with almost immediate relief of headache. Two days later he was placed on injections of anti-pneumococcic serum. He made an uninterrupted recovery and was discharged to a convalescent home 10/2/21.

In this case it appeared that remission of the acute symptoms succeeded each aspiration of cerebro-spinal fluid and on the occasion of the third puncture the patient's condition was so serious and the improvement following immediately on the relief of pressure so marked, that it appeared justifiable to conclude that the patient's life had been saved by this means.

A CASE OF STATUS EPILEPTICUS SUCCESSFULLY TREATED BY LUMBAR PUNCTURE.

A.P. admitted to hospital 7/12/20 with a history of epileptiform seizures. Subsequent to admission the patient had five fits, in two of which the onset was preceded by a cry. Each fit lasted about three minutes and consisted of a tonic stage followed by clonus. The face was livid, the tongue bitten, the pupils dilated and fixed. No incontinence of urine or faeces was observed. Between the fits which were at about ten minute intervals the patient regained consciousness but was very dazed. After the second fit paresis of the left side of the face was noted. After the fifth fit the patient did not regain consciousness, the pupils were now contracted and there was conjugate deviation of the eyes to the left. At the onset of the seizures hyoscine gr.1/100 and morphia gr.1/4 were given but did not bring about any change in the patient's condition. Lumbar puncture was performed and 25 c.c. of blood-stained fluid were withdrawn under greatly increased pressure. This was/

was followed by immediate cessation of the fits and the following morning the patient was quite rational. The paresis of the left facial nerve persisted and was presumably due to haemorrhage. The Wassermann reaction of the blood and cerebro-spinal fluid was positive.

It would be interesting to observe whether lumbar puncture were of benefit in cases of maniacal chorea but an opportunity of investigating a case of this disease has not so far arisen.

Enumeration of the cells of the cerebro-spinal fluid.

In hospital practice, this should be carried out immediately on withdrawal of the fluid as the cells undergo lysis on standing: they are also stated to tend to adhere to the glass.

Staining fluid of the following composition is employed.

Methyl Violet	0.2 gm.
Glacial acetic acid	5 c.c.
Water	100 c.c.

The staining fluid is drawn up to the mark 1 of the leucocyte pipette of a blood-counting apparatus and the cerebro-spinal fluid is drawn up to the mark 11.(5) A drop of the resulting mixture is placed on the ordinary Thoma-Zeiss counting stage: the number of cells in the ruled area x 10/9 = the number per c.m.m.

For routine cerebro-spinal fluid work it is preferable to employ the Fuchs-Rosenthal Chamber, the ruled area of which corresponds to 3.2 c.m.m. Hence the number of cells counted $\times \frac{1}{3.2} \times \frac{10}{9}$ (or roughly $\div$ 3) = number per c.m.m.

Different writers make varying statements as to the normal cell count of the cerebro-spinal fluid. These discrepancies are probably due to the fact that they have employed different methods/

methods in determining the number of cells. It may be stated generally that a normal count does not usually exceed 6 per c.mm. that a count of 6-20 per c.m.m. is abnormal and a number in excess of 20 is definitely pathological.

It is obvious that admixture with blood is a possible source of serious error and should this be suspected the fluid should be centrifugalized and the deposit stained for red blood corpuscles. If the fluid has definitely been contaminated with blood the specimen may still be utilized for cell counting if only a rough count is desired. It is known that under normal conditions the blood contains one lymphocyte in every four leucocytes. To obtain the number of lymphocytes therefore the white blood cells in the spinal fluid should be counted and the result divided by three.(6) The liability of error is least if the Fuchs-Rosenthal Chamber be employed and if the same method is always used the enumeration can be carried out very rapidly, a mere glance at the ruled area being sufficient to enable one to determine whether or not pleocytosis exists and in many cases this is all that is required. In addition the use of this chamber enables one to carry out a rough differential count, it being important to recognize the presence of large lymphocytes, which usually indicate the existence of a pathological condition.

Tests for Protein Content. The tests employed in the course

of/

of this research are:-

(1) The Ross Jones test,
(2) The Nonne-Apelt test, and
(3) The Alcohol test.

The Ross-Jones test:-(7) The reagent is prepared as follows:- 85 gm. of Ammonium Sulphate are put in 100 c.c. of water and boiled in an Erlenmayer flask until no more salt goes into solution. The fluid is then filtered. The reaction should not be acid. To carry out the test 0.3 c.c. of the reagent is superimposed upon an equal amount of cerebro-spinal fluid. If the globulins in the fluid are increased an opaque ring develops at the line of contact.

The Nonne-Apelt test:-(8)

Phase 1. The reagent employed in this test is the same as that used in the Ross-Jones test. Equal parts of the saturated ammonium sulphate solution and cerebro-spinal fluid are mixed instead of being superimposed one upon the other. A white precipitate forms in three minutes if the reaction is positive (englobulin).

Phase II. The precipitate is filtered, one drop of a 10% acetic acid solution is now added to the filtrate and the mixture is boiled. A precipitate forms if the reaction is positive (serum albumen).

The Alcohol Test was adopted by Morton.(9) It consists in taking equal parts of cerebro-spinal fluid and 96% alcohol and noting the density of the precipitate formed on mixing.

Noguchi's/

Ngguchi's test[10] gives very delicate results so far as indicating the presence of protein material is concerned.[11] It has not been carried out in the course of this research. More recently Dennis & Ayer[12] have elaborated a method for estimating the protein content of the cerebro-spinal fluid which, they claim, gives the total content to within approximately 5% but the technique is intricate and there-fore unsuitable for a large series of cases unless ample time is available.

LANGE'S COLLOIDAL GOLD REACTION:- The Colloidal Gold test of the cerebro-spinal fluid was introduced by Lange in 1912. Until quite recently it has not been much employed in this country.

A complete review of the literature of the reaction has been made by Cruickshank.[13]

The first experiments with Colloidal Gold were done by Zsigmondy, who found that on adding an electrolyte to Colloidal Gold the particles of gold became coagulated and precipitated. He also found that this reaction could be inhibited by the addition to the electrolyte of suitable amounts of varying protein substances. To these substances Zsigmondy gave the name of "protective colloids".

In view of the fact that in certain organic nervous diseases the protein content of the cerebro-spinal fluid was known to vary it occurred to Lange to test such fluids with/

with Colloidal Gold. He found that the cerebro-spinal fluid from cases of General Paralysis of the Insane precipitated the gold in low dilutions, and after examining a number of cases he suggested the test as of diagnostic value in this disease.

Felton (14) in a paper published in 1917 stated that the reactions were dependant on the relative amounts of globulin and albumen, the globulin exercising a precipitating action and the albumen a protective action. Zonal reactions were due to the inter-relationship of the two substances.

Cruickshank (13) considered that the reacting substance resided in the globulin fraction. He precipitated the globulin, centrifuged and washed the precipitate with Ammonium Sulphate to leave no trace of albumen and dissolved it in salt solution and then dialysed the solution till free from salt. The precipitate of globulin was then dissolved in an amount of 0.85% of Sodium Chloride solution equivalent to the original volume of the spinal fluid. This fluid was tested with the colloidal gold and with the Wassermann Reaction. It was found that the globulin had the precipitating power of the original spinal fluid and was even more active. The globulin also gave a positive Wassermann reaction. Cruickshank states that the precipitating substance is not altered by heating to the coagulation point of protein. The reaction is not due to peptone./

peptone. This view that the substance which reacts to colloidal gold is not dialyzable is opposed by Weston (15) who states that it dialyses freely. Miller and his associates also state that the reacting substance is dialysable.

The precipitation and reduction of Colloidal Gold in the test of cerebro-spinal fluid is, in the opinion of Cruickshank, not likely to be due to an electrolyte for, as he observes, only an electrolyte of high valency could produce the effect, and it would require to be attached to the globulin fraction in such a way that it is not freed by dialysis.

It has since been shown that zonal phenomena with colloidal gold are produced by cerebro-spinal fluid in other nervous diseases, notably Tabes and it has been still more recently claimed (16) that this reaction is obtained in Disseminated Sclerosis. The investigation of these facts is one of the objects of this research.

Technique of preparation of Colloidal Gold. The method employed in the preparation of colloidal gold is that of Lange. (17) An alternative method has been described by Miller, Brush, Hammers and Felton. (18) Colloidal gold can be prepared by other methods, e.g. by reduction of gold chloride by ethereal solutions of Phosphorous or by reduction with weak solutions of tannic acid. The fluids obtained by these methods are unsuitable for testing the cerebro/

cerebro-spinal fluid. The re-agents employed are:-

(1) A one per cent. solution of gold chloride,
(2) A two per cent. solution of pure potassium carbonate,
(3) A one per cent. solution of pure formalin.

All these reagents are made up in triple distilled water. Triple distilled water is obtained by distillation over glass condensers, no rubber connections being used. All the glassware employed in the preparation of the reagents and the carrying out of the test is carefully cleaned and then washed out with Nitrohydrochloric Acid. It is then thoroughly washed with tap water until the reaction as tested by litmus is no longer acid. Washing is then continued with double distilled and finally with triple distilled water. It was not found advisable to attempt to make more than 500 c.c. of colloidal gold at one time, as in spite of all precautions the result is occasionally unsatisfactory.

500 c.c. of triple distilled water are placed in a 1000 c.c. glass flask, preferably of Jena make. of which the cleanliness has been ensured by the above precautions. The water is slowly heated to 60° C. 3.5 c.c. of a 2% solution of pure Potassium Carbonate are now added followed immediately by 7.5 c.c. of 1% gold chloride solution. The mixture is then shaken vigorously and rapidly heated to 90° C. The Bunsen is then removed and 5 c.c. of a 1% Formaldehyde Solution is added quickly and in successive small amounts of about 1 c.c. during which time/

time the flask is being shaken as vigorously as possible. The fluid turns pink and finally a deep red develops. This usually takes from one to two minutes.

Cruickshank[13] who employs Lange's method of preparing the colloidal gold, recommends the addition of 5 c.c. of the 2% solution of potassium carbonate and 5 c.c. of the 1% solution of gold chloride.

Levinson[6] advocates the use of 3.5 c.c. 2% solution of Potassium Carbonate and 5 c.c. of 1% gold chloride solution.

The colloidal gold must be neutral in reaction, perfectly clear by transmitted and by reflected light. In the flask it is of a deep red colour, in a test tube it appears pink. The final criterion of the suitability of a specimen of colloidal gold for testing cerebro-spinal fluid is (a) That it should give a 'paretic' reaction (presently to be described) with the cerebro-spinal fluid from a case of general paralysis, (b) That it should show no change with a normal fluid, (c) that 5 c.c. should be completely precipitated in one hour by 1.7 c.c. of 1% solution of sodium chloride, (d) That it should be neutral to 1% alizarin red in 5% alcohol.[13] [19] [20] Occasionally a so-called "protected" solution is encountered which reacts neither to 1% Sodium Chloride solution nor to a known positive fluid. Such a solution is usually alkaline. Felton[14] considers that this phenomenon is due to an unusually wide distribution/

distribution of the particles produced by slow or irregular heating. The fluid should be stored in a darkened cabinet. It remains indefinitely without spoiling. Occasionally samples were obtained which showed slight turbidity by reflected light. They were not regarded as reliable in the carrying out of the tests though they gave satisfactory results when compared with controls of colloidal gold which conformed to the standard requirements.

TECHNIQUE OF EXAMINING CEREBRO-SPINAL FLUID BY THE COLLOIDAL GOLD TEST. The test is carried out as follows:- Eleven dry test tubes cleaned by the process previously described, are placed in a test tube rack and numbered. In the first test tube 0.9 c.c.of a 0.4% solution of pure sodium chloride is placed: in each of the rest of the tubes 0.5 c.c. To the first test tube 0.1 c.c. of the fluid under examination is added. After mixing, 0.5 c.c. is with-:drawn from tube No.1 and added to tube No.2. This process of abstraction of 0.5 c.c. from one tube and its addition to the next tube is repeated down the series, the last portion being rejected. This leaves each tube with a content of 0.5 c.c.and gives the follow-:ing series of dilution of cerebro-spinal fluid,1-10,1-20,1-40, 1-80,1-160, etc.

To eachtube 2.5 c.c. of colloidal gold are added. A control tube containing 0.5 c.c. of a 0.4% sodium chloride solution may be added to the series to serve as a standard of colour. Various types of reaction may occur. These fall into 3 groups, viz:-(1) PARETIC, (2)LUETIC, and (3)MENINGITIC. These names were employed before the test had been widely applied in diseases other than syphilis. They must be accepted as arbitrary terms and not necessarily carrying any aetiological significance as their names might imply.

(1)/

(1) The Paretic type of reaction:- Complete precipitation of gold occurs in the first three to six tubes on standing for 24 hours.

(2) The Luetic type of reaction:- Discolouration of the gold solution occurs in the third to sixth tubes (1-40, 1-80, 1-160 dilution) but complete precipitation does not result. In addition faint changes in colour are frequently observed in tubes 1 and 2.

(3) The Meningitic type of reaction:- The colour changes occur further down in the series, tubes 7 and 8 being chiefly affected.

In the course of this research it was found that the so-called meningitic reaction is not reliable, varying results being obtained in cases of meningitis and meningitic curves being encountered in diseases other than meningitis when the speciman of cerebro-spinal fluid was blood contaminated. Cruickshank suggests that the reactions found in acute and subacute meningitis are caused by leakage of serum protein through the damaged meninges.

The effect of varying degrees of blood contamination of a normal cerebro-spinal fluid on the colloidal gold reaction has been studied and will subsequently be referred to (see p.25.)

Incubations of normal fluids contaminated with organisms (staphyloccus albus, bacillus coli, and pneumococcus) did not produce/

produce meningitic curves.

Results cannot be read satisfactorily by artificial light. The readings are taken immediately and again in 24 hours time. Cerebro-spinal fluid, kept in a laboratory ice-chest would appear to retain its characteristic reaction with colloidal gold indefinitely. One specimen gave a typical luetic reaction after being stored for 3 months.

The Recording of Results:- For this purpose one of the three following methods may be employed:-

(1) The actual description of the colour changes observed. This is the method which is recommended for recording laboratory results, though somewhat cumbersome for reference in the course of a paper. By this method the three types of reaction would be shown as follows:-

(a) PARETIC REACTION.

(1. 2. 3. 4.) Precipitated. 5. Blue-purple. 6. Pur-ple. 7. Faint purple. (8. 9. 10. 11.) Pink.

(b) LUETIC REACTION.

1. Pink. 2. Faint purple. (3. 4. 5.) Purple. 6. Faint purple. (7. 8. 9. 10. 11.) Pink.

(c) MENINGITIC REACTION.

(1. 2. 3. 4. 5. 6.) Pink. (7. 8. 9.) Purple. (10. 11.) Pink.

(2) The colour changes may be indicated by numerals, this method being specially suitable for purposes of publication. Thus:-

5/

5 represents a tube in which complete coagulation and precipitation of gold has occurred, leaving the supernatant fluid quite colourless.

4. represents a slaty blue colour.

3. " " deep blue ".

2. " " purple "

1. " " faint purple colour.

0. " no colour change.

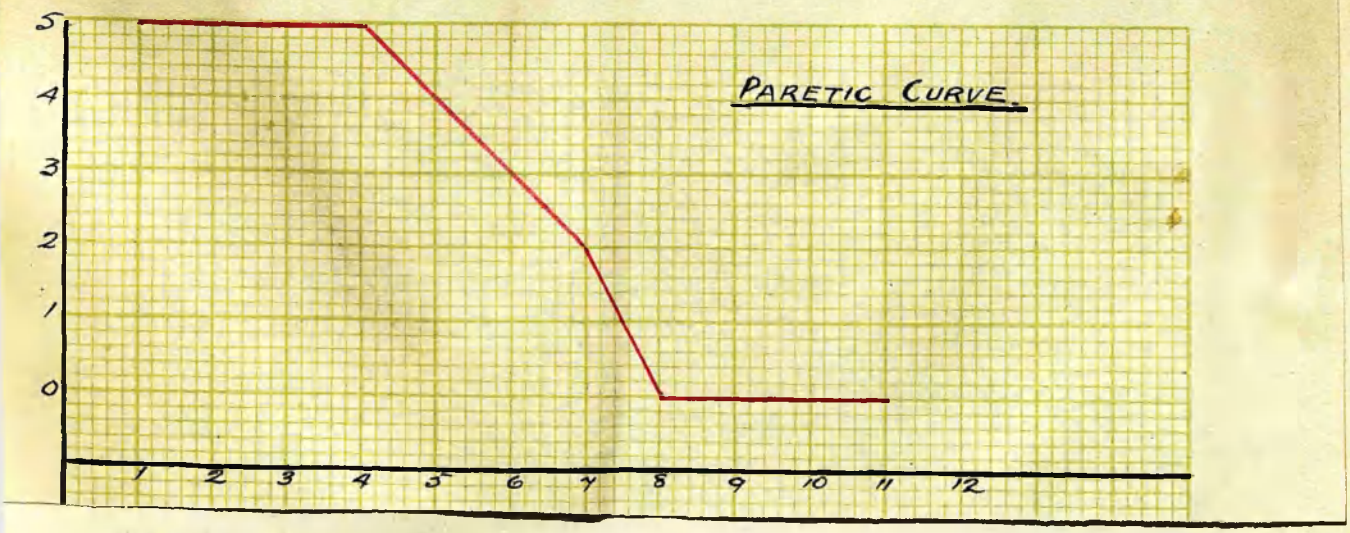
By this method the reactions would be shown as follows:-

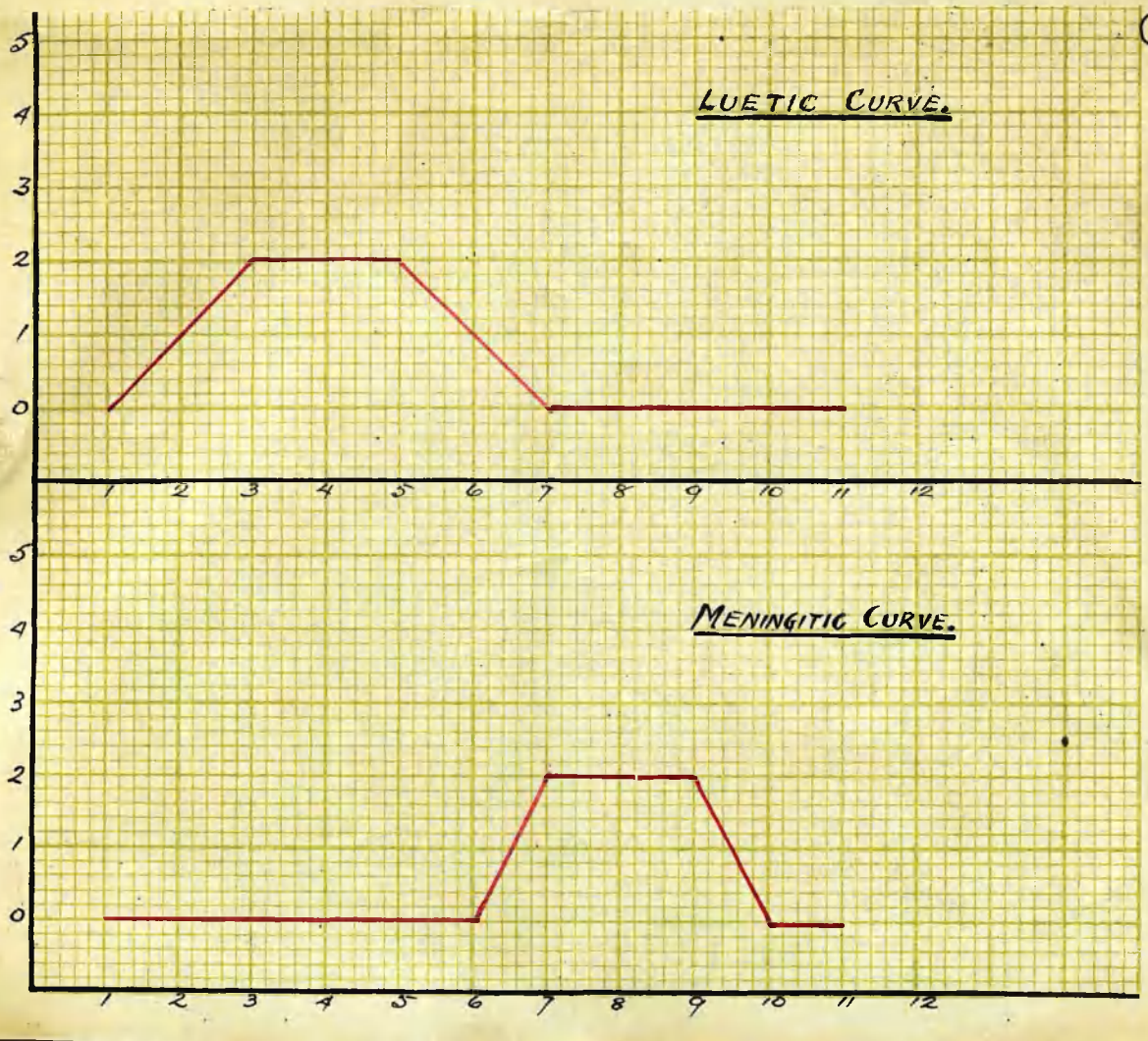
(a) PARETIC REACTION 5 5 5 5 4 3 2 0 0 0 0

(b) LUETIC " 0 1 2 2 2 1 0 0 0 0 0

(c) MENINGITIC " 0 0 0 0 0 0 2 2 2 0 0

(3) The results may be represented graphically as follows:-





It has already been stated that the meningitic curve would appear to be of doubtful value. The following experiment was carried out with a normal cerebro-spinal fluid:-

0.5 c.c. of a normal fluid was placed in each of four tubes. To the first 0.025 c.c. of normal blood was added, to the second 0.05 c.c. to the third 0.3 c.c. and to the fourth 0.4 c.c.

The fluids were then tested with colloidal gold with the following results:-

Tube 1/

Tube 1	(0.025 c.c. of blood)	0 0 1 1 2 2 1 0 0 0 0
Tube 2.	(0.05 c.c. of blood)	0 0 0 1 1 1 1 0 0 0 0
Tube 3.	(0.3 c.c. of blood)	0 0 0 0 1 1 2 2 2 2 1
Tube 4.	(0.4 c.c. of blood)	0 0 0 1 1 1 1 2 2 2 2

It would therefore appear that blood contamination renders a specimen of cerebro-spinal fluid unsuitable for testing with colloidal gold.

RESULTS OF THE EXAMINATION OF THE CEREBRO-SPINAL FLUID IN DISSEMINATED SCLEROSIS:- Forty-one cases of Disseminated Sclerosis ~~or sclerosis~~ were examined in the course of this investigation. All save two gave a luetic or paretic type of reaction to colloidal gold. It is interesting to note that these two cases had been clinically diagnosed as arteriosclerosis simulating disseminated sclerosis, in one case by Prof.T.K.Monro, in the other by myself. Five cases gave a paretic curve, the remainder produced a luetic reaction. The average cell count (One case being excepted) was five: the type of cell a small lymphocyte. In every case the cerebro-spinal fluid was centrifugalized and examined by dark ground illumination. In two cases doubtful, actively motile spirochaetes were observed. Attempts to stain them were unsuccessful and the result was accordingly regarded as negative. In all the other cases of this series dark ground illumination yielded no result.

Protein/

Protein content:- The Ross-Jones Test was positive in 7 cases or 17%.

Wassermann Reaction:- The Wassermann reaction was positive in 9 cases. Of these cases the Wassermann reaction was positive in blood and cerebro-spinal fluid in 4 cases: in 2 it was positive in blood and negative in cerebro-spinal fluid: in 2 it was positive in cerebro-spinal fluid and negative in blood. In 1 it was positive in cerebro-spinal fluid and the blood was not examined.

Moore (21) records the results of examination of the cerebro-spinal fluid in 28 cases of multiple sclerosis, in 20 of which the diagnosis was clinically certain. The Wassermann reaction was negative in all the cases. In the 20 cases of certain clinical diagnosis there was pleocytosis in 8 cases, a positive globulin reaction in 18 cases, and a paretic gold curve in 18 cases.

Nixon (16) found the globulin test positive in only 10% of cases and a positive colloidal gold reaction in about 50% of cases. These are the only published records of work on the colloidal gold reaction of the cerebro-spinal fluid in disseminated sclerosis that I have been able to discover. It will be noted that they show a considerable discrepancy. In Moore's cases 90% were positive to colloidal gold but he states that in each of these a paretic curve was obtained.

Nixon's/

Nixon's figure of 10% of cases showing globulin increase more closely approximates to the findings recorded in this paper.

Variations in records of cell count are inevitable until some standardization of method is established. As regards the results of the globulin tests, the Ross-Jones and Nonne-Apelt tests would appear to be unreliable as a negative result is frequently observed in the presence of an obvious blood contamination, the alcohol test is positive in almost every case and frequently causes a precipitate in a normal fluid. The application of percentages to a small number of cases such as is comprised in Nixon's and Moore's reports and also in this paper is bound to give misleading results. So far as the results of the present research are concerned the cerebro-spinal fluid picture in disseminated sclerosis is, in the majority of cases, (1) a normal cell count, (2) a negative Wassermann reaction, (3) a negative reaction to the globulin tests and (4) a luetic or paretic reaction to colloidal gold.

The Diagnosis of Disseminated Sclerosis.

The recognition of this disease presents little difficulty if the diagnosis be limited to cases in which we can demonstrate spastic paraplegia, intention tremor, scanning speech, primary optic atrophy and nystagmus. Such cases are of relatively rare clinical incidence and probably represent the terminal stage of the fully developed disease; a stage which it would appear/

appear by no means all cases attain.

Most clinicians would assent to a diagnosis of disseminated sclerosis in a case which presented all the above-mentioned signs of the disease with the exception of, say, optic atrophy or scanning speech, a fact which logically raises the question as to how many, and which, of these so-called classical signs are essential for a diagnosis. During the progress of this research the opinion has gradually been formed that the presence of any one of the classical signs should arouse grave suspicion of disseminated sclerosis and that the disease is of very much wider incidence than is generally supposed. In this connection there would appear to be insufficient appreciation of the importance of the early recognition of SYMPTOMS suggesting the onset of this dreadful disease. In the vast majority of cases a diagnosis of so-called 'functional' disease is made, more especially as the selected victim is preferably a girl in early adult life, with the result that the symptoms are dismissed as being of trifling clinical importance. On several occasions during this research cases have been encountered giving clearly such a history and in one or two instances the diagnosis of hysteria had been confirmed by expert neurologists. It would appear that the presently accepted arbitrary differentiation of nervous diseases into 'functional' and 'organic' is unjustifiable

as/

as there are many indications that derangement of function frequently, if not always, precedes demonstrable anatomical change and that many of the so-called functional diseases have a definite underlying bio-chemical basis, a fact which will probably receive wider recognition in the future when the importance of serological reactions is more fully recognized and their application adopted on a very much larger scale than at present obtains, even in scientific hospital practice. Such derangement of function gives definite indications of its presence in the form of symptoms which in disseminated sclerosis are frequently transient but none the less real, yet these warning signals, (for they are little else), are frequently disregarded until organic change has taken place and a so-called 'sign' has become demonstrable. The advent of such a sign really indicates failure to recognise the disease in what is perhaps the only stage in which cure may be looked for. The importance of this attitude towards medicine has been repeatedly urged by Sir James McKenzie.(22) (23)

The significance of slight transitory symptoms as an early manifestation of disseminated sclerosis has been recently emphasized by Head.(24) Of these the most important would appear to be transient diplopia and slight impairment of bladder function. As regards the incidence of diplopia, it/

it would seem that this is an early symptom which should carefully be inquired for in every case of suspected disseminated sclerosis. In many cases it is apparently fleeting in its manifestations and a very careful interrogation of the patient should be under-:taken with a view to ascertaining whether or not it has ever been experienced. Should the manifestation of diplopia be more lasting, such cases usually report to an ophthalmic surgeon and it is interesting to note, in the light of the aetiological basis presently to be discussed, that the routine treatment adopted by most eye specialists is the administration of iodide of potassium. This drug would appear to be used empirically. It is desired strongly to emphasize the desirability of all such cases being thoroughly examined and such examination should always include an investigation of the cerebro-spinal fluid picture. Diplopia is also a fairly common early symptom of tabes but in the latter disease permanent palsy of one or more of the external ocular muscles develops, with resulting strabismus. Such external ocular palsy is somewhat rare in disseminated sclerosis but does occur, as the case reported on page 66 will exemplify.

The recognition of slight impairment of bladder function is of no less importance among the earliest symptoms of disseminated sclerosis. Such impairment may take the form of slight retention, but more frequently patients complain (often/only/

(only when questioned) of precipitancy of micturition. There has, in addition, frequently been noted in the course of this investigation another symptom of relatively common occurrence in early disseminated sclerosis, viz:- the onset of persistent nocturnal emissions. This symptom also points to lumbar involvement.

Most writers attach great importance to the EXTENSOR PLANTAR REFLEX as being one of the most important and earliest definite signs of the presence of this disease but the fact that it is not absolutely essential to a diagnosis, the following case will exemplify:-

A CASE OF DISSEMINATED SCLEROSIS IN WHICH, ON ADMISSION TO HOSPITAL, THE PLANTAR REFLEXES WERE FLEXOR, ALL THE OTHER CARDINAL SIGNS OF THE DISEASE BEING PRESENT.

Case 9. D.McP. Aet.22. Admitted 16/1/20, complaining of loss of power of legs and general weakness of 3½ years' duration. Symptoms followed on his being buried alive by a shell (July,1916). At the beginning had incontinence and he then noted a change in speech. Previous health excellent.

CONDITION ON ADMISSION:- Pale and anaemic. Superficial abdominal reflexes absent. Knee jerks:- R.+ L. + +. Tendo Achillis jerk: R +: L + + . Ankle clonus R +. L + +. Patellar clonus R +. Left + +. Plantar reflexes both flexor on admission. Gross intention tremor. Lateral, vertical and oscillatory nystagmus. Speech slow, deliberate and typically "scanning". Fundi O/E Discs chalky grey with very clear cut margins.

This case was kept under observation for several months and the plantar response was found to be variable - finally it became definitely extensor on both sides.

Such cases would, however, appear to be rare and in the majority of instances the extensor plantar reflex is one of the/

the first definite signs that can be elicited. To this early and almost constant involvement of the pyramidal tract Brouwer[25] has ascribed a biological significance as this tract appears late both in phylogeny and ontogeny and may therefore be specially liable to attack. In man the pyramids are the last formations to appear in the development of the Rhombencephalon[26] and the direct tract is stated to be wanting in 15% of cases. A well-marked pyramidal tract appears to be absent in most animals even in monkeys although it is present in the anthropoid apes. Variations in the pyramidal tracts in man do occur.[27] It would appear more probable that a possible explanation of the vulnerability of the pyramidal tract may lie in its extreme length.

Once an extensor plantar reflex is established it is usually considered to be permanently present. Such a statement must be accepted with reserve. Variations in the plantar reflex have been frequently observed (due care being devoted to the exclusion of the fallacies of the Babinski sign) during the course of this research and this has been more specially noted in cases under treatment. In 1918 three cases of hemiplegia occurring in young bluejackets came under my observation - in none of these cases could obvious cause be found to account for the condition and in each case the signs completely disappeared after a short lapse of time. A provisional diagnosis of disseminated sclerosis was made, and received the support of Sir Humphrey Davy Rolleston. Service conditions prevented a careful serological investigation of/

of these cases.

These variations in the plantar response might be attributed either to the action of a toxin on the pyramidal tract, such action being temporary in incidence, or to pressure due to round celled infiltration, such pressure being subse-:quently removed. These theories will be discussed later when the aetiology of the disease is considered.

The one sign which is common to all the cases of dissem-:inated sclerosis included in this research is ABSENCE OF THE ABDOMINAL REFLEX. This may be, and in fact frequently is, at first unilateral but in the great majority of established cases the superficial abdominal reflexes are lost on both sides though the epigastric reflex may be retained. In hysteria and other functional nervous diseases this reflex has been found frequently to be exaggerated. A possible explanation of the constant loss of the superficial abdominal reflex is put forward later in this paper. (p. 45)
It is desired here to observe that in cases where the sclerosis is purely cerebral in distribution, the abdominal reflex might reasonably be expected to be retained.

As regards the OCULAR MANIFESTATIONS of this disease, reference has already been made to the importance, from the point of view of early diagnosis, to be attached to a history of transient diplopia and the occasional incidence of strabismus has also been mentioned. Clinically one is

frequently struck by a curious appearance of dissociated action of the eyes in cases of disseminated sclerosis and this appearance is frequently marked even when the patients do not complain of diplopia.(Heterophoria).

The optic atrophy which so frequently occurs in disseminated sclerosis was formerly regarded as being 'primary' in type though differing in colour and distribu-:tion from the atrophy of tabes and general paralysis of the insane. It is now recognised that the atrophy in disseminated sclerosis is frequently secondary to a retro-bulbar neuritis and that its onset is usually preceded by a central colour scotoma. In this connection it is inter-:esting to note that Dr. John Gilchrist has reported to me a case of diplopia occurring in a young adult and accompan-:ied by signs of slight retrobulbar neuritis. The reader is here referred to a consideration of Case 162, p. 102 and Case 174 p. 70. Reference has already been made in this paper to the opinion that has been formed, that a case which shows definitely a single one of the cardinal signs of disseminated sclerosis should be regarded with grave suspicion. It will be shown in the following pages that there is a definite picture in the cerebro-spinal fluid in disseminated sclerosis, and it is recommended that in all suspicious cases the cerebro-spinal fluid should be examined. Particularly is this urged in cases of so-called 'idiopathic' primary optic atrophy,

many/

many of which may be found to be cases of disseminated sclerosis which is purely cerebral in distribution. The importance of an investigation of these cases being made will be more evident when the aetiology and treatment of the disease have been considered.

No facts calling for special comment have been observed as regards the incidence of SCANNING SPEECH or NYSTAGMUS. A history of the past occurrence of INTENTION TREMOR may occasionally be elicited, the patient in such cases stating that he has noted a difficulty in performing certain acts, e.g. raising a cup to his lips; or the onset of the tremor may interfere with specialised function, as in the case of a professional violinist, whose attempts to play his instru-:ment produced a characteristic result. In this connection it is of interest to note that the intention tremor may be graphically recorded by asking the patient to sign his name rapidly. In such cases the Christian name is usually legibly written whereas the surname is indecipherable owing to the characteristic onset of the tremor at the end of the voluntary act. Such a method may be employed for the purpose of keep-:ing a permanent record of the degree of the tremor and is useful for purposes of comparison with later attempts in a patient under prolonged treatment where the question of clinical improvement arises.

The system of re-survey of pensioners by medical boards has/

has given rise to opportunities of investigating records which show plainly the progressive onset of the signs of this disease. The following case is appended as an example:- J.W. aet 35, was invalided out of army 11/5/17 with primary lateral sclerosis. A medical board 5/9/17 reported spastic paraplegia and slight pallor of optic discs. Subsequent boards up to 10/9/19 confirmed the above picture. On 17/3/20 intention tremor was first noted. He was admitted to hospital 2/11/20.

On admission:- There was weakness and spasticity of both legs. Both plantar reflexes were extensor. Complete ankle clonus elicited on both sides. Knee jerks + +, pseudo patellar clonus. Abdominal reflexes absent. Bilateral intention tremor. Pupils reacted normally. Lateral nystagmus. No history of diplopia. Speech was not staccato but patient stated that it became "muddled up" when he attempted to speak rapidly.

Visual Acuity: R= $\frac{6}{18}$ L = $\frac{6}{18}$. Optic Discs both distinctly pale, the arteries relatively small - an early stage of optic atrophy.

Comment:- In this case, from the time when primary lateral sclerosis was first established. a period of 3½ years elapsed before optic atrophy, intention tremor, nystagmus and alteration in speech were all demonstrable and these signs developed in the above order.

THE AETIOLOGY OF DISSEMINATED SCLEROSIS. Until recently, nothing has been known of the aetiology of disseminated sclerosis which has always been regarded as incurable and fatal.(28) The statement is made by most writers on the subject that disseminated sclerosis is not due to syphilis, though this is denied by Jacobsohn.(29) Special attention has been devoted in this research, to the investigation of the possibility of such a relationship. It has already been/

been stated that, in the majority of cases of disseminated sclerosis the globulin of the cerebro-spinal fluid is not increased and the cell count is within normal limits, i.e. there is in most cases an absence of the increase of protein and of the pleocytosis that are so characteristic of syphilitic infection. A possible explanation of the occurrence of a positive Wassermann reaction in 9 cases (or 22%) of this series is that in these patients the two diseases may co-exist; and it is doubtful if this percentage is higher than would be found to be the case, were the Wassermann reaction of a very large series of general hospital patients, or indeed of the popula-:tion at large, to be carried out. The following case will exemplify this difficulty in diagnosis:-

A CASE OF DISSEMINATED SCLEROSIS WITH A POSITIVE WASSERMANN REACTION IN THE BLOOD AND IN WHICH THE CEREBRO-SPINAL FLUID PICTURE PRESENTED ALL THE SIGNS OF SYPHILITIC INFECTION.

Case 72. S.M. Admitted 20/5/20 complaining of loss of power in both legs and incontinence of bladder and bowel of 8 months' duration.

CENTRAL NERVOUS SYSTEM:- Both legs spastic with loss of power. Tendon reflex of legs + +. Ankle clonus. Both plantar reflexes extensor. No abnormal sensory phenomena detected. Pupils react sluggishly to light. Abdominal reflexes absent. Arm reflexes normal. Tremor of eyelids. No tremor of tongue. Slight nystagmus. Exopthalmos. Von Gräfe's and Stellwag's signs positive. Optic fundi normal. Slight intention tremor.

CEREBRO-SPINAL FLUID:- Clear. Pressure +. Cell count 100. Small lymphocytes.

PROTEIN TESTS:- R.J.Test +. N.A. 1 & 2 +. Alcohol + +.
WASSERMANN REACTION:- Blood positive. C.S.F. positive.
COLLOIDAL GOLD REACTION:- 2 2 3 2 1 1 0 0 0 0

COMMENT:- It will be observed that this case presents the phenomena of spastic paraplegia, absence of the abdominal reflex, nystagmus and intention tremor, signs which by themselves would justify a clinical diagnosis of disseminated sclerosis; yet on the other hand the Wassermann reaction is positive in the blood, while in the cerebro-spinal fluid not only is the Wassermann reaction positive but there is marked increase of protein, a greatly increased cell count and a very strong luetic reaction to colloidal gold, i.e. the cerebro-spinal fluid picture is, as will be shown later, typical of syphilitic infection. The sluggish pupillary reaction to light is the only clinical evidence of neuro-syphilis. The aetiological basis of this case of nervous disease is left open, but it may be observed that if the condition is due to syphilis it would seem that syphilitic sclerosis can occasionally so closely simulate disseminated sclerosis that the two diseases are indistinguishable clinically and reliance must be placed on the Wassermann reaction as a basis for differentiation.

It has already been stated that in the great majority of cases the cerebro-spinal fluid picture in disseminated sclerosis differs from that in syphilis (the observations on syphilis are referred to in detail later in this paper). This may be represented in tabular form:-

	CEREBRO-SPINAL FLUID PICTURE IN DISSEMINATED SCLEROSIS.	CEREBRO-SPINAL FLUID PICTURE IN NEURO-SYPHILIS.
Cell count	Normal (average 5)	Pleocytosis (average 47).
Globulin	No excess.	Excess.
Wassermann Reaction	Negative.	Positive.
Colloidal gold reaction.	Luetic or paretic curve.	Luetic or paretic curve.

Exceptional cases are, however, occasionally met with as the/

the following example will show:-

A CASE OF DISSEMINATED SCLEROSIS, IN WHICH THERE WAS NO REASON TO SUSPECT SYPHILITIC INFECTION, AND IN WHICH THE CEREBRO-SPINAL FLUID SHOWED A WELL-MARKED PLEOCYTOSIS.

Case 65. M.McL. Aet.43. Complaining of stiffness and loss of power of legs. Onset 10 years ago following severe emotional disturbance. 2 years ago history of diplopia. Ho history of syphilitic infection. Completely healthy married history.

CENTRAL NERVOUS SYSTEM:- Both legs spastic. K.J. + +. Strong extensor plantar reflex both legs. Ankle clonus. Pupils react normally. Marked intention tremor. No alteration in speech. Abdominal reflexes absent. Sensory neurone normal.

CEREBRO-SPINAL FLUID:- Clear. Pressure -. Cell count 57. (blood contamination was excluded). R.J. negative. N.A. 1 & 2 negative. Alcohol negative.

WASSERMANN REACTION C.S.F. (done twice) Negative.

COLLOIDAL GOLD REACTION:- 1 2 2 2 2 1 0 0 0 0 0

Still more difficult of explanation on either basis is the cerebro-spinal picture in the following case:-

A CASE OF DISSEMINATED SCLEROSIS WITH A NEGATIVE WASSERMANN REACTION IN THE BLOOD AND IN WHICH THE CEREBRO-SPINAL FLUID PICTURE COMPRISED A NORMAL CELL COUNT, A NORMAL PROTEIN CONTENT AND A POSITIVE WASSERMANN REACTION.

Case 8. J.H. Aet 27. Admitted 7/11/19. Received injury to back by fall while vaulting in gymnasium April 1915. One year later complained of difficulty in walking and shakiness of the head. Two years later developed incontinence of urine and noted alteration in speech.

CENTRAL NERVOUS SYSTEM:- Pupils equal and react normally. Diplopia. Lateral and rotatory nystagmus. K.J. +. Plantar reflex flexor L, extensor R. Tactile sensation in legs defective: painful stimuli exaggerated in parts. Thermal and muscle sensibility normal. Some incontinence of bladder. No incontinence of bowels. Difficulty in walking: ataxia. Hyperaesthesia over dorsal spines.
OPTIC FUNDI:- O/E discs somewhat congested: fundi otherwise normal. Visual aguity. left eye counts fingers only at 7 feet. Right eye V.A. = $\frac{6}{18}$

Marked intention tremor and scanning speech. Abdominal reflexes absent.

CEREBRO-SPINAL FLUID:- Clear. Pressure + +. Cell count 3. R.J.T.Negative. N.A. 1 & 2 negative. Alcohol faint +.

WASSERMANN REACTION OF BLOOD negative, of C.S.F. weak positive.

COLLOIDAL GOLD REACTION:- 4 3 3 2 2 1 1 0 0 0 0.

The following case is of interest, in that there developed during treatment, a tibial swelling which clinically resembled a gumma, this diagnosis being concurred in by Dr.Robert Carslaw. No result was obtained from the experimental inoculation of a rabbit referred to in the case. The Wassermann reaction remained negative:-

A CASE OF DISSEMINATED SCLEROSIS WITH A NEGATIVE WASSERMANN REACTION IN THE BLOOD AND SPINAL FLUID, IN WHICH UNDER TREATMENT WITH MERCURY AND ARSENIC, A SWELLING PRESENTING THE CLINICAL CHARACTERISTICS OF A GUMMA DEVELOPED ON THE ANTERIOR ASPECT OF THE RIGHT TIBIA.

Case 33. J.McM. Aet 46. Grocer. Admitted 5/12/19. Complaining of loss of power in legs. Onset of illness January 1919, when he first complained of pains in legs, and slight urinary incontinence.

CENTRAL NERVOUS SYSTEM:- K.J. + +. Plantar reflexes: left extensor, right doubtful. Abdominal reflex increased on right, absent on left. Optic discs:- RIGHT central pale area, LEFT distinct pallor of temporal half. No alteration in speech. Legs very spastic. Walks with difficulty with stick.

CEREBRO-SPINAL FLUID:- Clear, Pressure -. Cell count 16. R.J. and N.A. 1 & 2 negative. Alcohol faint haze. Wassermann reaction C.S.F. negative: blood negative. COLLOIDAL GOLD REACTION:- 1 1 2 2 1 1 0 0 0 0 0(Luetic reaction)

July7:- Developed swelling, anterior aspect right tibia clinically resembling gumma. Swelling scraped and emulsion injected into rabbit (intra testicular).

July 20:- Wassermann reaction of blood negative.

Such/

Such cases are, however, exceptional and due weight must be given to the fact that this research was carried out chiefly on pensioner patients in whom possibly syphilis may be of more frequent incidence than is the case among the general population.

It is desired again to emphasize that in the majority of the cases investigated, the absence of pleocytosis, the normal protein content and the negative Wassermann reaction support the view that this disease is of non-syphilitic origin. It is also worthy of note that in a series of cases under treatment with Salvarsan (the rationale of which treatment will be later referred to) in no case did a Wassermann reaction of blood or cerebro-spinal fluid change from a negative to a positive result.

This serological evidence against a specific basis for disseminated sclerosis is supported by the vast bulk of clinical experience as this disease usually occurs in young and otherwise healthy subjects in whom there is no history or sign of syphilis congenital or acquired.

There have recently been circumstantial claims by various continental writers, to have reproduced disseminated sclerosis experimentally and to have demonstrated a spirochaetosis in the inoculated animals. Kuhn and Steiner (30) report that they carried out a series of experimental inoculations with guineapigs, rabbits, mice and a monkey. The best results were obtained with intraperitoneal injections of guineapigs and intra-ocular injections of rabbits. They claim that spirochaetes were detected/

detected, by dark ground illumination and also by staining by Levaditi's method, in the blood from the heart and from the ear vein. They state that the spirochaete is short and thin and resembles the spirochaete icterohaemorrhagica, than which it is slightly finer and often presents a refractile knob at the end. Simons (31) reports that he withdrew cerebro-spinal fluid from a case of disseminated sclerosis during a relapse. This fluid, kept ten days in an ice chest, was proved sterile, and then injected into three male rabbits, producing complete paralysis, and the cerebro-spinal fluid of one of these rabbits, injected intradurally into another rabbit produced paresis. Siemerling (32) has reported spirochaetes in the brain of a patient who had died of the disease and still more recently Schüster (33) has found fine spirochaetes in the lower layers of the cortex in a case of disseminated sclerosis, a site which coincides with the early clinical manifestations of the disease. There are, in addition, certain clinical phenomena which appear to be of special interest when considered in the light of a spirochaetal origin of this disease. It has already been stated that one of the earliest manifestations of disseminated sclerosis is diplopia and attention has already been drawn to the fact that the routine treatment in ophthalmic clinics for cases of idiopathic diplopia is the administration of Iodide of Potassium, the drug being used empirically and with beneficial results. Such transient ocular palsies also occur frequently in tabes, but in this disease/

disease permanent external ocular paralysis more frequently results. That this occasionally does occur in disseminated sclerosis, the following case will exemplify. It also illustrates other important points and is quoted in full:-

A CASE OF DISSEMINATED SCLEROSIS IN WHICH AN EARLY DIAGNOSIS WAS MADE BY MEANS OF THE COLLOIDAL GOLD REACTION, THE DIAGNOSIS BEING SUBSEQUENTLY SUPPORTED BY THE DEVELOPMENT OF AN INTENTION TREMOR AND BILATERAL EXTERNAL OCULAR PALSY.

Case 161. A.R. Aet 24. Sent in to Hospital 29/10/20 by a Medical Board for investigation as to whether his nervous condition was functional or organic in origin. His invalid-:ing disability was G.S.W. back and contusion of spinal cord dating from 16/4/18. He was subsequently a prisoner in Germany. On repatriation X-ray examinations showed lumbar vertebrae uninjured.

CENTRAL NERVOUS SYSTEM:- Weakness and spasticity of both legs. Knee jerks + + +. Pseudo ankle clonus. Plantar reflexes doubtful. KCC > ACC. No R.D. Abdominal reflexes absent. Pupils equal and react normally. No nystagmus. No external ocular palsy. No history of diplopia. No alteration in speech.

CEREBRO-SPINAL FLUID:- Clear. Pressure diminished. Faint blood contamination. Alcohol test +. Ross Jones and Nonne Apelt Tests negative. Wassermann Reaction of C.S.F. Negative. Blood negative.

COLLOIDAL GOLD REACTION:- 0 2 3 3 3 3 1 0 0 0 0

A report was furnished that in view of the positive colloidal gold reaction the case was presumably one of early organic disease and the patient was discharged the following day. He was subsequently readmitted 15/12/20, complaining of weakness and stiffness of legs. Plantar reflexes:- left flexor, right indefinite. Knee jerks + + +. Ankle jerks + +. Pseudo ankle clonus both sides. Abdominal reflexes absent. Bilateral Intention tremor. Grip with right hand weaker than with left. Pupils react normally and consensual reaction to light present. No nystagmus. Paralysis of right external rectus muscle. V.A. R.eye $= \frac{6}{12}$

" L. eye $= \frac{6}{24}$

Refraction - low myopia. In the left eye central faint corneal opacity. In each lens a single radial opacity and in the right a few minute spots in addition. Both fundi normal. Well marked Rombergism. The gait was shuffling with/

occasional tendency to stagger, not in any particular direction. No abnormality of touch, pain, or temperature sense detected. There was slight loss of muscle-joint sensation in the toes. The patient complained of precipitancy and frequency of micturition. There was no incontinence of faeces. On the 28/12/20 a paresis of the left external rectus developed, the patient now having a bilateral external rectus palsy.

Patient was discharged owing to breach of hospital discipline and consequently no further observations were possible.

COMMENT:- This case presents certain points of interest. The condition developed following on an injury to the back. The man's symptoms were for long regarded as functional in origin by re-survey Medical Boards and as no improvement in his condition took place the first examination of the cerebro-spinal fluid was carried out. In view of the positive reaction to Colloidal Gold a diagnosis of organic nervous disease, presumably disseminated sclerosis, was made. This was supported subsequently by the development of intention tremor and external ocular palsies.

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Head and Fearnside in their research on syphilis of the nervous system state "of all the root areas which appear in syphilis, those from the seventh thoracic to the first lumbar are the most frequent. These roots carry the afferent paths from the liver, kidney, suprarenal and testicle organs above all others liable to be crowded with spirochaetes." With reference to this statement it would appear desirable to emphasize the almost constant absence of the abdominal reflex in disseminated sclerosis. This reflex arises from segments 9th thoracic to 1st lumbar.

In view, therefore, of the clinical, serological and experimental evidence, it would appear that the time has now arrived when spirochaeticidal treatment should be given

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a fair trial in disseminated sclerosis. Such treatment was commenced in the course of this research, in December 1919, a few selected cases first being tried with great caution as the evidence in favour of a spirochaetal theory was then of the slightest character, the only work in this connection having been done in Germany and the records being consequently difficult of access. More recently, a strong plea has been put forward by Reasoner and Nichols[35] for the use of Salvarsan in non-syphilitic diseases, although no reference to disseminated sclerosis is made in the course of their paper. They refer to the work of Noguchi[36] and Akatsu[37] who have shown that the spirochaetes, especially those parasitic to the higher animals have many characteristics in common. Of these one is their reaction to the so-called spirochaeticidal substances. They recall the fact that the original work which led to the production of '606' was done not only with spirochaeta pallida but also with spirochaeta recurrentis of relapsing fever, speronema gallinarum, a disease in fowls, and treponema pertenue of yaws. Favourable results were observed from the administration of '606' to cases of rat-bite fever when the aetiology of the disease was unknown. Later the causal spirochaete was detected. The authors state, however, that in Weil's disease and Yellow Fever Salvarsan has no beneficial effect.

It/

It is claimed that the Salvarsan group act as a specific in Vincent's angina, relapsing fever, yaws and pulmonary spirochaetosis in equine influenza. A limited effect is seen in certain protozoal diseases, but this effect may be non-specific. Few favourable results are reported in bacterial diseases with the exception of anthrax. The action of the Salvarsan and its derivatives would appear to constitute a group effect due to a chemical affinity between the drug and the vital structure of the organism.

The routine administration of the Salvarsan group in cases of suspected spirochaetal infection of the central nervous system, by intravenous injections would appear to be strongly indicated, as research has shown that arsenic in such cases does reach the cerebro-spinal fluid in fair concentration, a fact which has not been known until quite recently. Nierenstein (38) found arsenic in the cerebro-spinal fluid of experimental donkeys in approximately the same concentration as in the blood serum following on intra-:venous injections of atoxyl. Hall, Callendar and Holmblad (39) state that araphenamin given intravenously in 0.6 gm. doses may be detected in the cerebro-spinal fluid in from 25% to 35% of the cases.

Hall, Schlegel and McNally (40) found that the cerebro-spinal fluid withdrawn twelve hours after an intravenous injection/

injection of a Salvarsan preparation contained arsenic but that after twenty-four hours none could be detected.

SPIROCHAETICIDAL TECHNIQUE ADOPTED IN THIS RESEARCH IN THE ROUTINE TREATMENT OF DISSEMINATED SCLEROSIS.

The routine adopted was the treatment of cases on energetic antisyphilitic lines. The Salvarsan preparation selected was Novarsenobillon (914) as previous personal experience in the treatment of syphilis in Naval Hospitals had convinced me that this was a thoroughly efficient and relatively non-toxic preparation. The initial dose should be small (0.2 gm. in acute cases). It was found that occasionally severe reactions followed, as evidenced chiefly by shooting pains in the legs and an exacerbation of the existing symptoms. The occurrence of such a reaction may be rendered less likely by placing the patient on mercurial inunction and by giving in addition mercury and iodide by the mouth for a period of one week before the administration of the first intravenous injection of Novarsenobillon. It is rarely necessary to exceed a dose of 0.45 gm. of the Salvarsan preparation and a very large number of injections is required. The injections should be given at 6 day intervals with a short break after every fourth dose, the administration of mercury and iodide being continued throughout.

In acute cases where the tremors are severe and the spasticity/

spasticity excessive it has been found desirable before commencing spirochaeticidal treatment, to administer to the patient hypodermic injections of Hyoscine hydrobromide gr. $\frac{1}{150}$ twice daily for a few days. As already stated, a large series of Novarsenobillon injections is required before any improvement may be hoped for - many of the cases referred to in this paper have received more than twenty injections and their treatment is still being continued. More recently Intramine (di-ortho-di-amino-thio-benzene) has been used in the course of this research in the treatment of both disseminated sclerosis and syphilis and the distinct impression has been formed that improvement both from the clinical and serological aspects, has followed its administration.

Intramine is a non-metallic compound. It is a stable pale greenish yellow crystalline substance, faintly basic in reaction. It is insoluble in water, but soluble in ether, alcohol and acetone. It is injected intra-muscularly in the form of a fine colloidal emulsion. This drug was introduced in 1915 by Mr.J.E.R.McDonagh, who claims that he has successfully treated syphilitic lesions which failed to respond to Salvarsan administration.(41) These claims have been adversely criticised by Baylis(42) and Harrison.(43) Intramuscular injection of intramine is frequently followed by a rise in temperature and severe sweating. In this connection/

connection it is interesting to note that in the Archives of the Austrian Army, official documents (44) refer to 4134 cases of syphilized officers, the records extending over 50 years. Of these cases, 198 (or 4.78%) developed general paralysis of the insane, 113 (or 2.73%) developed tabes, 132 (or 3.19%) developed cerebro-spinal syphilis while 80% developed psychoses. Of those syphilitics who soon after infection underwent a febrile infectious disease, none acquired general paralysis.

Experimental treatment has also been commenced with NORMAL HORSE SERUM and also with COLLOIDAL MANGANESE but the results are not yet sufficiently definite to permit of their inclusion in this paper. It would appear desirable to widen the application of treatment and to try the effects of the administration of any drugs or sera which are known to be inimical to the protozoa group.

Before referring to the results obtained by the spirochaeticidal treatment of disseminated sclerosis it would appear advisable at the outset, to consider the extent to which improvement may be looked for. It is obvious that extensive damage to highly specialized nervous tissue is irreparable and that under such circumstances return to normal function is an impossibility. If in this disease the early symptoms which invariably present themselves, are disregarded, the signs allowed to develop

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one by one and the diagnosis withheld until the fully established picture is presented, the damage has been done and no treatment will undo it.

On reviewing the clinical and serological evidence that has presented itself during the progress of this investigation, one is driven to the conclusion that the need for the early diagnosis of disseminated sclerosis cannot be over-emphasized and it is in the possibility of early diagnosis alone that the hope of future successful treatment of this disease lies. Throughout this research a large number of cases of Neurosyphilis (i.e. cases of a nervous disease of known spirochaetal origin) have been kept under clinical and serological observation by way of control and these cases have been treated on lines exactly similar to those described in the treatment of disseminated sclerosis. It may be useful here to draw a simile between the two diseases from the point of view of treatment. If the value of the administration of Salvarsan preparations in syphilis were estimated solely on the clinical and serological results obtained in the treatment of cases of advanced tabes or general paralysis of the insane, the drug would be less likely to be regarded as specific: indeed it is little used in such conditions even in modern hospital practice as the damage is regarded as irreparable and the results are frequently disappointing.

The/

The earliest stages of disease are indicated by derange-:ment of function and in these early stages patients rarely come within the view of the hospital physician. The whole hope of the early recognition of disseminated sclerosis lies in the hands of the general practitioner and to a lesser extent of the eye specialist. Slight transient diplopia may not be complained of by the patient even when being examined by his doctor unless he is directly asked if he has ever noticed its occurrence and I have frequently been convinced by the look of surprise on a patient's face when he was questioned on the subject, that the fact that he had occasionally and for a transient moment 'seen double' had not impressed itself on his consciousness but had been registered in his subconscious mind. Still less frequently will a patient complain voluntarily of slight precipitancy of micturition yet these premonitory symptoms would seem to arise in the great majority of cases of this disease. All such cases should be most carefully examined and this examina-:tion should always include the application of the Wassermann and Colloidal gold reaction to the cerebro-spinal fluid. The great difficulty in the early diagnosis of disseminated sclerosis lies in the exclusion of functional disease. It is strongly urged that functional disease should only be diagnosed when all possibility of organic disease has been excluded and that even then the diagnosis should be regarded

as/

as purely temporary and subject to review from time to time. It will be subsequently shown that, in the cases of functional disease investigated in this research, the colloidal gold reaction of the cerebro-spinal fluid was negative but the total number of such cases is too small to enable any definite statement to be made on this point. Loss of the abdominal reflex on one or both sides should always arouse suspicion. In doubtful cases, Neo-salvarsan administration should be considered. At worst, it can do no harm and it is hoped that it may be the means of arresting in some cases the onward progress of the disease.

RESULTS OF TREATMENT:-

Twenty-two cases have undergone prolonged courses of treatment and in sixteen of these cases subsequent examinations of the cerebro-spinal fluid have been carried out.

Eighteen of the cases treated represented a relatively advanced stage of the disease, i.e. in addition to spastic paraplegia, one or more of the other cardinal signs of the disease were present. Of these eighteen cases, nine showed no marked improvement, except in minor details. In the other nine, definite improvement was noted, as shown by decrease in the spasticity of the legs, regain of bladder control when this had been partially lost, and increase in muscular power. In one case the speech, which prior to treatment had been markedly scanning, returned practically

to/

to normal.

Three cases in the spastic paraplegia group were treated and all appeared greatly to benefit. These cases on admission had markedly spastic gait and could walk only with the help of two sticks. On discharge they could walk without support and their gait was apparently normal. These cases subsequently complained of symptoms suggestive of the phenomena of intermittent claudication. They stated that they could easily walk a certain distance, when they would suddenly complain of weakness and stiffness of the legs and be unable to proceed further without rest.

A case of spastic monpplegia, which will later be referred to, underwent an intensive course of treatment with beneficial results. Individual cases will subsequently be described but it would here appear desirable to emphasize that the best results have been obtained in early cases and that even in these, treatment must be prolonged over a considerable period of time.

As already stated, in sixteen cases under treatment, repeated examinations have been made of the cerebro-spinal fluid. In all, modifications of the colloidal gold reaction have been found to occur. Individual examples with actual readings will be given but, generally, the modifications that have been observed may be summarised as follows:- A curve which, prior to treatment, was paretic, becomes/

becomes luetic under Neo-salvarsan administration. The discolouration in the tubes giving a luetic curve becomes fainter and the number of tubes involved becomes progressively less. In two cases completely negative results were ultimately obtained. The possible significance of these changes will be discussed when the present position of the colloidal gold reaction is considered, but it may perhaps be hoped that the change from a strongly positive (paretic) to a negative reaction may indicate that the further progress of the disease is being arrested.

The following is a series of illustrative cases:-

A CASE OF ESTABLISHED DISSEMINATED SCLEROSIS IN WHICH PROLONGED ADMINISTRATION OF NOVARSENOBILLON APPARENTLY PRODUCED AN ALMOST COMPLETE REMISSION OF SYMPTOMS ACCOMPANIED BY A NEGATIVE COLLOIDAL GOLD REACTION.

Case 23. G.H. Aet 23. Pensioner. Admitted 12/1/20 complaining of stiffness and weakness of legs of 2½ years' duration.

HISTORY OF ONSET:- In the summer of 1917 he was capsized in a whaler and immersed for 10 minutes in the sea in cold weather. A few weeks later he complained of stiffness and weakness of the right leg on route marching. His previous health had been uniformly good and his family history contained no fact of note. He stated he had never suffered from venereal disease, was moderate in his consumption of tobacco and an abstainer from alcohol.

CONDITION ON ADMISSION:- A well-developed, well-nourished man of 23. His chief complaint was weakness and stiffness of his legs.

CENTRAL NERVOUS SYSTEM:- Legs markedly spastic with considerable muscular weakness. Knee jerks:- Right + + +. Left + +. Tendo Achillis jerks both +. Patellar clonus marked on right, could not be elicited on left. Plantar reflex left flexor, right doubtfully extensor. Epigastric and superficial abdominal reflexes absent. Arms:- Muscular power apparently/

apparently unimpaired. Supinator jerks +, other tendon reflexes normal. Organic reflexes normal. Eyes:- Pupils equal and react to light and accommodation. Consensual reaction present. Marked lateral nystagmus easily elicited. Rotatory nystagmus present to a lesser degree. Vertical nystagmus not elicited. O/E left disc, distinct pallor of temporal half of disc: veins congested. Right disc, slight pallor of temporal half: nasal and inferior margins blurred. Speech:- No alteration from normal noted. Intention tremor present in both arms. Special senses:- smell, taste and hearing normal. No history of memory defect or other mental symptom. Sensory neurone:- Slight impairment of superficial tactile sensation over scattered areas in right leg. Tactile sensation otherwise apparently normal. Pain and temperature sense normal. Muscle joint sense normal. Stereoscopic sense normal.

CEREBRO-SPINAL FLUID on admission:- Fluid clear. Pressure normal. Cell count 9. Ross Jones test negative. Alcohol faint haze. Wassermann reaction:- Blood negative. Cerebro-spinal fluid negative.

COLLOIDAL GOLD REACTION:- 2 3 3 3 3 1 0 0 0 0 0.

Treatment was commenced in February 1920 and carried out on routine antispecific lines. It comprised 12 intravenous injections of 0.45 gr. N.A.B. given in series of 4 doses at 7 day intervals, with a period of 2 weeks between each series. In addition mercurial inunction was carried out.

COLLOIDAL GOLD REACTION OF CEREBRO-SPINAL FLUID AFTER TREATMENT:- 31/7/20. 0 0 0 0 0 0 0 0 0 0 0

SUBSEQUENT HISTORY:- Patient subsequently reported for examination on 5/1/21. There was great improvement in his condition. The muscle tone of the legs was apparently normal. The gait appeared normal and he stated he could walk a distance of about 1½ miles when he would suddenly complain of symptoms of fatigue and be unable to proceed further. There was very slight lateral nystagmus seen only on extreme deviation to the left and confined chiefly to the left eye. A very slight tremor at the end of a voluntary act could be elicited in the right hand only. The left abdominal reflex was weakly present and easily exhausted. The right was absent. No clonus could be elicited. The plantar reflexes were indefinite.

His general improvement was such that his pension had been stopped and he had for several months been earning his/

his living by continuous employment as an oil refiner - his pre-war occupation.

COMMENT:- It might be argued that the improvement in this case was due to one of the usual remissions of the disease which render the study of disseminated sclerosis so baffling a problem and a considerable period of time would require to elapse before a definite conclusion could be drawn.

The following case is of considerable interest:-

A CASE OF DISSEMINATED SCLEROSIS COMPLICATED BY GLYCOSURIA, IN WHICH INTENSIVE SPIROCHAETICIDAL TREATMENT RESULTED IN APPARENT CURE.

Case 37. W.B. Aet 22. A patient of Dr.T.D.Laird. Was sent into Hospital 12/3/20 as a case of Diabetes Mellitus. He stated that his illness commenced in July 1918 when he complained of thirst, progressive loss of weight and marked weakness of both legs.

ON ADMISSION:- His general nutrition was fair. The urine contained 3.5% sugar and the urinary output was 130 oz. The ferric chloride reaction was negative.

CENTRAL NERVOUS SYSTEM:- Both legs were markedly spastic. Knee jerks + +. Bilateral extensor plantar response. Abdominal reflexes absent.

ORGANIC REFLEXES:- Patient gave history of occasional retention and incontinence of urine. Bowel sphincters normal.

EYES:- Pupils equal and react normally. No external ocular palsy. No history of diplopia. No nystagmus. O/E discs paler than normal and lamina cribrosa unduly distinct. Speech and special senses normal. No intention tremor.

CEREBRO-SPINAL FLUID:- 31/3/20. Fluid clear. Pressure +. Cell count 2. Type of cell small lymphocytes. Ross Jones, Alcohol and Nonne Apelt tests negative.
WASSERMANN REACTION:- Cerebro-spinal fluid negative: Blood negative.

COLLOIDAL GOLD REACTION:- 2 3 3 3 2 2 1 0 0 0 0 (Luetic reaction)

PROGRESS OF CASE:- Starvation diet for 24 hours produced a fall in the sugar percentage from 3.5% to 0.45% and a week later after/

after 24 hours' starvation the urine gave a negative reaction for sugar. On normal ward diet the sugar percentage varied from 3.5% to 5%.

In view of the spastic paraplegia, absence of abdominal reflexes, sphincter involvement and early optic atrophy a provisional diagnosis of disseminated sclerosis involving the fourth ventricle was made and the patient was treated by mercurial inunction and intravenous injections of Novarsenobillon (20 in all) and Graham's Diabetic Diet.

RESULT:- A gradual but almost uninterrupted recovery was made. The cerebro-spinal fluid was subsequently re-examined on two occasions. The average cell count was 1, the protein tests and Wassermann reaction remained negative. Slight modification of the colloidal gold reaction was observed. Prior to treatment tubes 1-7 showed colour alterations (vid.sup.). On the conclusion of treatment only tubes 1-5 showed a reaction and the colour alterations were less marked, the readings being as follows:-

1 2 2 2 1 0 0 0 0 0.

The sugar completely disappeared from the urine. The legs became much less spastic and the muscular power improved. The plantar reflexes were no longer constantly extensor. The abdominal reflexes remained absent.

On discharge (30/11/20) the patient could walk with an apparently normal gait without the help of a stick and the urine had been free from sugar for over a month. I was subsequently informed (8/1/21) by Dr.Laird that the urine was still constantly free from sugar and the patient stated that he was enjoying a practically normal diet and appeared to have regained his health.

(45)

COMMENT:- Marie in 1895 drew attention to a series of cases reported by Richardière and Edwards in which disseminated sclerosis and glycosuria co-existed and expressed the opinion that the islets of sclerosis presumably existed in the floor of the fourth ventricle.

A CASE OF ADVANCED DISSEMINATED SCLEROSIS WITH A POSITIVE WASSERMANN REACTION IN THE CEREBRO-SPINAL FLUID, IN WHICH TREATMENT WITH NOVARSENOBILLON PRODUCED A NEGATIVE WASSERMANN REACTION AND A NEGATIVE COLLOIDAL GOLD REACTION BUT IN WHICH NO CLINICAL IMPROVEMENT WAS NOTED.

J.H. Case No.8. The clinical aspects of this case have already been described in detail (see p.40). It is again referred/

referred to here for the purpose of showing the modifications of the serological reactions following intensive anti-specific treatment.

CEREBRO-SPINAL FLUID PICTURE:- 5/3/20. C.S.F.clear. Pressure + +. Cell count 3. Small lymphocytes. Ross Jones test negative. Nonne Apelt phases I and II negative. Wassermann reaction C.S.F. weak positive.
" " blood negative.

COLLOIDAL GOLD REACTION:- 4 3 3 2 2 1 1 0 0 0 0.

TREATMENT:- 12 intravenous injections of Novarsenobillon accompanied by the administration of Mercury and Iodide.

LUMBAR PUNCTURE 21/7/20.
Colloidal gold reaction:- 0 1 0 0 0 0 0 0 0 0 0.

WASSERMANN REACTION C.S.F. negative.
" " blood negative.

Ne definite clinical improvement was recorded.

THE FOLLOWING CASE OF EARLY DISSEMINATED SCLEROSIS IS OF INTEREST IN THAT THE COLLOIDAL GOLD REACTION ON ADMISSION WAS NEGATIVE BUT BECAME LUETIC AFTER THE ADMINISTRATION OF A 'PROVOCATIVE' DOSE OF NOVARSENOBILLON.

A.P: Case No.147. Aet 41. Admitted 12/10/20. Complaining of loss of power of legs of 3 years' duration. Knee jerks + +. Plantar reflexes left extensor, right doubtful. Abdominal reflexes absent. Frequency and precipitancy of micturition, no absolute incontinence. Pupils react normally, slight lateral nystagmus: supinator triceps and wrist jerks increased. Tremors of arms not definitely of 'intention' type. States his speech is becoming slower.

CEREBRO-SPINAL FLUID:- 15/10/20. Clear. Pressure + +. Cell count 2. Alcohol, Ross Jones, and Nonne Apelt I & II tests negative.

WASSERMANN REACTION C.S.F. negative.
" " blood positive.

COLLOIDAL GOLD REACTION:- 0 0 0 0 0 0 0 0 0 0 0 (negative).

25/10/20. Provocative dose 0.4 gm. N.A.B. given.
29/10/20. C.S.F. Clear. Pressure + +. Cell count 4.
COLLOIDAL/ GOLD REACTION:- 1 1 1 2 1 1 0 0 0 0 0 (weak luetic)

A CASE OF SPASTIC MONOPLEGIA TREATED BY NEO-SALVARSAN WITH RESULTING CLINICAL IMPROVEMENT.

Case 104. G.R. Admitted 16/6/20. Complaining of spasms in right leg. Onset 3 months ago. No history of diplopia. Slight atrophy right calf and thigh muscles. Knee jerks both present. R.+. Clonus of right ankle.
Plantar reflexes:- flexor left, indefinite right.
Walks dragging right leg: inner side of boot worn.

OPTIC FUNDI:- Outline of discs slightly blurred. No definite neuritis. Pupils react normally. No Romb^ergism. Definite weakness of right ankle. No anaesthesia or analgesia. No sphincter involvement. Tremor of both hands especially right.

CEREBRO-SPINAL FLUID:- Clear. Pressure normal. No excess of protein. Cell count 4. Wassermann reaction negative.

COLLOIDAL GOLD REACTION:- 1 1 2 2 1 1 0 0 0 0 0 0

WASSERMANN REACTION blood negative.
" " C.S.F. negative.

TREATMENT:- Consisting of fourteen intravenous injections of Novarsenobillon was followed by great clinical improvement. On discharge his gait was normal, and there was a slight increase in the girth of the right thigh muscles. He still occasionally complained of spasm. He refused further lumbar puncture so it was not possible to carry out the colloidal gold reaction subsequent to treatment.

A CASE OF DISSEMINATED SCLEROSIS WITH A NEGATIVE WASSERMANN REACTION SHOWING A PARETIC COLLOIDAL GOLD CURVE.

Case 82. Mrs.D. Admitted 26/5/20. Complaining of paresis right leg. Onset 6 years ago following cystitis in pregnancy. 8 years ago also during pregnancy lost the power of speech. K.J.Right exaggerated. Left normal. Bilateral extensor plantar reflex. Abdominal reflexes absent. Sphincters normal. Some loss of power in right leg. No apparent wasting. No sensory phenomena. Pupils medium. Right larger than left. React normally. No history of diplopia. Slight nystagmus on deviation to right. No alteration in speech. Ataxia. Optic fundi normal.

24/5/20. Nystagmus both eyes. No intention tremor. No change in speech.

CEREBRO/

CEREBRO-SPINAL FLUID:- Clear. Pressure +. Cell count 4. small lymphocytes. All protein tests negative. Dark ground illumination negative.

WASSERMANN REACTION C.S.F. negative.

COLLOIDAL GOLD REACTION:- 5 5 5 5 2 2 2 0 0 0 0.

COMMENT:- This case is an example of the fact that a paretic colloidal gold reaction is not found only in General Paralysis.

A CASE OF DISSEMINATED SCLEROSIS SHOWING FACIAL PALSY AND A TYPICAL CEREBRO-SPINAL FLUID PICTURE.

Case 76. J.W. Aet 35. Admitted 24/5/20 complaining of loss of power in legs of 3 years' duration. Paresis of left facial nerve. Marked int ention tremor. Abdominal reflexes absent. Knee jerks + +. Plantar reflex left flexor, right extensor. Patellar and ankle clonus on left. Superficial tactile sensation impaired over left thigh and knee.

FUNDI:- O/E pallor of both discs. Pupils equal and react normally. No diplopia. Slight nystagmus.

CEREBROSPINAL FLUID:- Clear. Pressure +. Cell count 4. Small lymphocytes. Alcohol faint haze. R.J.faint +. Nonne Apelt I faint haze, II negative.

WASSERMANN REACTION C.S.F. negative.

COLLOIDAL GOLD REACTION:- 1 1 2 2 2 2 1 0 0 0 0.

THE FOLLOWING CASE IS OF INTEREST IN THAT THE CLINICAL IMPROVEMENT FOLLOWING NEO-SALVARSAN ADMINISTRATION WAS INDEPENDENTLY OBSERVED.

Case 39. A.B. Aet 22. Female patient of Dr.W.K.Anderson. Clinically typical disseminated sclerosis. C.S.F. Clear. Cell count 3. Small lymphocytes. All protein tests negative.

WASSERMANN REACTION C.S.F. Positive.

COLLOIDAL GOLD REACTION:- 5 5 5 3 2 1 0 0 0 0 0 0 0 (paretic reaction)

TREATMENT:- Intravenous Novarsenobillon. (12 injections)

CEREBRO/

CEREBRO-SPINAL FLUID AFTER TREATMENT. 19/12/20.

COLLOIDAL GOLD REACTION:- 1 2 3 3 2 2 0 0 0 0 0 0 (luetic reaction)

WASSERMANN REACTION C.S.F. suspicious.

Dr.Anderson reported great clinical improvement (Dec.,1920).

A CASE OF ADVANCED DISSEMINATED SCLEROSIS GIVING A PARETIC COLLOIDAL CURVE IN WHICH TWELVE INTRAVENOUS INJECTIONS OF NOVARSENOBILLON PRODUCED A NEGATIVE REACTION TO COLLOIDAL GOLD.

Case 172. M.B. Female. aet 29. Admitted 28/10/20. Complain-:ing of inability to walk, tremors of hands and shaking of head. She states that 2½ years ago she first complained of difficulty in walking and dragging of right leg. Some months later tremors of the hands developed and she noticed that she was unable to convey a cup to her lips without spilling the contents. Twelve months after the first onset of her symptoms she noticed a marked alteration in her speech and six months later she complained of involuntary shaking of her head.

ON ADMISSION patient was well nourished and of healthy appearance. Speech was slow and markedly 'scanning'. There was involuntary tremor of head and coarse intention tremor of arms especially on the right side, which prevented her from feeding herself. Pupils were equal and reacted actively to light and accommodation - the consensual reflex was present. There was coarse lateral nystagmus but no history of diplopia could be elicited. Knee jerks exaggerated on right side, absent on left. The right plantar reflex was extensor. Ankle clonus was elicited on the right side only. No abnormal-:ity was detected in the sensory neurone, tactile, pain and temperature sensations being apparently normal. There was no evidence of sphincter involvement. The fundi were normal.

CEREBRO-SPINAL FLUID PICTURE:- Fluid clear. Pressure +. Cell count 3. Ross Jones and Nonne Apelt Tests negative.

WASSERMANN REACTION OF BLOOD NEGATIVE, C.S.F. negative (query)

COLLOIDAL GOLD REACTION:- 5 5 5 5 2 1 0 0 0 0 0 0 (paretic reaction)

TREATMENT:- Twelve intravenous injections of 0.4 gr. Novarseno-:billon.

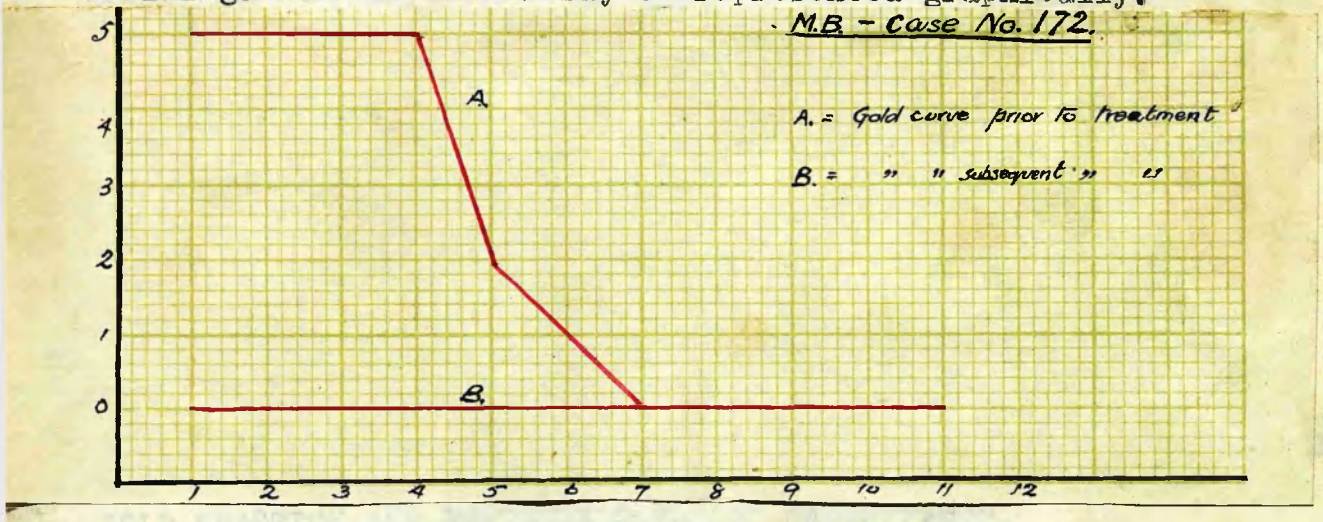
Subsequent lumbar puncture 19/1/21.

COLLOIDAL GOLD REACTION:- 0 0 0 0 0 0 0 0 0 0 0 0

CLINICAL/

CLINICAL RESULT:- Definite improvement was noted as regards intention tremor and speech. There was also improvement in her general condition but not to any very marked extent. On discharge she was able to feed herself and the right abdominal reflex was weakly active. Arrangements were made for treatment to be continued at home by her own doctor.

COMMENT:- Although the clinical improvement in this case was not marked, the modification of the colloidal gold reaction was striking. These curves may be represented graphically.



A CASE OF EARLY DISSEMINATED SCLEROSIS IN WHICH NEO-SALVARSAN TREATMENT WAS FOLLOWED BY CLINICAL IMPROVEMENT WITHOUT ANY MARKED ALTERATION IN THE COLLOIDAL GOLD REACTION.

Case No.14. A.D. Aet.24. Miner. Admitted to Hospital 12/12/19. Complaining of difficulty in walking of 9 months' duration. He also stated that prior to the onset of the weakness of his legs he had occasionally experienced diplopia, also that he had some difficulty in micturition shown by symptoms of slight retention.

ON ADMISSION:- A well built muscular man of healthy appearance.

CENTRAL NERVOUS SYSTEM:- Weakness and spasticity of legs. Knee jerks +. Plantar reflexes, left extensor, right flexor, abdominal reflexes absent. Slight lateral nystagmus, no altera-:tion in speech. Fundi O/E left disc rather pale, right disc vessels congested.

CEREBRO-SPINAL FLUID:- Clear. Faint blood contamination. Ross Jones test faint +. Nonne Apelt phases 1 and 2 faint +. Alcohol test +.

COLLOIDAL GOLD REACTION:- 5 5 4 5 3 2 1 0 0 0 0

WASSERMANN/

WASSERMANN REACTION C.S.F. negative.
" " blood negative.

TREATMENT:- 7 intravenous injections 0.45 gr. N.A.B.

Lumbar puncture 24/5/20.

COLLOIDAL GOLD REACTION:- 5 5 5 3 1 1 1 0 0 0 0

Three further injections of Novarsenobillon were given when the patient was transferred to another hospital - consequently no further examination of the cerebro-spinal fluid was possible.

CLINICAL RESULTS:- On discharge the spasticity of the legs was greatly diminished and the gait much improved. Bladder function was apparently normal.

COMMENT:- Treatment in this case was incomplete but the improvement in gait and regain of complete bladder control appeared to indicate that his condition had undergone some improvement. Little importance was attached to the nystagmus as he was by occupation a miner and worked with a Davy lamp.

A CASE OF ADVANCED DISSEMINATED SCLEROSIS TREATED WITH SALVARSAN AND INTRAMINE FOLLOWED BY MARKED MODIFICATION OF THE COLLOIDAL GOLD REACTION AND DEFINITE CLINICAL IMPROVEMENT.

H.H. Case No.30. This patient developed weakness of his legs following on an attack of pyrexia of unknown origin while serving in France in 1917. There was no history of injury. He was admitted to St.Luke's Hospital, Halifax, where he was diagnosed as suffering from trench fever. During his residence at St. Luke's Hospital he developed incontinence of urine and faeces. Six months later he was transferred to a hospital at Bradford - at this stage he states he was able to walk on crutches. While in hospital at Bradford tremors developed in his arms and he noticed an alteration in his speech. He was transferred to Stobhill in March 1919 and thence to Ralston Hospital in May 1919, where he was diagnosed as suffering from disseminated sclerosis. While he was an inmate of Ralston Hospital a speciman of his cerebro-spinal fluid presented the following picture:-
Fluid clear. Cell count 2. Ross Jones test negative.
Nonne Apelt test Phase 1 negative.
" II negative.
WASSERMANN REACTION C.S.F. Negative.
" " blood Negative. 27/3/20.

COLLOIDAL GOLD REACTION:- 5 5 5 4 2 3 1 0 0 0 0

He/

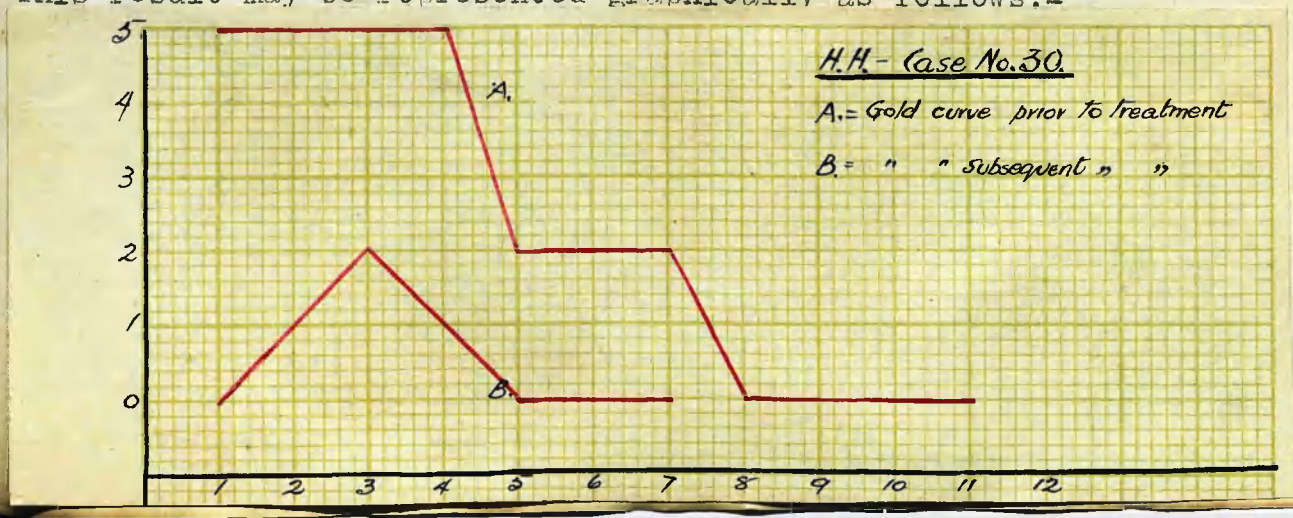
He was subsequently admitted (11/11/20) to Bellahouston Hospital not having received anti-specific treatment in the interval. On admission a specimen of cerebro-spinal fluid was obtained and examined with the following colloidal gold result:- 55552220000. At this date the case presented the following clinical features:- There was almost complete loss of power of the legs which were very spastic. Knee jerks + + +. Plantar reflexes strongly extensor: ankle and patellar clonus present. Abdominal reflexes absent. Complete incontinence of urine and faeces (which had persisted since 1917): gross intention tremor with exaggeratedly choreiform movements of the arms; lateral, vertical and rotatory nystagmus: speech slow, scanning and deliberate. Fundi O/E both discs pale and parchment-like, cribriform plate being distinctly seen, the optic atrophy being more advanced in the left than in the right. There was no history of diplopia although there was apparent incoordination of the eyes.

TREATMENT:- 15/11/20. Intramine (intramuscular) 3 c.c.
22/11/20. Intramine. " 5 c.c.
24/11/20. 0.45 gm. Novarsenobillon (intravenous)
29/11/20. 0.45 gm. " "

Lumbar puncture performed 6/12/20.
COLLOIDAL GOLD REACTION:- 0 1 2 2 2 1 1 0 0 0 0.
Further treatment:-

6/12/20.	0.45 gm. Novarsenobillon.	17/1/21.	0.45 gm. N.A.B.
13/12/20.	0.45 gm. "	25/1/21.	0.45 " "
20/12/20.	0.45 gm. "	1/2/21.	" " "
27/12/20.	Intramine 4.c.c.	8/2/21.	" " "
11/1/21.	Intramine 5 c.c.	15/2/21.	" " "

Lumbar puncture 15/2/21.
COLLOIDAL GOLD REACTION:- 0 1 2 1 0 0 0 0 0 0 0.
CLINICAL RESULT:- There has been definite improvement in his clinical condition. Bladder control, which had been lost for over 2 years, was completely re-established 2/2/21 and has since been retained. There is great diminution in the intention tremor, the patient now being able to pick up and read a newspaper. The nystagmus is much less marked. There is no improvement in speech. His general condition has greatly improved. Treatment is being continued.
This result may be represented graphically as follows:-



COMMENT:- This case shows very clearly the modifications in the colloidal gold reaction. It is of particular interest to note that the first reading was 5 5 5 4 2 2 1 0 0 0 0, that after a period of 8 months without treatment the reading was 5 5 5 5 2 2 2 0 0 0 (i.e. a slightly stronger reaction) and that after the administra-:tion of 2 injections of intramine and 2 injections of Novarsenobillon the reading became 0 1 2 2 2 1 1 0 0 0 0 and that subsequent treatment reduced this to 0 1 2 1 0 0 0 0 0 0 0. Treatment is being continued and an ultimately negative result is hoped for. In connection with this case it is desired to emphasize firstly that the use of intramine as an adjuvant to Novarsenobillon produced a much more rapid modification of the colloidal gold reaction than has been observed in a series of similar cases treated by Novarseno-:billon alone and secondly that definite clinical improvement followed such treatment although the clinical picture was one of advanced disseminated sclerosis.

A CASE OF DISSEMINATED SCLEROSIS WITH A POSITIVE WASSERMANN REACTION IN THE BLOOD IN WHICH PROLONGED NEO-SALVARSAN TREATMENT PRODUCED A NEGATIVE WASSERMANN REACTION IN THE BLOOD BUT IN WHICH THERE WAS LITTLE CLINICAL IMPROVEMENT AND IN WHICH THE CEREBRO-SPINAL FLUID PICTURE DID NOT SHOW THE USUAL MODIFICATIONS.

Case No.35. W.E. aet 37. Labourer. Admitted 29/3/20. Complaining of weakness and stiffness of legs of 3¼ years' duration. No history of specific infection.

CENTRAL NERVOUS SYSTEM:- Legs weak and spastic. Knee jerks + +. Plantar reflexes extensor. Abdominal reflexes absent. Ankle and patellar clonus easily elicited in both legs. Pupils equal and react actively to light and accommodation. Consensual reflex present. Slow lateral nystagmus especially to right. Well marked intention tremor. No history of bladder deraggement or diplopia. Slight alteration in speech.

CEREBRO-SPINAL FLUID. 29/3/20:- Clear. Cell count 6.
WASSERMANN REACTION C.S.F. Negative.
COLLOIDAL GOLD REACTION:- 5 5 5 5 4 3 1 0 0 0 0 (paretic reaction)
WASSERMANN REACTION BLOOD POSITIVE.

TREATMENT:- From 16/4/20 to 8/2/21 patient received 23 injections of 0.45 gm. Novarsenobillon combined with the administration of biniodide of mercury.

CEREBRO-SPINAL FLUID 20/12/20. Clear. Pressure +. Cell count 27.
Wassermann reaction C.S.F. Suspicious.
" " blood negative.
COLLOIDAL GOLD REACTION:- 5 5 5 5 4 2 1 0 0 0 0.

CLINICAL/

CLINICAL RESULT:- There was a slight but definite improvement in his general condition. Patient stated that he was confident that he had gained strength and was much less 'shaky'. The physical signs remained unaltered as the result of treatment.

COMMENT:- This case is remarkable in that, in spite of prolonged treatment, the cell count in the cerebro-spinal fluid increased from 6 to 27: the Wassermann reaction changed from 'negative' to 'suspicious' and there was no improvement in the colloidal gold reaction. The only definitely beneficial result obtained was a negative Wassermann reaction in the blood and a very slight improvement in general health.

The following case is of interest in that there is a definite history of injury to which the patient attributes the onset of his symptoms - a point which has been repeatedly observed in the course of this investigation.

A.B. Aet 27. Admitted 19/1/21. Patient served 5 years in the army. He was wounded in the lower third of the left leg on 1st July 1916 and fell into a trench 10 feet deep sustaining severe concussion. In June 1917 he complained of 'shakiness' and unsteadiness in walking. He was diagnosed as 'Neurasthenia' and sent back to duty. He was demobilized in 1919. After demobilization his shakiness and difficulty in walking increased. By September 1919 he was unable to walk. He has since been in various hospitals. Personal and family history contains nothing of note.

CONDITION ON ADMISSION:- 19/1/21. Unable to walk or stand.

CENTRAL NERVOUS SYSTEM:- Eyes:- Pupils react to light directly and consensually and also on looking at a near object. Very slight lateral nystagmus. Has had diplopia frequently, the first occasion being about the beginning of 1920. He states that he lost the sight of his left eye from September 1919 until April, 1920. No external ocular palsy.
Eye specialist's report:- "V.A.R.6/18 to 6/36. Optic atrophy, right and left, involving axial fibres only. Fields of vision uncontracted. Central scotoma for all colours. Optic discs both white and with exudate on them indicating past optic neuritis (probably 2 years ago).

OTHER CRANIAL NERVES:- Apparently normal. Special senses normal except as regards sight. SPEECH:- Patient has not personally/

personally noted any change in his speech. He appears to speak slightly more slowly than normal. Intention tremor very coarse on both sides. Has great difficulty in feeding himself: grip with both hands is good. Abdominal reflexes absent. Knee jerks + +. No patellar clonus. Complete ankle clonus both sides. Plantar reflexes both strongly extensor. There is marked spasticity and loss of power of the legs. Sensory neurone:- No abnormality detected.

ORGANIC REFLEXES:- Has absolute incontinence of urine and faeces.

The cerebro-spinal fluid picture in this case was not obtained, owing to gross blood contamination, but the case is quoted here on account of the eye signs and of the definite history of original injury. Osnato(46) quotes a series of cases of general paralysis in which the symptoms began very soon after an injury. As a result of his researches he suggests that trauma in a syphilitic may give the spirochaetes an opportunity for invasion, that the course of the disease may be hastened by the changes secondary to injury and that toxins such as influenza or alcohol may have an influence similar to trauma in syphilitics.

As already stated, disseminated sclerosis would appear to be of relatively frequent occurrence among pensioners and in very many cases, there is a definite history of injury. In this connection Osnato's observations would seem to apply equally to this disease and to explain also the acknowledged clinical fact that the onset of disseminated sclerosis frequently follows on the occurrence of an acute infectious condition.

A CASE OF DISSEMINATED SCLEROSIS IN WHICH DIPLOPIA WAS SUCCEEDED BY EXTERNAL OCULAR PALSY.

Case No.194. D.T. Aet.32. Admitted 17/1/21. History of onset:- This man joined the army in 1914 and did not serve abroad. There was no history of injury. He first noticed weakness of his legs in January, 1916, when he began to fall out on route marches. By the summer of 1918 he was unable to walk. Tremors, diplopia, incontinence of urine and change in speech all came on together in the summer of 1918. The family and personal history contains no fact of note.

CONDITION ON ADMISSION:- Patient unable to stand.

CENTRAL NERVOUS SYSTEM:- Pupils equal and react to accommodation and light directly and consensually. Very slight nystagmus on looking to the right. Complains of diplopia/

diplopia. Slight intention tremor on both sides. Abdominal reflexes both lost. Epigastric reflexes sluggish. Knee jerks + + +. Weakly sustained patellar clonus on both sides. Ankle clonus sustained on right, absent on left. Plantar reflexes both strongly extensor. Sensory neurone:- No abnormality of touch, pain, temperature or muscle joint sense detected. Speech markedly staccato. Organic reflexes:- Has frequency and partial incontinence of urine, precipitancy of bowels.

EYE SPECIALIST'S REPORT:- (Dr.Wright Thomson) "The ocular paralytic lesion is, I think, of the left internal rectus but the condition has probably been complicated by compensatory action of other muscles so that the distribution and character of the diplopia is anomalous. The visual acuity is good and both fundi are normal."

CEREBRO-SPINAL FLUID, 10/1/21:- Fluid clear. Pressure normal.
Wassermann reaction of C.S.F. Negative.
" " " blood negative.
COLLOIDAL GOLD REACTION:- 1 2 3 2 1 0 0 0 0 0 0.

COMMENT:- This case is of interest in that, although there is a history of diplopia and also a definite external ocular paresis, the optic disc so far shows no abnormality.

A CASE OF DISSEMINATED SCLEROSIS OF 2 YEARS' DURATION IN WHICH NEOSALVARSAN PRODUCED CLINICAL AND SEROLOGICAL IMPROVEMENT.

C.R. Case No.87. Admitted 19/5/20. Complaining of loss of power of legs dating since April 1918. The onset of paresis was gradual and was first noted in the left leg. There was no history of specific infection.

CONDITION ON ADMISSION:- Knee jerks + + +. Ankle and patellar clonus, bilateral extensor plantar reflex, legs extremely spastic. No abnormality of sensation detected. ORGANIC REFLEXES:- Bowel function normal. Occasional slight urinary retention. EYES:- Pupils equal and react normally to light and accommodation. Consensual reflex active. Slight lateral nystagmus. FUNDI:- O/E Right disc is paler and has more clearly defined edges than left. Vessels normal. No external ocular palsy. Wassermann reaction of blood negative.

CEREBRO-SPINAL FLUID:- 31/5/20. Fluid clear. Cell count 6. Ross Jones and Nonne Apelt tests negative. Alcohol test faint +.
WASSERMANN REACTION C.S.F. Negative.
COLLOIDAL GOLD REACTION " :- 5 5 4 4 2 2 1 0 0 0 0.

TREATMENT:-/

TREATMENT:- 14/6/20 to 27/9/20, Twelve injections 0.75 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID:- 29/9/20. Fluid clear. Pressure normal. Cell count 3. Alcohol test faintly +. Ross Jones and Nonne Apelt tests negative.
WASSERMANN REACTION C.S.F. negative.
COLLOIDAL GOLD REACTION " 1 3 3 3 1 0 0 0 0 0 0

FURTHER TREATMENT:- 4/10/20 to 15/11/20. Four injections 0.45 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID 20/11/20. Fluid clear. Pressure +. Cell count 1. Alcohol test +. Ross Jones and Nonne Apelt tests negative.
Wassermann reaction C.S.F. negative.
" " blood negative.
COLLOIDAL GOLD REACTION:- 3 2 2 3 1 0 0 0 0 0 0.

FURTHER TREATMENT:- 29/11/20 to 20/1/21. Four injections 0.45 gm. Novarsenobillon and one injection 3 c.c. intramine.

CEREBRO-SPINAL FLUID 26/2/21. Colloidal gold reaction:-
1 1 1 4 4 0 0 0 0 0 0.
CLINICAL RESULT:- Treatment in this case is being continued. There is very definite diminution in the spasticity of the legs and bladder control has been apparently regained.

COMMENT:- This case shows modification of the colloidal gold reaction, the reading before treatment was commenced being 5 5 4 4 2 2 1 0 0 0 0 and after treatment 1 1 1 4 4 0 0 0 0 0 0 and this was accompanied by clinical improvement. It will be noted, here, as always, that the Wassermann reaction before, during and after treatment, remains persistently negative in the blood and cerebro-spinal fluid.

A CASE OF DISSEMINATED SCLEROSIS WHICH IN THE EARLY STAGES SIMULATED CEREBRAL NEOPLASM.

Case No.174. W.C. Aet 24. Occupation apprentice glass bottle blower. This man, who is a pensioner, was buried alive in September 1915, by a shell explosion. A few days later he began to be troubled with numbness of the left side of the body and difficulty in walking. He also had frequent 'fits' and spasms of his left leg accompanied by very severe headache. On his discharge from the army a diagnosis of cerebral neoplasm was made.

CONDITION/

CONDITION ON ADMISSION:- Central nervous system:- Pupils equal, react normally to light and accommodation. Consensual reflex present. Slight lateral nystagmus, no external ocular palsy: intention tremor more marked on left. Abdominal reflexes absent. Knee jerks + +. Plantar reflexes left definitely extensor, right doubtfully extensor. Speech somewhat hesitating. No definite sensory disturbance made but man complains of occasional numbness in his left leg. Visual acuity:- Right eye 6/6. Left eye 6/9. Optic discs somewhat grey in colour with marked choroidal rings but they could not be called pathological in appearance. There is slight precipitancy of micturition. In walking he tends to drag the left leg.

CEREBRO-SPINAL FLUID:- 17/11/20. Fluid clear. Pressure normal.
WASSERMANN REACTION C.S.F. Negative.
" " blood Negative.
COLLOIDAL GOLD REACTION:- 2 2 5 4 4 4 1 1 0 0 0.

TREATMENT:- 24/11/20 to 13/12/20, four injections 0.45 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID. Clear. Pressure normal. Cell count 2 per c.m.m. Alcohol test positive. Other protein tests negative.

COLLOIDAL GOLD REACTION:- 1 2 1 0 0 0 0 0 0 0 0.

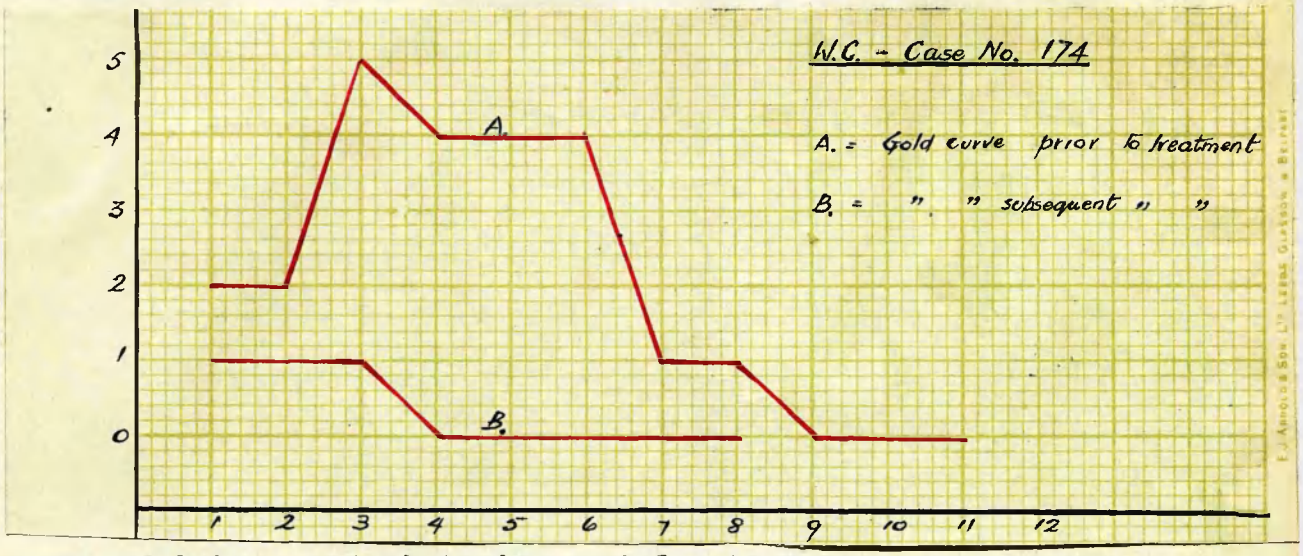
FURTHER TREATMENT:- 11/1/21 to 8/2/21, four injections 0.45 gm. Novarsenobillon.
CEREBRO-SPINAL FLUID 14/1/21:-
COLLOIDAL GOLD REACTION:- 1 1 1 0 0 0 0 0 0 0 0.

CLINICAL RESULT:- There is definite clinical improvement (26/2/21). The spasticity of the legs is less marked, the gait is steadier and bladder function is normal.

COMMENT:- This case presents points of considerable interest. It will be noted that the patient was originally diagnosed by an Army Board as suffering from cerebral neoplasm. See also case 162, p. 102). It has already been pointed out that retro-bulbar neuritis frequently occurs in the early stages of disseminated sclerosis, and at this stage a cortical spirochaetosis (as described by Schuster) might easily produce severe headache and vomiting. This picture would provisionally justify a clinical diagnosis of cerebral neoplasm. It will also be observed that at a later stage the spastic paresis was/

was largely hemiplegic in distribution from which again an error in diagnosis might have arisen. Finally, it is desired to emphasize the marked modification produced in the colloidal gold reaction by 8 injections of Neo-salvarsan, viz:- COLLOIDAL GOLD REACTION before treatment 22544411000,
" " " after " 1 1 1 000000000

This may be represented graphically:-



It will be noted that this modification was accompanied by distinct clinical improvement. Attention is also drawn to the fact that in this, as in so many similar cases, the onset of symptoms followed rapidly on a severe injury - a phenomenon for which a provisional explanation has been already advanced.

PART II.

It has already been stated at the commencement of this paper, that clinical and serological observations were carried out on a series of cases of nervous diseases other than disseminated sclerosis. Particular attention was devoted to cases of syphilitic disease of the nervous system which would appear likely to form the best controls for the observations made on disseminated sclerosis. In all these cases the examination comprised the same routine as that already described in the introductory pages.

The diseases investigated in the second portion of this research may conveniently be grouped as follows:-

(1) Nervous Syphilis.

(2) Functional Nervous Diseases.

(3) Cerebral Neoplasm.

(4) Epilepsy.

(5) Miscellaneous nervous diseases.

1. CASES OF NERVOUS SYPHILIS.

Forty-one cases falling into this group were investigated and they represent those cases in which a diagnosis of syphilitic infection appeared probable or possible on clinical grounds alone. They do not include cases in which a diagnosis of syphilis was not suggested by the clinical/

clinical picture but in which a positive Wassermann reaction in blood or cerebro-spinal fluid was subsequently ascertained to be present. Some of such cases have already been considered under disseminated sclerosis, the remainder will be included in Group 5. (Cases of Miscellaneous Nervous Diseases).

The forty-one cases falling into Group I. comprise Tabes Dorsalis (28 cases; General paralysis of the Insane (3 cases); other forms of central syphilis (3 cases); Hemiplegia due to endarteritis obliterans (3 cases); Transverse myelitis (one case); Spastic paraplegia (2 cases); Charcot's joint (one case).

The group, taken as a whole, gives the following results of the Wassermann reaction of the blood and analysis of the cerebro-spinal fluid picture.

CELL COUNT:- 36 cases (or 87.8%) showed an increase in the cell count. Of the 5 cases in which the number of cells was not in excess of normal, two had previously received antispecific treatment. The average cell count for the whole group was 49 per c.m.m. In addition the presence of large and small lymphocytes was frequently noted. It would therefore appear that a marked pleocytosis is an almost constant factor in syphilitis nervous disease.

PROTEIN CONTENT:- There was definite evidence of increased protein/

protein content in 26 cases (63.4%).

WASSERMANN REACTION ANALYSIS:-

Positive in blood & cerebro-spinal fluid	22 cases.
Negative in blood & cerebro-spinal fluid	5 "
Positive in blood & negative in cerebro-spinal .	6 "
Negative in blood: positive in cerebro-spinal fluid	2 "
Blood not examined:positive in cerebro-spinal fluid	5 "
'Suspicious' in blood; positive in cerebro-spinal "	1 case.
	41 cases.

COLLOIDAL GOLD REACTION:- The colloidal gold reaction was positive (luetic or paretic reaction) in 40 cases. In one case (Charcot's Joint) it was suspicious.

DARK GROUND ILLUMINATION:- Spirochaeta pallida was detected in the cerebro-spinal fluid in 1 case of general paralysis of the insane and in 1 case of Tabes.

In addition a definite increase in fluid pressure was noted in the majority of cases.

It would therefore appear that there is a fairly definite cerebro-spinal picture in syphilitic diseases of the nervous system, viz:-

(1) Pleocytosis (87.8%)
(2) Increased protein content (63.4%)
(3) A positive Wassermann reaction in blood or cerebro-spinal fluid (87.9%)
(4) A luetic or paretic reaction to colloidal gold (97.5%)

In a series of selected cases, prolonged intensive antisyphilitic treatment was carried out and the resulting clinical and serological modifications were studied as this was considered likely to form the most useful control of the work/

work done on disseminated sclerosis.

A short series of cases will now be referred to:- They have been selected as likely to illustrate points of importance and such points are mentioned in the comment on individual cases.

A CASE OF TABES DORSALIS WITH A NEGATIVE WASSERMANN REACTION IN THE BLOOD AND A TYPICAL CEREBRO-SPINAL FLUID PICTURE.

Case 101. A.C. Aet.48. Admitted 10/6/20 complaining of difficulty in walking and slight retention of urine.

CENTRAL NERVOUS SYSTEM:- Knee jerks absent, sensation of legs impaired. Argyll Robertson pupil right. Left pupil fully dilated and inactive. Paresis of left external rectus. No contraction of visual fields. Has occasional diplopia. Marked Rombergism and ataxia.

CEREBRO-SPINAL FLUID:- 10/6/20. Fluid clear: pressure normal. Cell count 45 per c.m.m. Ross Jones and Nonne Apelt tests positive. Alcohol test positive. Wassermann reaction C.S.F. positive.
COLLOIDAL GOLD REACTION:- 1 1 2 2 2 1 1 0 0 0 0
Wassermann reaction of blood negative.

TREATMENT:- 28/6/20 to 6/11/20. 10 injections of 0.75 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID:- 6/11/20. Fluid clear. Cell count 6.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction " 2 2 3 2 1 0 0 0 0 0
Wassermann reaction blood negative.

FURTHER TREATMENT:- 6/11/20 to 28/1/21, 6 injections 0.45 gm. Novarsenobillon and 2 injections intramine.

CEREBRO-SPINAL FLUID:- Clear. Cell count 4.
Colloidal gold reaction:- 1 2 2 1 0 0 0 0 0 0 0.
Wassermann reaction C.S.F. Positive.
" " blood negative.

CLINICAL RESULT:- There was only slight improvement noted. Patient stated that he felt stronger and steadier. On discharge the left pupil was noted to be distinctly smaller than on admission.

COMMENT/

COMMENT:- The cerebro-spinal fluid under treatment shows the usual fall in cell count and modification of the colloidal gold reaction which is however still positive on discharge. It is of interest to compare this case of neurosyphilis in which 16 injections of Novarsenobillon failed to produce a negative colloidal reaction with that of Case 30. (p. 64), a case of disseminated sclerosis in which a much more rapid modification of the colloidal gold picture was obtained. In addition it is to be observed that the clinical improvement under treatment in these cases of neurosyphilis is rarely more marked than in the cases of disseminated sclerosis which have been referred to in part I of this paper.

A CASE OF TABES DORSALIS IN WHICH PROLONGED TREATMENT WITH SALVARSAN AND INTRAMINE PRODUCED A NEGATIVE WASSERMANN REACTION IN THE BLOOD BUT IN WHICH THE CEREBRO-SPINAL FLUID REMAINED POSITIVE TO THE WASSERMANN AND COLLOIDAL GOLD TESTS:-

Case No.22. J.McI. Aet 48. Admitted 1/3/20, complaining of pains in legs and inability to stand. The onset of his symptoms dated from 1918.

CENTRAL NERVOUS SYSTEM:- Pupils moderately dilated, react to accommodation but not to light. Knee jerks absent. Anaesthesia of legs. Patient practically unable to stand with the help of two sticks. Complains of girdle sensation and lightning pains. Fundi O/E left disc, margin blurred, central aera of pallor, right disc congested.

CEREBRO-SPINAL FLUID:- 19/3/20. Clear, pressure normal, cell count 44, small lymphocytes. Ross Jones +. Nonne Apelt 1 & 2 +. Alcohol +.
Wassermann reaction C.S.F.positive.
Colloidal gold reaction:- 5 5 5 5 4 2 2 1 0 0 0 (paretic)
Wassermann reaction blood weak positive.

TREATMENT:- 23/3/20 to 21/6/20 twelve injections of 0.75 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID 20/7/20. Cell count 70. Small and large lymphocytes. Protein tests as before.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 1 2 3 2 2 3 0 0 0 0 0

FURTHER TREATMENT:- 9/8/20 to 30/8/20, 4 injections of 0.75 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID, 29/9/20. Fluid clear. Pressure +.
Cell count 11, protein tests as before.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 1 3 3 3 3 3 3 1 0 0 0.

FURTHER TREATMENT:- 27/9/20 to 20/1/21, eight injections 0.45 gm. Novarsenobillon and two injections of intramine (3 c.c. and 5 c.c.)

CEREBRO-SPINAL FLUID, 30/1/21:- Fluid clear, pressure normal.
Cell count 6.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction 2 3 3 2 1 0 0 0 0 0 0
Wassermann reaction of blood negative.

CLINICAL RESULT:- Discharged from hospital 11/2/21. On discharge patient's condition had considerably improved - he was able to walk fairly easily with the help of a stick but still required a broad base and experienced difficulty in turning.

COMMENT:- Although the Wassermann reaction of the cerebro-spinal fluid remained positive throughout, the cell count fell from 44 to 6 and there was a definite modification in the colloidal gold reaction, a strong paretic changing to a luetic curve. It is also notable that this case presented a moderately dilated Argyll Robertson pupil. In one case in this research the presence of a unilateral loss of the light reflex has been observed.

A CASE OF TABES DORSALIS SHOWING THE SO-CALLED 'PROVOCATIVE' ACTION OF SALVARSAN.

Case 79. A.R. admitted 14/5/20, complaining of girdle sensation, lightning pains and symptoms suggestive of gastric crises: onset 5 years previously. History of venereal infection.

CENTRAL NERVOUS SYSTEM:- Knee jerks absent, anaesthesia of legs. Myosis. Argyll Robertson pupils, Rombergism. Wassermann reaction of blood negative.

CEREBRO-SPINAL FLUID 26/5/20. Fluid clear. Cell count 113, per c.m.m. Ross Jones and Nonne Apelt tests positive. Alcohol test positive. Wassermann Reaction negative. Colloidal gold reaction:- 1 1 2 2 1 1 0 0 0 0 0.

A provocative dose of 0.3 gm. Novarsenobillon was given 30/6/20. The Wassermann reaction of the blood was examined 13/7/20 and found to be weakly positive.

TREATMENT:- 10/8/20 to 30/8/20 four injections Novarsenobillon (0.45 gm., 0.6 gm., 0.75 gm., 0.75 gm.)
Cerebro-spinal fluid 29/9/20. Clear. Cell count 23. Alcohol test +. Ross Jones and Nonne Apelt tests +.
Wassermann reaction C.S.F. negative.
" " blood positive.
Colloidal gold reaction 0 0 0 0 0 0 0 0 0 0 0.
Further/

FURTHER TREATMENT:- 4/10/20 to 4/2/21. Ten injections 0.45 gm. Novarsenobillon and two injections intramine.

CEREBRO-SPINAL FLUID:- Fluid clear. Cell count 4.
Colloidal gold reaction:- 0 0 0 0 0 00 0 0 0 0 0
Wassermann reaction C.S.F. negative.
" " blood suspicious.

Clinical improvement was only slight.

COMMENT:- This case contains several points of interest. In the first place the clinical picture was typical of Tabes dorsalis. There was a history of untreated venereal infec-:tion and yet the Wassermann reaction was negative in blood and cerebro-spinal fluid. In the second place the cerebro-spinal fluid showed a marked pleocytosis, excess of protein and a luetic reaction to colloidal gold. Thirdly a provocative dose of 0.3 gm. Novarsenobillon produced a 'weakly positive' reaction in the blood which finally became 'positive'. Fourthly the cerebro-spinal fluid picture of a pleocytosis and luetic colloidal gold curve was rapidly modified by treatment with neosalvarsan and intramine.

A CASE OF CENTRAL SYPHILIS IN WHICH NEO-SALVARSAN TREATMENT COMBINED WITH INTRAMINE PRODUCED A NEGATIVE WASSERMANN REACTION IN THE CEREBRO-SPINAL FLUID.

Case 70. J.G. Admitted 17/5/20. Aet 31. Contracted specific infection 1906. Was treated with mercury for 6 months. In 1919 had 4 injections 606.

ON ADMISSION:- Central nervous system:- K.J. + +. No ankle or patellar clonus. Plantar reflexes flexor. No nystagmus. Left eye complete third nerve paralysis. Also paralysis of external rectus of right eye. Marked Stellwag's sign right eye. No sensory phenomena detected.

CEREBRO-SPINAL FLUID:- 17/5/20. Clear, pressure normal. Cell count 42. Small and large lymphocytes. Alcohol +. Other protein tests negative.

WASSERMANN REACTION C.S.F. positive.
" " blood suspicious.
Colloidal gold reaction:- 1 1 2 2 2 1 1 0 0 0 0 0.

Treatment:-	24/5/20.	0.45 gm.	Novarsenobillon.
	31/5/20.	0.45 "	"
	7/6/20.	0.75 "	"
	14/6/20.	0.75 "	"
	22/6/20.	0.75 "	"
	29/6/20.	0.75 "	"

TREATMENT (Contd.) 5/7/20. 0.75 gm. Novarsenobillon.
12/7/20. 0.75 " "
26/7/20. 0.75 " "
16/8/20. 0.75 " "
22/8/20. 0.75 " "
30/8/20. 0.75 " "

LUMBAR PUNCTURES- 29/9/20. Cerebro-spinal fluid clear, pressure normal. Cell count 7. Protein tests as before. Wassermann reaction C.S.F. positive.

TREATMENT:- (Continued)
4/10/20. 0.45 gm. Novarsenobillon.
18/10/20. 0.45 " "
25/10/20. 0.45 " "
1/11/20. 0.45 " "

LUMBAR PUNCTURE 30/10/20. Cerebro-spinal fluid clear. Pressure normal. Cell count 2. Protein test as before. Wassermann reaction of C.S.F. positive.
Colloidal gold reaction:- 0 1 1 1 0 0 0 0 0 0 0

TREATMENT:- (Continued).
8/11/20. Intramine 5 c.c. intramuscularly.
15/11/20. Intramine 5 c.c. "
17/11/20. 0.75 gm. Novarsenobillon.
29/11/20. 0.45 gm. Novarsenobillon.

LUMBAR PUNCTURE 5/12/20. Fluid clear. Cell count 3. Protein test as before.
Wassermann reaction C.S.F. Negative.
" " blood suspicious.
Colloidal gold reaction 0 0 1 1 0 0 0 0 0 0 0.

CLINICAL RESULT:- There was distinct clinical improvement under treatment. The ptosis of left eye and paralysis of right external rectus cleared up, the patient no longer complained of double vision, the muscular power of the legs increased and the gastric crises subsided.

COMMENT:- In this case intramine would appear materially to have influenced the Wassermann reaction of the cerebro-spinal fluid, although the result may be attributable to a cumulative effect. It has already been observed that intramine appears to intensify the action of Salvarsan in disseminated sclerosis. It is also notable that in this case the Wassermann reaction became negative in the cerebro-spinal fluid whereas the reaction in the blood remained suspicious. Finally, attention is drawn to/

to the fact that whereas under treatment the cell count had fallen from 42 per c.m.m. to 3 per c.m.m. and the Wassermann reaction had changed from Positive to Negative, the colloidal gold reaction was still weakly positive.

A CASE OF CENTRAL SYPHILIS WITH A POSITIVE WASSERMANN REACTION IN THE BLOOD AND A TYPICAL CEREBRO-SPINAL FLUID PICTURE, IN WHICH 26 INJECTIONS OF NOVARSENOBILLON AND TWO INJECTIONS OF INTRAMINE FAILED TO PRODUCE A NEGATIVE WASSERMANN REACTION IN EITHER BLOOD OR SPINAL FLUID.

Case No.61. D.P. aet 43. Admitted 26/4/20. Complaining of inability to stand and numbness of legs. He states that his symptoms commenced 18 months ago and followed on a fall from his cycle. He denied specific infection but his wife has a history of two miscarriages and 2 still-born children.

CENTRAL NERVOUS SYSTEM:- Wasting and weakness of both legs. Knee jerks absent. No plantar reflex elicited. Sensation in legs defective. Pupils react to accommodation but not to light. Paresis of right internal rectus and history of diplopia. Hands show wasting of thenar and hypothenar eminences. Wassermann reaction of blood positive.

CEREBRO-SPINAL FLUID 28/4/20. Fluid clear. Pressure +. Cell count 46. Ross Jones test + +. Nonne Apelt 1 & 2 + +. Alcohol + +. Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 5 5 5 4 3 2 1 1 0 0 0.

TREATMENT:- 15/5/20 to 12/7/20 nine injections 0.75 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID 20/7/20. Fluid clear. Pressure +. Protein tests all positive. Cell count 50.
Wassermann reaction C.S.F. positive.
" " blood positive.
Colloidal gold reaction:- 1 1 3 2 3 2 2 1 0 0 0

FURTHER TREATMENT:- 19/7/20 to 11/10/20, nine injections 0.75 gm. Novarsenobillon.

LUMBAR PUNCTURE 7/11/20. Fluid clear. Protein tests negative.
Colloidal gold reaction:- 2 3 3 3 2 1 0 0 0 0 0.
Wassermann reaction C.S.F. positive.
" " blood suspicious.

FURTHER TREATMENT:- 8/11/20 to 25/1/21 seven injections 0.45 gm. Novarsenobillon and two injections of intramine.

LUMBAR/

LUMBAR PUNCTURE 28/1/21. Fluid clear. Pressure +. Cell count 5.
Wassermann reaction C.S.F. Positive.
" " blood Weak positive.
Colloidal gold reaction:- 1 2 2 2 1 0 0 0 0 0 0.

CLINICAL RESULT:- Practically no clinical improvement was noted in this case.

COMMENT:- Treatment of this case must be regarded as a failure. The Wassermann reaction remained positive throughout in blood and spinal fluid. On the other hand the cell count fell from 46 to 5, the excess of protein disappeared and the colloidal gold readings gave the following contrast:-

Before treatment:- 5 5 5 4 3 2 1 1 0 0 0
After treatment:- 1 2 2 2 1 0 0 0 0 0 0

The failure in this case is not surprising owing to the clinical evidence of extensive damage to the nervous system: clinically and serologically it is a more marked failure than any of the cases of disseminated sclerosis that have been subjected to intensive treatment and it is a good example of the need for early diagnosis of neuro-syphilis, if cure is to be hoped for.

A CASE OF GENERAL PARALYSIS OF THE INSANE IN WHICH SALVARSAN TREATMENT WAS FOLLOWED BY NO CLINICAL OR SEROLOGICAL INPROVEMENT:-

Case No.24. M.G. Admitted 24/3/20 complaining of loss of weight, generalized pains and constant and severe headache. On admission his mental condition was defective. Speech was stammering. Pupils contracted and reacted to accommodation but not to light. Marked tremors of face muscles and tongue. Gait slightly ataxic. Leg muscles flabby and poor in tone. Knee jerks + +. No clonus elicited. Plantar reflexes sluggish but flexor. Incontinence of urine of 2 years' duration.

CEREBRO-SPINAL FLUID PICTURE:- Fluid clear. Pressure +.
Cell count 160 per c.m.m. Small and large lymphocytes.
Ross Jones and Nonne Apelt tests negative. Alcohol test positive.
Wassermann reaction of C.S.F. positive.
Colloidal gold reaction:- 5 5 5 5 5 4 2 1 0 0 0.
Wassermann reaction blood positive.
Dark ground illumination:- Spirochaeta pallida actively motile detected.

TREATMENT:- 5 injections 0.45 gm. Novarsenobillon.
Lumbar puncture 10/11/20.
Cerebro-spinal fluid clear.
Pressure normal. Cell count 21.
Wassermann/

Wassermann Reaction C.S.F. positive.
Colloidal gold reaction:- 5 5 5 5 4 4 4 4 0 0 0.

FURTHER TREATMENT:- Four injections 0.45 gm. Novarsenobillon.
Lumbar puncture 6/12/20. Fluid clear. Pressure +.
Cell count 40..
Wassermann reaction C.S.F. positive.
" " blood positive.
Colloidal Gold reaction:- 5 5 5 5 4 4 4 4 0 0 0.

CLINICAL RESULT:- No improvement whatever was noted.

COMMENT:- This case is of interest in that spirochaeta pallida was detected in the cerebro-spinal fluid. It is also worthy of note that, in spite of the otherwise strongly specific picture, the protein tests gave a negative reaction. It will be observed that beyond a fall in the cell count, the administra-:tion of Necsalvarsan did not produce any modification of the serological picture.

A CASE OF SYPHILITIC MYELITIS SHOWING A TYPICAL CEREBRO-SPINAL FLUID PICTURE AND THE MODIFICATIONS RESULTING FROM NEO-SALVARSAN ADMINISTRATION.

Case No.80. A.K. Aet 47. Admitted to Hospital 30/12/19 com-:plaining of loss of power in legs of 11 weeks' duration.

CONDITION ON ADMISSION:- Patient unable to stand on account of weakness of legs. Legs spastic. REFLEXES:- Knee jerks + +. Plantar reflex extensor right, flexor left. Patellar and ankle clonus both legs. Sensation much impaired in legs. Abdominal reflexes absent.
ORGANIC REFLEXES:- Incontinence of urine and faeces.
EYES:- Pupils unequal, right reacts to light: left smaller and fixed. Fundi O/E Right shows detachment of retina, left less opaque and light reflected back from it.

CEREBRO-SPINAL FLUID:- (after 8 injections Novarsenobillon, lumbar puncture being previously refused) 26/5/20. Clear, Pressure + +. Cell count 27 per cm.m. small and large lymphocytes. Ross Jones and Nonne Apelt tests negative.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction " 5 5 5 5 5 2 2 1 0 0 0.
Wassermann reaction blood positive.

FURTHER TREATMENT:- Four injections 0.75 gm. Novarsenobillon.
Lumbar puncture 19/7/20.
Colloidal gold reaction:- 1 4 2 2 2 2 1 0 0 0 0.
FURTHER/

FURTHER TREATMENT:- 9/8/20 - 30/8/20. Four injections 0.75 gm.Novarsenobillon. Lumbar puncture 19/9/20.
Cerebro-spinal fluid:- Clear. Pressure + +. Cell count 21. per c.m.m. Ross Jones and Nonne Apelt tests positive.
Wassermann reaction C.S.F. positive.
" " blood suspicious.
Colloidal gold reaction:- 3 3 2 2 1 1 0 0 0 0 0.

FURTHER TREATMENT:- 27/9/20 - 27/11/20. Seven injections 0.45 gm. Novarsenobillon and two injections of intramine.
Lumbar puncture 5/12/20. Fluid clear. Pressure +. Cell count 30.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction " 2 2 2 2 1 1 0 0 0 0 0.

FURTHER TREATMENT:- 21/12/20 - 17/1/21, four injections 0.45 gm. Novarsenobillon.
Lumbar puncture 21/12/21. Fluid clear. Pressure -. Cell count 11. Large and small lymphocytes.
Wassermann reaction C.S.F. Positive.
Colloidal gold reaction " 1 2 2 1 0 0 0 0 0 0 0
Wassermann reaction blood negative.

CLINICAL RESULT:- There was some improvement in the general condition with regain of bowel control. Some flattening out of retinal detachment with improvement in visual acuity was noted.

COMMENT:- This case shows clearly the modifications of the colloidal gold reaction that occur in cases of nervous syphilis under Salvarsan treatment, viz:-

Before treatment:- 5 5 5 5 5 2 2 1 0 0 0
After treatment:- 1 2 2 1 0 0 0 0 0 0 0

A CASE OF SYPHILITIC SPINAL SCLEROSIS ORIGINATING IN A PATIENT 19 YEARS OF AGE.

Case No.122. R.McC. Aet 22. Admitted 3/3/20 complaining of inability to walk and incontinence of urine and faeces. These symptoms first commenced in August 1917. In 1914 when he was 16 years of age he was treated in the Glasgow Royal Infirmary for acquired syphilis. The clinical picture on admission was spastic paraplegia with incontinence of urine and faeces. No abnormality was detected in the sensory neurone and the nervous system appeared to be otherwise normal, i.e. the case presented the signs of primary lateral sclerosis and had it not been for the history of specific infection the case might reasonably, in view of his age, have been regarded as early disseminated sclerosis.

CEREBRO/

CEREBRO-SPINAL FLUID:- 21/9/20. Clear, Pressure + +.
Cell count 8. Ross Jones, Nonne Apelt and Alcohol tests all positive.
Wassermann reaction of C.S.F. positive.
Colloidal gold reaction of C.S.F.:- 0 1 2 2 1 0 0 0 0 0 0.
Wassermann reaction of blood positive.

TREATMENT:- Thirteen injections of Novarsenobillon (0.45 gm.) and injection of intra line.
Lumbar puncture 14/1/21.:- C.S.F. Clear. Pressure + +.
Cell count 18.
Wassermann reaction C.S.F. suspicious.
" " blood positive.
Colloidal gold reaction:- 1 1 0 0 0 0 0 0 0 0 0.

CLINICAL RESULT:- There was slight improvement in muscular power of legs and regain of bladder control.

COMMENT:- The chief sign of improvement as the result of treatment in this case was shown in the alteration of the serological reactions of the cerebro-spinal fluid. In addition it may be hoped that, although the clinical improvement was not marked, the treatment may arrest or modify the further progress of the syphilitic invasion of the nervous system. This view in fact would appear to be the chief rationale for intensive treatment of such cases as clinical results are almost invariably disappointing. In addition this case is of interest as regards the extremely early age of the patient, spinal sclerosis at 19 being rarely syphilitic.

A CASE OF EARLY GENERAL PARALYSIS OF THE INSANE TREATED WITH SALVARSAN WITH CLINICAL AND SEROLOGICAL IMPROVEMENT:-

Case No.150. J.B. Aet 42. This man was a regular soldier and served in India, South Africa and Salonika. He was sent in to Hospital as a case of general paralysis. The pupils were unequal, the right larger than the left; both reacted sluggishly to light. There was no nystagmus, the organic reflexes were unimpaired and the abdominal reflexes active. His speech was somewhat slow and there was paresis of the left facial nerve. The knee jerks were normal. Over the front of both legs there were many deeply pigmented scars stated by the patient to be due to old velat sores contracted in S.Africa. The diagnosis of general paralysis was based on his mental condi-:tion, the presence of well-marked tremors and the sluggish pupillary reaction to light.

CEREBRO/

CEREBRO-SPINAL FLUID, 14/10/20.:- Fluid clear. Pressure diminished. Cell count 16. Ross Jones, Nonne Apelt and alcohol tests all positive.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction " 5 5 5 5 3 3 3 0 0 0 0 (paretic reaction).
Wassermann reaction of blood positive.

TREATMENT:- 12 intravenous injections of 0.45 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID SUBSEQUENT TO TREATMENT:- Fluid clear.
Cell count 8.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction 1 1 2 3 3 2 1 0 0 0 0 (luetic reaction)
Wassermann reaction of blood 'suspicious'.

CLINICAL RESULT:- There was distinct clinical improvement noted, chiefly in respect of his mental condition and tremors.

COMMENT:- If the clinical diagnosis in this case was correct (and it is supported by the cerebro-spinal fluid picture) it is surprising that the abdominal reflexes were active. The serological improvement is shown by the fact that the Wassermann reaction of the blood changed from 'positive' to 'suspicious' and the colloidal gold reaction changed from a paretic to a luetic curve, these changes being accompanied by a fall in the cell count. The clinical improvement under treatment in this case compares favourably with the case described on page 81 and is presumably due to the recognition of the disease in a relatively early stage.

A CASE OF TABES DORSALIS IN WHICH THE COLLOIDAL GOLD REACTION WAS PARETIC WITHOUT ANY MARKED INCREASE IN THE PROTEIN CONTENT OF THE CEREBRO-SPINAL FLUID:-

Case No.163. H.S. Admitted 30/10/20. History of onset:- Patient was admitted to a medical ward in Shakespeare Hospital 18/10/18 complaining of pain in the stomach and vomiting. He was transferred to a surgical ward 13/3/19 and gastro enterostomy was performed 29/4/19. He was discharged to a convalescent home 20/5/19 and was readmitted 11/7/19 with the same complaint. He was treated as a case of gastritis and discharged 20/11/19. He was subsequently admitted to Ward X. Bellahouston Hospital 4/6/20 labelled 'abdominal adhesions' and was thence transferred to Ward XVI. On admission he gave a typical history of gastric crises recurring at 3-weekly intervals and usually lasting for about 4 days. The pupils were equal, moderately contracted, reacted to accommodation but not to light. The knee jerks were absent, the plantar reflexes flexor, and the abdominal reflexes active. No impairment of tactile sensation was detected in the legs but marked hypotonus of hip joints was noted.
CEREBRO/

CEREBRO-SPINAL FLUID:- Clear. Pressure +. Cell count 7.
Ross Jones and Nonne Apelt tests negative.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 5 5 5 3 3 2 0 0 0 0 0.

COMMENT:- The history of onset in this case is quoted in full as it illustrates the fact that the gastric derangement of early tabes is frequently overlooked even in hospital practice. The cerebro-spinal fluid picture is also of interest as it will be noted that the cell count and protein content are normal and yet the colloidal gold reaction is paretic and the Wassermann reaction positive.

A CASE OF ? TABES IN WHICH THERE WAS GREAT EXCESS OF PROTEIN IN THE CEREBRO-SPINAL FLUID AND YET IN WHICH THE COLLOIDAL GOLD REACTION WAS LUETIC.

Case No.106. C.C. Admitted 8/6/20 complaining of incontinence of urine, giddiness and headaches. Onset of symptoms dated 5 years ago. On admission there was sluggishness of the knee jerks, marked Rombergism and some anaesthesia of the legs. The pupils reacted both to light and to accommodation. Wassermann reaction of blood positive.

CEREBRO-SPINAL FLUID:- 24/6/20. Fluid clear, pressure normal. Cell count 80 per c.m.m. Small lymphocytes.
Alcohol test + + +. Ross Jones test + + +.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 1 2 2 3 2 2 1 0 0 0 0(luetic reaction)

A CASE OF TABES DORSALIS IN WHICH SPIROCHAETA PALLIDA WAS DETECTED BY DARK GROUND ILLUMINATION OF THE CEREBRO-SPINAL FLUID:-

Case No.29. A.C. Aet 49. Admitted 26/3/20 complaining of stabbing pains in legs, failing eyesight and a sense of constriction round the waist. Pupils extremely contracted. Knee jerks sluggish, abdominal reflexes absent, anaesthesia of legs, slight Rombergism, Fundi O/E both discs grey, vessels congested, temporal margin of right disc indistinct. Wassermann reaction of blood positive.

CEREBRO-SPINAL FLUID:- 26/3/20. Fluid clear. Pressure normal. Cell count 80 per c.m.m. Ross Jones test negative. Nonne Apelt test Phase I negative, phase II positive. Alcohol test positive. Dark ground illumination - spirochaetae pallidaedetected.

Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 1 1 2 2 2 2 2 0 0 0 0(luetic reaction)

THE FOLLOWING CASE IS OF INTEREST IN THAT TABES DORSALIS AND AORTIC REGURGITATION CO-EXIST, AND THE SEROLOGICAL REACTIONS ARE TYPICAL.

Case No.189. D.F. Aet 57. Admitted 24/12/20 complaining of shooting pains in legs and paroxysmal attacks of pain in stomach. He also complains of difficulty in walking especially at night and of accasional attacks of diplopia. History of venereal infection in 1886.

On admission: Extreme myosis. No reaction to light. No external ocular palsy. Knee jerks normal (!), plantar reflexes strongly flexor. Abdominal reflexes present, epigastric reflex very active. Slight anaesthesia detected on outer side of right leg below the knee. No Rombergism. Organic reflexes:- complete loss of bladder control with occasional incontinence of bowels. Heart hypertrophied with systolic and diastolic aortic murmur and pulse of water-hammer type.
Wassermann reaction of blood positive.

CEREBRO-SPINAL FLUID:- Clear. Pressure diminished. Cell count 70 per c.m.m. (large and small lymphocytes).
Ross Jones test negative.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction 1 1 2 2 2 1 1 0 0 0 0 (luetic reaction).

COMMENT:- This case is of interest in that the knee jerks are normal and the abdominal reflexes present. The co-existence of tabes and aortic regurgitation is of relatively infrequent occurrence. Ormerod(47) regards the majority of such cases as a pure coincidence while admitting that occasionally the aortic disease and spinal sclerosis may have a common cause in syphilitic infection. The spirochaeta pallida would certainly appear to have a selective action on the cerebral nervous system and the aorta, the gastro-intestinal, respiratory and urinary systems being either relatively immune or syphilitic lesions occurring in them being possibly not yet recognized. One cannot but be impressed by the fact that whereas in one syphilitic patient the whole brunt of the attack appears to fall on the nervous system, in another the aorta alone is involved, there being no obvious clinical manifestations of neurosyphilis. Whether or not, as has been suggested, one type of spirochaete is neurotrophic and another type dermotrophic is not yet clear but it would be of use in this connection to investigate the cerebro-spinal fluid picture in cases of syphilitic aortic incompetence. The work of Fildes, Parnell and Maitland (48) would appear to indicate that the central nervous system is involved in a larger percentage of cases of early syphilitic infection/

infection than is generally supposed. In a series of 1314 men infected with syphilis and examined in the early stages of the disease 18% showed pathological changes in the cerebro-spinal fluid with no obvious sign of nervous disease. They recommend lumbar puncture and examination of the cerebro-spinal fluid in all cases of syphilitic infection. The work of Schou[49] supports the observations of Fildes, Parnell and Maitland. He publishes the results of the examination of the cerebro-spinal fluid in 300 cases of syphilis of less than 3 years' standing. In 491 cases of recent untreated syphilis morbid changes in the cerebro-spinal fluid were found in the following proportions:- In twelve per cent. of 56 cases of primary syphilis in which Wassermann reaction of the blood was positive: in twelve per cent. of 75 cases of primary syphilis with a negative Wassermann reaction in the blood: in twenty-three per cent. of 300 cases of secondary syphilis: in thirty-nine per cent. of 41 cases of syphilis of six to twelve months' duration, and in twenty-seven per cent. of 15 cases of syphilis of one to two years' duration.

It is of interest to note that the number of cells in Schou's series was usually within the limits of 10 to 50 per c.m.m. - a figure that corresponded closely with the results obtained in the course of the present investigation. Schou gives one reading as high as 2,500 cells and states that the figures for the protein content showed wide variation which he attributes to faulty technique. The opinion has already been expressed that the present methods of examining the protein content of the cerebro-spinal fluid are unreliable.

Observations on the cerebro-spinal fluid in still earlier cases of syphilitic infection are recorded by Wile and Hasley.[50] Deviations from the normal in the spinal fluid of 221 cases of syphilis in which only the chancre was present were found in 49 cases or 22%. Increase of globulin and albumin virtually parallel was the most constant of the abnormal findings, occurring in 25 of the 49 cases. Pleocytosis was the next most frequent finding, occurring in 12 cases. The positive Wassermann test in the fluid occurred less frequently then the other two findings, being present in but 8 cases. Of the entire number of cases examined symptoms indicating central nervous involvement were present in only a single case. The colloidal gold reaction was examined in only 3 cases, and in these the curves were identical. Similar observations have been recorded by Wechselman.[51]

A/

A CASE OF CENTRAL SYPHILIS WITH TYPICAL SEROLOGICAL REACTIONS.

Case No.4. R.H. Admitted 24/12/19. Complaining of weakness of legs and incontinence of urine and faeces of 2 years' duration.

Condition on admission:- Legs markedly spastic. Knee jerks + +. Tendo achillis jerk + +. Plantar reflexes strongly extensor. Marked ankle and patellar clonus. Triceps, supinator and wrist jerks + +. Organic reflexes:- Bowel-constipation alternating with diarrhoea. Incontinence of urine. Superficial tactile and pain sensation absent in legs and deficient over abdomen. Pupils unequal, do not react to light: react to accommodation. No external ocular palsy. Fundi O/E L.disc central area of pallor, veins engorged. R.disc margins blurred, marked engorgement of vessels. Wassermann reaction of blood positive.

CEREBRO-SPINAL FLUID:- Fluid clear. Pressure +. Cell count 32 per c.m.m. Small lymphocytes. Ross Jones, Alcohol and Nonne Apelt tests all positive. Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 2 2 4 4 2 2 1 0 0 0 0.

TREATMENT:- 6/3/20 to 20/5/20 patient received 10 injections 0.75 gm. Novarsenobillion.

CLINICAL RESULT:- Very definite clinical improvement was noted. The legs became much less spastic, the motor power was improved and bladder control was regained. Patient was discharged for a disciplinary offence and the opportunity for subsequent examination of the cerebro-spinal fluid and blood was consequently lost. On discharge he could walk with one stick with a slightly spastic gait.

THE FOLLOWING IS AN EXAMPLE OF THE FACT THAT CASES ARE ENCOUNTERED WHICH IT IS DIFFICULT TO DIAGNOSE EVEN WHEN IN POSSESSION OF THE SEROLOGICAL REACTIONS IN ADDITION TO THE CLINICAL PICTURE:-

Case 185. W.S. Admitted 8/12/20 complaining of difficulty in walking in the dark and a slightly staggering gait. History of excess of alcohol. Knee jerks +. Plantar reflexes flexor. No impairment of sensation in legs. No definite Rombergism. Gait slightly ataxic and distinct difficulty experienced in turning. Pupils equal and react directly and consensually to light. No external ocular palsy or history of diplopia. Wassermann reaction of blood positive.

CEREBRO/

CEREBRO-SPINAL FLUID:- Cell count 7 per c.m.m.
Protein tests negative.
Wassermann reaction negative.
Colloidal gold reaction 0 0 0 0 0 0 0 0 0 0 0 (negative).

COMMENT:- This case is presumably either early tabes or early polyneuritis. There is at present no evidence of central nervous infection in the cerebro-spinal fluid.

THE FOLLOWING CASE ALSO PRESENTS DIFFICULTY IN DIAGNOSIS:-

Case 183. M.E. sent in to hospital for a report on the cerebro-spinal fluid. On 23/9/19 a report from the 3rd London General Hospital stated 'He has the optic form of tabes dorsalis: there is optic atrophy, capsular cataracts, contraction of visual fields and absence of knee, tendo achillis and wrist jerks'. A diagnosis of optic tabes was made by Col.Mott. The man was subsequently examined for the Ministry of Pensions 16/11/20 when his sole complaint was headache. Pupils reacted to light though somewhat sluggishly. Optic atrophy was noted but no contraction of the visual fields detected. There was no evidence of ataxia. In addition knee jerks and tendo achillis jerks absent. The urine contained a trace of albumen, granular and hyaline casts and defective urea concentration.
Wassermann reaction of blood negative.

CEREBRO-SPINAL FLUID:- 6/12/20. Fluid clear. Pressure + +.+. (stream). Cell count 35 per c.m.m. Protein tests negative.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction:- 0 0 1 2 2 2 1 0 0 0 0 (luetic reaction)

COMMENT:- From the clinical point of view primary optic atrophy combined with loss of the deep reflexes of the legs might possibly justify a diagnosis of tabes. It is noteworthy that whereas the Wassermann reaction is negative in blood and cerebro-spinal fluid and the protein content is not above normal, yet there is a well-marked pleocytosis and a luetic reaction to colloidal gold. Possibly this is a case of tabes that had undergone spontaneous arrest in the early stages - the syphilitic infection having 'burned itself out'.

EVEN MORE DIFFICULT OF DEFINITE DIAGNOSIS IS THE FOLLOWING CASE:-

Case 159. W.O'M. Admitted 27/10/20. Complaining of weakness in the legs and occasional attacks of double vision. States he has great difficulty in walking in the dark. Denies venereal infection: states his wife has had two miscarriages. Pupils contracted/

contracted: sluggish reaction to light. Abdominal reflexes;- L.present, R. absent. Epigastric reflexes present.
Knee jerks:- + +. Plantar reflexes flexor. Hypotonus of knee joints.
Wassermann reaction of blood negative.
Cerebro-spinal fluid 27/10/20. Fluid clear. Pressure +.
Cell count 3. All protein tests negative.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction " negative.

TREATMENT:- Provocative dose 0.45 gm. Novarsenobillon.

CEREBRO-SPINAL FLUID:- 17/11/20. Fluid clear. Cell count 15. large and small lymphocytes.
Protein tests negative.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction negative.

COMMENT:- The history of diplopia, difficulty in walking in the dark, sluggish pupillary reaction to light and hypotonus of the knee joints certainly suggest tabes and it will be noted that his wife gives a history of miscarriages. Yet on the other hand, the serological results are entirely negative and the only effect noted from the administration of a provocative dose of Novarsenobillon was an increase in the cell count and the appearance of large and small lymphocytes in the cerebro-spinal fluid.

IN THE FOLLOWING CASE THE PREDOMINANT CLINICAL FEATURE WAS CONSTANTLY RECURRING GASTRIC CRISES FOR WHICH HE HAD HAD THE OPERATIONS OF APPENDICECTOMY AND GASTRO-JEJUNOSTOMY PERFORMED, (THE CONDITION PRESUMABLY NOT HAVING BEEN RECOGNISED AS SYPHILITIC), WITHOUT ANY CLINICAL IMPROVEMENT:-

Case 125. R.S. Admitted 24/7/20.

CLINICAL RESUMÉ:- Lightning pains, girdle sensation, sluggish pupillary reaction to light. Knee jerks absent. Sensation in legs defective. Frequently recurring attacks of typical gastric crises. Wassermann reaction of blood positive.

CEREBRO-SPINAL FLUID:- Clear. Pressure normal. Cell count 87 per c.m.m. All protein tests negative.
Colloidal gold reaction:- 2 3 2 2 2 2 1 0 0 0 0.
Wassermann reaction C.S.F. positive.

TREATMENT:- 10 injections 0.75 gm. Novarsenobillon.

No/

No clinical serological improvement was obtained. The Wassermann reaction remained positive in blood and cerebro-spinal fluid and the last colloidal gold reading was a stronger reaction than the first, viz:- 2 3 3 4 4 4 0 0 0 0 0. There was little, if any, clinical improvement.

THE FOLLOWING CASE OF WHAT WAS PRESUMABLY MENINGO-VASCULAR SYPHILIS IS OF INTEREST, IN THAT THE SEROLOGICAL REACTIONS WERE NEGATIVE 4 YEARS AFTER TREATMENT HAD CEASED:-

Case No.25. R.McC. Aet 37. Admitted 24/3/20. Contracted syphilis in 1913 and subsequently suffered from hemiplegia of gradual onset in Dec., 1915. In 1913 he was treated with mercury and in 1915 he received salvarsan treatment but does not remember how many injections were given. On admission the tendon reflexes of the left arm and leg were all definitely increased. In addition the left leg was slightly spastic with ankle clonus and the plantar reflex was extensor. Wassermann reaction of blood negative.

CEREBRO-SPINAL FLUID:- Clear. Pressure normal.
Cell count 4 per c.m.m. Ross Jones Test negative.
Nonne Apelt phase I and phase II negative. Alcohol faint haze.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction C.S.F. negative.

COMMENT:- This case is an example of the fact that meningo-vascular syphilis yields rapidly to neo-salvarsan treatment and is another example of the need for the early diagnosis and energetic specific treatment of neurosyphilis.

A CASE OF EARLY TABES WITH A POSITIVE WASSERMANN REACTION IN THE BLOOD, AND IN WHICH THE CEREBRO-SPINAL FLUID PICTURE COMPRISED PLEOCYTOSIS, EXCESS OF PROTEIN, A LUETIC REACTION TO COLLOIDAL GOLD AND A POSITIVE WASSERMANN REACTION:-

Case No.49. C.McC. Admitted 10/4/20 complaining of attacks of abdominal pain for which he had had a laparotomy performed in 1916. The history was suggestive of gastric crises. The only abnormal clinical signs detected were myosis, a slightly sluggish pupillary reaction to light and very slight diminution in the knee jerks.

CEREBRO-SPINAL FLUID 10/4/20. Cell count 197 per c.m.m.
Alcohol, Ross Jones and Nonne Apelt tests all definitely positive.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction C.S.F.:- 2 3 3 3 2 2 2 0 0 0 0:
Wassermann reaction blood positive.

TREATMENT/

TREATMENT:- 10 injections 0.75 gm. Novarsenobillon.
Cerebro-spinal fluid 29/10/20:-
Colloidal gold reaction 1 2 2 2 2 1 0 0 0 0 0.
Wassermann reaction C.S.F. positive.

RESULT:- Little, if any, clinical improvement was noted.

COMMENT:- This case is quoted to draw attention in the first place to the fact that a laparatomy was performed for a gastric crisis. Five cases giving a similar history have been encountered in a series of 41 cases of neurosyphilis. In the second place, it will be observed that although the clinical signs are not strongly marked, the cerebro-spinal fluid gave all the signs of syphilitic infection.

A CASE OF CROSSED HEMIPLEGIA WITH A TYPICAL CEREBRO-SPINAL FLUID PICTURE:-

Case No.175. K.W. Admitted 20/11/20 complaining of loss of power of right arm and leg which developed gradually in 1916. At the time of onset of these symptoms he noticed slight difficulty in speaking but this has since improved. There is no history of any injury.

CENTRAL NERVOUS SYSTEM:- Pupils equal and react actively. Knee jerks:- left normal: right exaggerated. Slight loss of power of right leg. Plantar reflexes left flexor, right doubtful. Tongue deviates to left. There is loss of left labionasal fold and very slight paresis of left side of face. Some loss of power right arm and hand: reflexes exaggerated.

CEREBRO-SPINAL FLUID:- Clear. Pressure +. Cell count 30. Ross Jones, Nonne Apelt Phase I and II, Alcohol tests all strongly +.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction 3 4 4 4 4 1 0 0 0 0 (very strong luetic reaction).
Wassermann reaction of blood positive.

COMMENT:- This case clinically is typical of specific thrombosis and this is supported by a cerebro-spinal fluid picture in which all the characteristic changes are present. Such cases of meningovascular syphilis are specially amenable to neo-salvarsan treatment.

A CASE OF ENDARTERITIS OBLITERANS SHOWING A TYPICAL CEREBRO-SPINAL FLUID PICTURE:-

Case No.44. W.S. Aet 32. Admitted 15/4/20.
In 1916 he suffered from paralysis of left arm, leg and face, accompanied/

accompanied by loss of speech. These symptoms gradually subsided. He now complains of headaches, attacks of faintness and general weakness. His wife has had 2 miscarriages and no living children.

CENTRAL NERVOUS SYSTEM:- Knee jerks + +. Plantar reflexes flexor. No ankle or patellar clonus. Abdominal reflexes active. No involvement of organic reflexes. No abnormality detected in sensory neurone.

Cerebro-spinal fluid picture:-
Fluid clear. Pressure diminished. Cell count 44 per c.m.m. Small lymphocytes. Ross Jones and Nonne Apelt tests positive. Alcohol test positive.
Wassermann reaction C.S.F. Weak positive.
Colloidal gold reaction " 1 2 2 2 2 1 1 0 0 0 0.

COMMENT:- This case shows little clinical evidence of active syphilitic disease of the central nervous system but the cerebro-spinal fluid shows all the typical specific changes.

A CASE OF TABES (?) WITH A POSITIVE WASSERMANN REACTION IN THE BLOOD AND IN WHICH THE CEREBRO-SPINAL FLUID PICTURE COMPRISED PLEOCYTOSIS, NORMAL PROTEIN CONTENT, A NEGATIVE WASSERMANN REACTION AND A STRONG LUETIC REACTION TO COLLOIDAL GOLD:-

A.R. Aet 26. No.149. Admitted 24/10/20. Complaining of weakness of legs.

CENTRAL NERVOUS SYSTEM:- Knee jerks absent: plantar reflexes flexor. Epigastric reflex active ~~xxxxx~~ on right, absent on left. Abdominal reflexes: active on left, absent on right (!) No external ocular palsy. No diplopia. No involvement of organic reflexes. No history of girdle sensation or lightning pains.

CEREBRO-SPINAL FLUID:- Clear. Pressure normal. Cell count 17. Large and small lymphocytes. Protein tests negative.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction C.S.F. 1 2 2 3 2 1 0 0 0 0 0 (luetic)
Wassermann reaction blood positive.

COMMENT:- The clinical diagnosis here is based on a sluggish pupillary reaction to light, absence of knee jerks and anaesthesia of legs. The Wassermann reaction is positive in the blood and negative in the spinal fluid but the presence of pleocytosis and a definitely luetic reaction to colloidal gold would appear to indicate that there is early syphilitic invasion of the central nervous system.

The value of anti-specific treatment of tabes, general paralysis of the insane, myelitis and hemiplegia is not generally admitted and indeed such treatment is rarely carried out even in hospital practice. The view that tabes and general paralysis are 'parasyphilitic' diseases is no longer tenable as it would appear that in many instances we are dealing with what is in reality an active spirochaetosis: the discovery of motile spirochaetae pallidae in the cerebro-spinal fluid in two cases of this series is in support of this view. It would seem that the present attitude towards the question of anti-specific treatment of such cases is based on the following arguments:-

(1) That such treatment is not unattended by risk.

(2) That clinical improvement is at best doubtful.

(3) That arsenic administered intravenously does not reach the cerebro-spinal fluid.

(4) That serological improvement is rarely obtained.

It would appear that the risk of neo-salvarsan administration is greatly over-estimated. In no case in this series has any untoward result been noted and the opinion has been formed that the administration of novarsenobillon is a perfectly safe proceeding in the absence of nephritis. The so-called Herxeheimer Jarisch phenomenon has never been encountered. Should serious symptoms arise, good results have/

have been obtained by some observers by intramuscular injection of intramine. Such cases would, however, appear to be extremely rare. As regards the doubtful clinical improvement following such specific treatment, it may well be argued that if these cases are neglected until irreparable damage has been done to highly specialized nervous tissues, no obvious improvement can be hoped for.

Evidence has already been brought forward (pp.47 & 48) of the recent work of various authorities, to support the statement that arsenic can be detected in the cerebro-spinal fluid of patients who have received intravenous injections of organic arsenical preparations, and the results obtained in the course of this investigation would appear to demonstrate conclusively that in practically every case treated some improvement of the cerebro-spinal picture has been produced. A marked fall in the cell count is an almost constant result, the excess of protein is usually removed, in many cases a negative Wassermann reaction may be obtained and occasionally a negative colloidal gold reaction is finally observed, though this would appear the last morbid sign to be removed. In view of these facts it may reasonably be argued that there is an urgent need for the earliest recognition and prompt treatment of neuro-syphilis, and such treatment should comprise the administration of mercury and iodide of potassium combined with a large series of injections of Novarsenobillon./

Novarsenobillon. This treatment would appear to be indicated even in relatively advanced cases in view of the progressive nature of these diseases, it being now admitted that tabes may go on to the development of paresis. The view here expressed accords generally with opinions put forward by Sicard, Milian, Tinel and Babinski at the Neurological Society of Paris (52) and an exactly similar opinion is advanced by Schröder (53). In neither of these papers is any reference made to the colloidal gold reaction. The modifications of the colloidal gold reaction shown in this paper still further support this view. Clinically it is well known that occasionally tabes undergoes apparent spontaneous arrest, a phenomenon presumably due to the fact that the syphilitic infection has 'burned itself out', and in this connection the importance of intercurrent acute infectious disease with its possible production of heterogenetic anti-bodies has been referred to. It would therefore appear that energetic antispecific treatment may supply the assistance which is needed to turn the scale and enable the patient to resist the further progress of the infection.

A comparison may now be drawn between the results obtained in anti-specific treatment of disseminated sclerosis on the one hand and neuro-syphilis on the other. As regards the clinical aspect of such a comparison, it would appear necessary to select approximately similar stages of the two diseases./

diseases. It is therefore of interest to contrast the results obtained in a late stage of disseminated sclerosis and a correspondingly established case of neurosyphilis. (Case 39,p.64: Case 61,p.80: Case 172,p.62: & Case 24,p.81.)

Generally, the opinion has definitely been formed that the clinical results obtained by treatment were at least as satisfactory in disseminated sclerosis as in neurosyphilis.

As regards the serological modifications observed in the treatment of the two diseases, a reference to the cerebrospinal fluid pictures on page 39 will demonstrate the fact that the colloidal gold reaction is the only basis of comparison as it is the only morbid serological change constantly common to the two diseases. The reader is specially referred to the rapid modification of the colloidal gold reaction obtained in case 30, page 64 , and this may be contrasted with the amount of treatment required to produce a similar modification in case 61, page 80.

No conclusion can be drawn as to the exact significance of these changes until more light is shed on the exact meaning of Lange's reaction, a subject on which our present knowledge is extremely imperfect and reference to which is made on p.118.

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(2)CASES OF FUNCTIONAL NERVOUS DISEASES.

Seventeen cases fell into this group and they included Neurasthenia, 'D.A.H.' syndrome, hysteria, delusional insanity, myokymia, and hystero-epilepsy. In all the Wassermann reaction was negative in the blood.

As regards the cerebro-spinal fluid, the average cell count was 5, the type of cell a small lymphocyte. In no case was an excess of protein detected and the Wassermann reaction of the cerebro-spinal fluid was negative throughout the group. As regards the colloidal gold reaction, 15 cases gave a negative result. In two cases in which the symptoms originated in a severe head injury the colloidal gold reaction was weakly luetic. There would therefore appear to be a fairly definite cerebro-spinal fluid picture in the so-called 'functional' nervous diseases, viz:- A normal cell count, a normal protein content, a negative Wassermann reaction and a negative colloidal gold reaction. It must, however, be observed that the cases comprised in this group were too few to enable definite conclusions to be drawn, but if similar results were obtained in a large series of cases it would appear to indicate that the colloidal gold reaction of the cerebro-spinal fluid is of considerable value in differentiating hysteria from early disseminated sclerosis, often a problem of considerable difficulty. Attention is also called to the

fact/

fact that in almost every case investigated in this group the abdominal reflex was active and in many cases greatly exaggerated. It has already been shown that in spinal disseminated sclerosis the loss of the abdominal reflex on one or both sides, is an almost constant phenomenon. Emphasis is therefore laid on these two points as they would seem to be of considerable assistance in enabling one to arrive at a diagnosis. It is also desired to repeat an opinion that has already been expressed that the border line between 'functional' and 'organic' disease is often almost indistinguishable, and to emphasize the fact that functional nervous disease should be diagnosed only when every possibility of co-existing organic disease has been excluded and even then the diagnosis should not be regarded as final but subject to constant review. Cases have repeatedly been encountered which presented well marked signs of neurasthenia but in which co-existing diseases such as early tabes, disseminated sclerosis, pulmonary tuberculosis, or nephritis had been overlooked, by re-survey boards under the Ministry of Pensions. The exclusion of any possible underlying organic basis is of great importance from the point of view of treatment of functional diseases. It is well known that Psychotherapy yields excellent results in the anxiety neuroses, and it would appear that this line of treatment

has/

has partially fallen into disrepute owing to its application to cases that are in reality quite unsuitable.

The case of myokymia included in this group is of no special interest and therefore is not recorded in detail. The condition is one of no pathological importance.(54) Cases of the so-called 'D.A.H.' syndrome have been encountered in large numbers but only one or two typical cases were investigated serologically as lumbar puncture appeared perhaps unjustifiable. The inclusion of such cases under the heading of functional nervous disease is perhaps open to question, as the work of Haldane(55) has shown that the condition is really one of anoxaemia produced by shallow breathing, resulting in the respiratory centre being starved of oxygen. In the course of work done for the Clinical Uses of Oxygen Committee of the Medical Research Council, I treated one case of 'D.A.H.' with marked tachycardia and tremor, that had refused to yield to other treatment, by 7 days' continuous administration of oxygen by means of a Haldane's portable oxygen apparatus. The remission of symptoms especially as regards tachycardia and tremors was marked, but the improvement was not sustained beyond a few days after treatment had ceased. Other observers have, however, obtained better results.

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(3) CASES OF CEREBRAL NEOPLASM:-

Six cases were examined in this group. All were negative to the Wassermann reaction. In two cases the colloidal gold reaction was negative, and in these cases the clinical diagnosis was confirmed by the post mortem findings, one being a carcinoma of the cerebellum, the other a carcinoma of the calloso-marginal gyrus. In the other four cases there was a weak luetic reaction to the colloidal gold test, but this reaction was much less definitely positive than in cases of disseminated sclerosis or syphilitic infection. One of the cases in this group is of considerable interest:-

Case No.162. A.M.G. Aet 26. Admitted 3/10/20 complaining of very severe headache, vomiting and attacks of giddiness. The headache was almost constantly present, dull and boring in character and referred chiefly to the right side of the head. He stated that it frequently awakened him after he had fallen asleep and was becoming progressively worse. It did not yield to the administration of aspirin or bromides. The attacks of vomiting occurred three or four times a day and were unaccompanied by nausea. He also complained of giddiness and stated that on one or two occasions he had fallen down and lost consciousness. The pupils were equal and reacted normally. The abdominal reflexes were present, the knee jerks slightly increased, the plantar reflexes flexor.
FUNDI:- Dr.Wright Thomson reported 15/10/20. O/E right disc normal. Left disc showed swelling of lower half and distinct perivascular lines along lower artery and vein.
WASSERMANN REACTION OF BLOOD NEGATIVE.
CEREBRO-SPINAL FLUID:- 30/10/20.Fluid clear. Pressure + +. Cell count 2 per c.m.m. Alcohol test gave a faint haze. Ross Jones and Nonne Apelt tests gave negative results.
Wassermann reaction C.S.F. negative.
COLLOIDAL GOLD REACTION:- 1 2 2 1 0 0 0 0 0 0 0 (weak luetic)

The clinical picture in this case strongly suggested a diagnosis of cerebral neoplasm and as the Wassermann reaction in blood and spinal fluid was negative, glioma or sarcoma appeared to be the most probable lesion. In view of Head and Fearnside's observation that in a single syphilitic lesion of the brain the Wassermann/

Wassermann reaction of the ~~blood~~ C.S.F. may be negative, two injections of Neo-Salvarsan were administered intravenously, though little result was hoped for. This treatment was followed by a complete remission of the symptoms. The headache cleared up, the vomiting and giddiness ceased and Dr.Wright Thomson reported 23/11/20 that the swelling of the optic disc had disappeared. Lines were still present along the vessels but these he regarded as likely to be permanent. Neo-salvarsan administration was continued and the cerebro-spinal fluid was subsequently re-examined, when the colloidal gold reaction was found to be negative. No relapse was observed and the patient on discharge was instructed to report for re-examination should any recurrence of symptoms be noted.

COMMENT:- This case is difficult to explain. At the time it was regarded as probably specific though this seemed contra-indicated by the negative Wassermann reaction, normal protein content, and absence of pleocytosis. It would now appear that the question of early disseminated sclerosis would have to be considered as a possible diagnosis but the exact nature of the lesion must remain doubtful.

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(4) CASES OF EPILEPSY.

Seven cases fall into this group and no facts of special serological interest were observed.

Five of these were cases of true epilepsy. One was a case of Hystero-epilepsy. One was a case of Jacksonian Epilepsy. Of the five cases in which the seizures were typically epileptiform in character, one gave a positive Wassermann reaction in the blood and the cerebro-spinal picture comprised:- Cell count 2 per c.m.m. No excess of protein: a positive Wassermann reaction and a strongly luetic reaction to colloidal gold. Of the remaining 4 cases the cerebro-spinal fluid picture was a normal cell count, a normal protein content and a negative Wassermann reaction:

two/

two gave a 'weak luetic' reaction to colloidal gold, and in the other two the gold reaction was 'suspicious'.

In the case of hystero-epilepsy the Wassermann reaction of the blood was negative and the cerebro-spinal fluid examination gave the following result:- Cell count 2 per c.m.m. Protein tests negative. Wassermann reaction negative. Colloidal gold reaction negative.

(5) MISCELLANEOUS NERVOUS CASES.

A series of cases of miscellaneous nervous diseases were investigated also by way of control, and some of these are considered in the following pages, only cases raising points of general interest having been selected for this purpose.

Two cases occurred during this research in which a clinical diagnosis of Motor Neurone disease (Amyotrophic Lateral Sclerosis) appeared reasonable. In view of their serological reactions they are quoted here.

Case 158. W.H. Aet 50. Admitted 26/10/20. No definite history could be obtained as to the onset of his illness, but he states that 5 weeks ago on awakening, he found he was unable to speak above a whisper. On admission patient was cyanosed and dyspnoeic. The voice was whispering and articulation was defective. There was difficulty in swallowing, the tongue when protruded deviated to the left. In both hands there was flattening of the thenar and hypothenar eminences. There was marked loss of power of the right arm and the right hand was held in a claw-like attitude. Weakness was also noted in the left arm but not to so marked a degree. In both arms almost constant fibrillary tremors were observed. The knee jerks were greatly increased, the right plantar reflex was extensor, the left doubtful. Laryngoscopic examination showed a generalized/

paresis of the laryngeal muscles, the abductors of the cord being chiefly affected. No abnormality was detected in the sensory neurone. The patient's mental condition was not clear and no coherent history could be obtained but in view of the paresis of the legs with the evidence of pyramidal involvement, the old standing progressive muscular atrophy of the hands and the symptoms suggestive of bulbar palsy of rapid onset, a provisional diagnosis of amyotrophic lateral sclerosis was made.

CEREBRO-SPINAL FLUID:- 26/10/20. Fluid clear. Pressure normal. Slight blood contamination. Alcohol test +. Ross Jones and Nonne Apelt tests negative.
Wassermann reaction of C.S.F. negative. (done twice).
Colloidal gold reaction " 1 2 2 2 1 0 0 0 0 0 0(luetic reaction)
Wassermann reaction of blood positive.

In view of the acute bulbar symptoms (dysarthria, dyspnoea, dysphagia and slight left facial palsy with paresis of vocal cords) combined with a positive Wassermann reaction, treatment was commenced at once with mercury, iodide, and novarsenobillon. Rapid clinical improvement was noted. Speech became practically normal, the patient stated that he no longer experienced difficulty in swallowing and the motor power of the legs was much improved. Unfortunately he was transferred to another hospital before treatment was completed and when he had received only 7 injections of 0.45 gm.Novarsenobillon. On discharge his serological reactions were as follows:-
Wassermann reaction of blood weak positive.
Cerebro-spinal fluid. Clear, pressure normal. Cell count 14.
Protein tests as before.
Wassermann reaction of C.S.F. negative.
Colloidal gold reaction " 0 0 1 1 1 0 0 0 0 0 0.

COMMENT:- In this case the Wassermann reaction alone established the aetiological basis and enabled treatment to be undertaken and such treatment produced rapid improvement of symptoms that were threatening life.

A CASE OF AMYOTROPHIC LATERAL SCLEROSIS WITH A POSITIVE WASSERMANN REACTION IN THS BLOOD AND IN WHICH THE CEREBRO-SPINAL FLUID PICTURE COMPRISED A NORMAL CELL COUNT, A NORMAL PROTEIN CONTENT, A POSITIVE WASSERMANN REACTION AND A PARETIC REACTION TO COLLOIDAL GOLD.

Case No.63. Mrs F.C. aet 38. Admitted 27/4/20 complaining of loss of power of arms and weakness and stiffness of legs of several years' duration. On admission both arms and forearms flaccid and greatly atrophied. There was complete wrist drop and marked atrophy of the muscles of both hands especially noticeable in the case of the thenar and hypothenar eminences and lumbricales. The deltoids, pectorals, trapezei, rhomboid, and/

and scapular muscles were also markedly atrophied. The sterno-mastoid muscles had apparently escaped. Both legs were very spastic, the knee jerks were greatly increased, patellar and ankle clonus was sustained on both sides and the plantar reflexes were strongly extensor. The abdominal reflexes were absent. There was no nystagmus, strabismus or diplopia. No abnormality was detected in the sensory neurone. There was no evidence of involvement of the cranial nerves. The fundi were normal. Wassermann reaction of blood positive.
CEREBRO-SPINAL FLUID:- Fluid clear, pressure normal, Cell count 2 per c.m.m. Ross Jones and Nonne Apelt tests negative, Wassermann reaction of C.S.F. positive.
Colloidal gold reaction:- 2 5 5 5 5 3 2 2 1 0 0 (paretic)
The patient left hospital and refused antispecific treatment. .

COMMENT:- In view of the positive Wassermann reaction and paretic colloidal gold curve, it is surprising that the cell count should be normal and the protein content not increased. It is somewhat remarkable that the only two cases encountered in this investigation which clinically simulated amyotrophic lateral sclerosis should both have yielded positive Wassermann reactions. Beevor, Batten and Gordon Holmes[56] state that the aetiology of this disease is unknown, that the atrophy is often attributable to a blow, (the significance of such a history in cases of specific infection has already been referred to) and that lead[57] and syphilis[58] [59] may produce the condition. The case quoted above (No.158) would appear to support this latter statement, as not only was there a positive Wassermann reaction in the blood, but the administration of neosalvarsan produced almost immediate clinical improvement.

A CASE OF PARKINSON'S DISEASE IN WHICH THERE WAS A LUETIC REACTION TO COLLOIDAL GOLD AND A NEGATIVE WASSERMANN REACTION IN THE CEREBRO-SPINAL FLUID:-

Case 164. E.P. Aet 50. Admitted 30/10/20 complaining of tremors of arms, head and legs. The tremor first commenced in the right arm which he states became stiff and weak.

CONDITION ON ADMISSION:- There was rhythmical tremor of arms, legs and head. The tremor in the hands was compound, was increased by excitement, could be temporarily arrested by voluntary effort and ceased during sleep. The affected limb was weak but not markedly rigid. There was very little emotional play of the features. The speech was slow and distinct. There was no suggestion of the Parkinsonian gait. The pupils reacted normally, the abdominal reflexes were present, the knee jerks normal, the plantar reflexes flexor.
Well/

Well marked thickening of the accessible arteries was noted.

CEREBRO-SPINAL FLUID:- Clear. Cell count 1. No excess of protein. Wassermann reaction C.S.F. negative.

Colloidal gold reaction:- 1 2 3 3 2 2 0 0 0 0 0 (strong luetic)

Several cases of cerebro-spinal meningitis were investigated more especially with a view to ascertaining the value of Lange's test in such diseases. It has already been stated (p. 24) that there is doubt as to the actual value of the so-called meningitic curve in the colloidal gold reaction. Cases have been encountered in which, in the presence of a slight blood contamination of the cerebro-spinal fluid, a meningitic curve was obtained although clinically there was no reason to suspect meningitis. The following case is quoted as an example of a typical cerebro-spinal fluid picture of pneumococcal meningitis.

Case 32. J.W. Admitted 28/3/20 suffering from severe headache and vomiting. Patient semi-comatose and unable to give definite history. Illness of 6 days' duration. Temperature on admission was 101.4°F. Pulse 96.

NERVOUS SYSTEM:- Pupils moderately dilated and fixed. No spasticity of limbs, no retraction of neck. Plantar reflexes flexor. Right knee jerk absent, left knee ankylosed. No tenderness over spine. LUNGS:- Dulness to percussion at apices and also at left base with subcrepitant rales.

CEREBRO-SPINAL FLUID ON ADMISSION:- Pressure +. Fluid of yellowish tinge. Cell count 256 per c.m.m. Ross Jones test + +. Nonne Apelt test + +. Alcohol test + +.
Wassermann reaction C.S.F. suspicious.
Colloidal gold reaction 0 0 0 0 1 2 2 I I 0 0 (meningitic reaction)

Microscopical examination of stained films showed the presence of gram positive encapsulated diplococci.

The patient died 36 hours after admission. Post mortem examination/

examination showed fibrosis of both apices and tuberculous meningitis of base of brain. Cultures gave growth of pneumococci.

The meningitic reaction to Lange's test, in addition to being unreliable, is of little value to the clinician as the cytological, and bacteriological examination of the cerebro-spinal fluid is of much more diagnostic importance.

A somewhat anomalous colloidal gold reading was obtained in a case diagnosed by Dr.Crockett, Bridge of Weir Sanatorium, as cerebral abscess. Examination of the spinal fluid of this case gave the following results:-

Cell count 71 per c.m.m. Ross Jones, Nonne Apelt and Alcohol tests all + +. Wassermann reaction C.S.F. negative. Colloidal gold reaction 0 0 0 1 2 2 2 1 0 0 0 .

In cases of transient toxic meningismus the colloidal gold reaction was negative.

LETHATGIC ENCEPHALITIS. The serological study of this disease is of interest as the work of Loewe and Strauss (59) has shown that the cerebro-spinal fluid is infective to rabbits and they claim to have isolated globular bodies with Brownian movement.

A CASE OF LETHARGIC ENCEPHALITIS WITH A REPORT ON THE CEREBRO-SPINAL FLUID PICTURE.

Case No.94. M.H. Aet 30. This patient was a nurse in charge of cases of lethargic encephalitis. She was admitted to hospital 9/6/20. The history given was that she took ill 4/6/20 with vomiting, pain in the right upper limb and insomnia. On admission she was stuporose. The grip of both arms was feeble. The right abdominal reflex was absent, the left active. Both knee jerks were absent. There was paresis of the right facial nerve, also moderate pyrexia: pupils equal, medium, and reacted normally. On 11/8/20 a purpuric eruption/

eruption of generalized distribution appeared. FUNDI. O/E Congestion of left disc, fundi otherwise normal. Patient complained of slight difficulty in swallowing and in protruding the tongue. Slight nystagmus noted. 14/6/20 rigidity developed in both upper limbs. Power of opening the eyes was practically lost. Nystagmus was well marked and hiccough developed. Breathing threatened to stop. Continuous oxygen was administered. On 15/6/20 hyperpyrexia developed and the following day stupor set in. On 17/6/20 there were widely distributed muscular twitchings and 48 hours later the patient died. The cerebro-spinal fluid picture 10/6/20 was as follows:- Fluid Clear. Pressure + +. Cell count 8 per c.m.m. type of cell small lymphocytes. Protein tests:- Ross Jones test +. Nonne Apelt test Phase I +.
" II Negative.
Alcohol test +.
Wassermann reaction of C.S.F. Negative. Colloidal gold reaction 1 1 2 2 1 1 0 0 0 0 0 (Luetic)
Wassermann reaction of blood negative.
Dark ground illumination of the cerebro-spinal fluid yielded no result. Culture showed no growth after 72 hours at 37°C. (Agar and glucose broth).

COMMENT:- In view of the clinical signs of acute infection of the central nervous system the normal cell count is surprising. An increase in protein content and a luetic reaction to colloidal gold are the only abnormalities detect-:ed in the cerebro-spinal fluid.

That the colloidal gold reaction in lethargic encephalitis is not invariably positive the following cases will show.

Case 41. A.L. Aet 31. Admitted 8/4/20 complaining of severe headache of 4 days' duration. On admission the knee jerks were normal, the plantar reflexes flexor. Pupils medium equal and active. Slight drooping of eyelids was noted especially on the left side. There were fine tremors of the extended hands. Optic fundi were normal. Homonymous diplopia elicited on looking upwards and to the left. No obvious strabismus with eyes at rest. No nystagmus. On 12/4/20 marked lassitude developed and ptosis, myosis and photophobia were noted. The following day the patient became stuporose, incontinence of urine set in and tâche cérébrale was elicited. The temperature throughout had varied from 100°F. to 102°F. On 20/4/20 she was transferr-:ed to a Fever Hospital with a diagnosis of lethargic encephalitis. 5/5/20 patient died.

CEREBRO/

CEREBRO-SPINAL FLUID PICTURE:- 12/4/20. Fluid clear. pressure + +. Cell count 11 per c.m.m. Small lymphocytes and 2 endothelials.
All protein tests negative.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction negative.

In five cases of convalescent lethargic encephalitis the colloidal gold reaction of the cerebro-spinal fluid was examined with negative results.

The two cases cited above would appear to indicate that the cerebro-spinal fluid picture in this disease is variable, and it may be observed that these discrepancies are not surprising as the disease is as yet in many cases hardly a clinical entity.

A CASE OF EXOPTHALMIC GOITRE WITH A POSITIVE WASSERMANN REACTION IN WHICH INTRAVENOUS INJECTIONS OF NOVARSENOBILLON PRODUCED GREAT CLINICAL IMPROVEMENT.

Case No.138. J.G. Aet 23. Admitted 21/9/20 complaining of palpitation and swelling of neck.
History of onset:- Patient served for 3 years in the Army and was discharged in 1917. In France he suffered from an attack of Trench Fever in 1915 and was gassed in 1916. He states that in July 1916 after a 3 days' bombardment he wakened up with a swelling in his neck. He reported sick and was sent down the line. Six months later he noted protuberance of his eyes. On admission there was considerable enlargement of the thyroid gland - the swelling was more noticeable on the right side than on the left and was pulsat-:ile in character. There was marked exopthalmes, Stellwag's, Von Gräfe's and Moebius' Signs were present. There were fine tremors of the outstretched arms. Pulse rate 140. No other abnormality was detected in the Nervous System and the other systems were apparently normal.

The case was treated with sodium phosphate and weekly application of X-rays. A certain amount of improvement was noted but X-ray treatment had to be discontinued on account of dermatitis and the patient was discharged.

CEREBRO-SPINAL FLUID:- 29/9/20. Fluid clear. Cell count 60 per/

per c.m.m. Alcohol test faintly +. Other protein tests negative. Wassermann reaction C.S.F. weak positive. Colloidal gold reaction:- 0 1 1 1 0 0 0 0 0 0 0 (weak luetic)

The case was readmitted 10/1/21 when he was placed on anti-specific treatment. Three injections of Novarsenobillon (0.2 gm. 0.45 gm. 0.45 gm.) at 6 day intervals produced great clinical improvement. The exophthalmos was visibly reduced, the pulse rate fell to 100. The most noticeable alteration was the diminution in size of the thyroid gland. Treatment is being continued.

COMMENT:- Attention is called in the first place to the history of sudden onset, of exophthalmos and thyroid enlargement following on emotional trauma. Pfeiffer (61) records three cases of acute Graves disease in which the causal emotion, which was insufficient by itself to produce a permanent anatomical change, was accompanied by an important factor, viz:- Active syphilitic infection. As these three cases were the only examples of so-called emptional exophthalmic goitre which he had met with during 18 months' observation of several hundred cases of commotion, Pfeiffer is convinced that every case of exophthalmic goitre of so-called emotional origin occurs on a syphilitic soil.

The favourable reaction to arsenic of cases of this disease is admitted by many writers (62), the course of the disease clinically is one of exacerbations and remissions. The blood changes in exophthalmic goitre have recently been investigated by Blank (63) in a series of cases. He found evidence of poikilocytosis in 30% of cases of hyperthyroidism, a normal haemoglobin content in 28% of cases, in 50% polychromasia/

polychromasia and in 50% - 75% punctate basophilia. In addition attention is drawn to the fact that in this disease diplopia occurs and that this occasionally may go on to external ocular palsy.(64) One of the cardinal eye signs (Moebius' Sign) would appear to be due to weakness of the internal recti muscles. It is of interest to note that in the course of this investigation exophthalmos has repeatedly been observed in pensioner patients suffering from tabes.

Much attention has recently been devoted to the part played by syphilis in producing lesions of the endocrine glands.(65) Schulman emphasizes the fact that these glands by reason of their vascularity are especially liable to spirochaetal infection; and the spirochaeta pallida has been demonstrated in them by Jacquet and Sezary.(66)

Presumably the spirochaetal infection of the thyroid gland may give rise to perversion of the normal secretion resulting in the symptoms and signs of Grave's disease and it would appear probable that in cases of this disease which do not occur on a syphilitic soil we may be dealing with an infection of the thyroid gland - the nature of such an infection is unknown but it may possibly be of a spirochaetal nature - No work on this subject has, however, been published.

A CASE OF PERNICIOUS ANAEMIA WHICH, WHILE UNDER OBSERVATION, DEVELOPED SIGNS OF COMBINED SCLEROSIS.

Case No.211. W.I. Admitted 4/5/21. On admission patient was weak and emaciated with a distinct lemon-tinging of the skin/

skin. The teeth were defective and there was a well-marked glossitis. Examination of the blood yielded the following result:-

Reds	1,620,000
Whites	7,800
HB.	40%
Colour Index	1.25.

Blood films showed definite megalocytosis with relatively deep staining. Nucleated reds were detected and there was well marked polychromatophilia. The patient was placed on antistreptococcic serum and later on arsenic and for a time his condition appeared to improve. He subsequently complained of increasing weakness of his legs, the knee jerks were noted to be absent and the plantar reflexes definitely extensor in character. He died of syncope 15/2/21.

CEREBRO-SPINAL FLUID:- 4/2/21. Fluid clear. Pressure normal. Cell count 1. Wassermann reaction C.S.F. Negative:
" " blood negative.
Colloidal gold reaction negative.

COMMENT:- This case is of interest in that there was clinical evidence of spinal sclerosis. Redwood(67) reports a case of pernicious anaemia in which nervous symptoms eventuating in combined sclerosis preceded the appearance of marked anaemia. MacCallum (68) states 'another lesion characteristic of pernicious anaemia is found in the white matter of the spinal cord. Especially in the posterior tracts there occur focal areas of degeneration of the nerve fibres and neuroglial scarring which, by interrupting these tracts produce irregular ascending secondary degenerations. These, described by Lichtheim, Minnich, Nonne, Milne, and others bring about very distinct sensory disturbances during life, sometimes amounting to ataxic phenomena closely resembling those of tabes'. He also draws attention to the monotonously uniform clinical course of this disease. The beneficial results obtained by the administration of antistreptococcic serum are strongly urged by Hunter(69) who emphasizes also the necessity for antisepsis in the treatment of pernicious anaemia. Adami(70) states 'based upon the close resemblance between the clinical picture and post mortem appearances in man and those of surra and dourine in the horse, the latest hypothesis is that we deal with a condition of trypanosomiasis. The riddle has still to be solved.' There is, therefore, a considerable mass of presumptive evidence that in this disease we are dealing/

dealing with an infective condition - a condition which by general consent reacts at least temporarily to arsenic. The clinical course of exacerbations and remissions is also suggestive and it might appear reasonable to investigate this disease with a view, at least to disproving the possibility of a spirochaetal infection in certain cases of as yet unknown aetiology. The trypanosome theory put forward by Adami would appear more improbable as trypanosomes are of extremely rare incidence in this country and their size renders them relatively easy to detect. The improvement which occasionally follows the use of antistreptococcic serum may be due to a heterogenetic effect - the bactericidal properties of horse serum are well known and the striking results claimed by Hunter for this line of treatment would appear to support the theory of an infective basis for this disease.

A CASE OF NEUROSYPHILIS CLINICALLY SIMULATING LETHARGIC ENCEPHALITIS IN WHICH ANTISPECIFIC TREATMENT PRODUCED A RAPID REMISSION OF SYMPTOMS.

Case No.191. W.K. Aet 22. Admitted 31/12/20 with a history of gradually increasing lethargy of a few days' duration. On admission the patient was semi-comatose, he could be roused only with difficulty and took no interest in his surroundings. Speech was slow and monotonous and memory was defective. Respirations were quiet and numbered 18 per minute. The pulse rate was 60. Temp.100°F. He complained of intense frontal headache. There was a slight discharge from the right ear, but no pain or tenderness over the mastoid process or other sign of acute mastoiditis. There was distinct paresis of the right side of the face and the tongue deviated towards the right. The mouth was in a septic condition and the breath very offensive. No retraction of the neck was noted, and Kernig's sign was not elicited. The pupils were equal, moderately dilated and reacted to light. There was no external ocular palsy but there appeared to be some inco-ordination in the movements of the eyes. The grip with both arms was much diminished and the arm reflexes lost. The abdominal reflexes were active, the knee jerks absent, the plantar reflexes flexor in character. The abdomen was retracted. No enlargement of liver or spleen was detected. Heart and lungs were apparently normal. Urine:- specific gravity 1015. No albumen or sugar present. Forty-eight hours after admission his condition was worse. The pulse rate had fallen to 48 - there was no local sign of mastoid involvement. Lumbar puncture was performed 2/1/21. The cerebro-spinal fluid was under very great increase of pressure and came out in a stream projecting 6 inches from the handle of the needle. 30 c.c. of cerebro-spinal fluid were removed. Analysis yielded the following result:-

The/

The fluid was clear, cell count 240 per c.m.m. A film of the centrifugalised deposit showed large and small lymphocytes. No polymorphs were detected. Examination of stained films did not demonstrate the presence of organisms. The alcohol and Ross Jones tests were positive. The Wassermann reaction of the cerebro-spinal fluid was positive.
Colloidal gold reaction:- 1 2 2 2 2 1 0 0 0 0 0 (luetic)
Wassermann reaction of the blood positive.

Immediately after lumbar puncture the patient's condition improved, he was able to answer questions and the pulse rate rose to 58. Examination of the fundi showed blurring of the nasal margin of the left disc. The patient was placed on mercury and iodide in large doses and this produced gradual improvement. Intravenous injections of Novarsenobillon were then commenced and the patient made an uninterrupted recovery. The paresis of right facial nerve persisted.

As regards acute myelitis the aetiology of such cases as have been encountered in this investigation is by no means clear; the following case will serve as an example:-

Case 68. W.G. Aet 42. Admitted 11/5/20 complaining of loss of power of both legs of one week's duration. There was no preceding history of acute illness, injury or exposure. The patient's previous health was good and there was no history of specific infection. On admission there was paralysis of both legs with complete anaesthesia. The knee jerks and plantar reflexes were absent and bladder and bowel control were lost., i.e. the clinical picture was one of a complete transverse myelitis of sudden onset.
The Wassermann reaction of the blood was negative.

CEREBRO-SPINAL FLUID:- Clear. Pressure + + +. Cell count 3 per c.m.m.
Wassermann reaction C.S.F. negative.
Colloidal gold reaction:- 0 1 4 4 1 0 0 0 0 0 0.

TREATMENT:- 6 injections of 0.45 gm. Novarsenobillon, mercury and potassium iodide.

RESULT:- Bladder and bowel control were completely regained and motor and sensory function had partially returned when the patient was irregularly discharged (24/8/20) before treatment was completed.

COMMENT:-/

COMMENT:- The early loss of reflexes in this case, though difficult to explain theoretically, accords with observations made extensively during the war, viz. that immediately following on a spinal wound the reflexes disappear - a phenomenon presumably due to shock. The aetiology of such cases would appear to be quite unknown and in the present state of our knowledge the use of the term idiopathic is justifiable. It is open to question whether in this case the treatment had any effect on the condition as the recovery may have been spontaneous. It is surprising that in such an acute involvement of the central nervous system the cell count of the cerebro-spinal fluid should be normal. A case has already been described(71) in which the onset was similar to that above recorded, and in which a rapidly ascending paralysis developed followed by sudden spontaneous arrest and ultimate recovery. A presumptive diagnosis of acute infective ascending myelitis was made and received the approval of Sir Humphrey Rolleston. Such cases clinically resemble Landry's paralysis(72) though on reading his original paper, written in 1859, one cannot but conclude that the group comprises various conditions which the application of modern serological methods would serve to differentiate.

A CASE OF ANOREXIA NERVOSA WITH A NEGATIVE WASSERMANN REACTION IN THE BLOOD AND POSITIVE WASSERMANN AND COLLOIDAL GOLD REACTIONS IN THE CEREBRO-SPINAL FLUID.

Case No.13. Mrs.C. 8/6/20. On admission this patient presented an extreme degree of wasting of the entire muscular system. She gave a history of onset 2½ years before since when the emaciation had been slowly progressive. Three children died in infancy - two were still-born. There was no history of diphtheria. Heart and lungs were normal. No abnormality detected in abdomen - superficial abdominal reflexes absent. All tendon reflexes normal. Plantar reflexes flexor. No specific involvement. No abnormality detected in sensory neurone. Pupils normal. Fundi normal. Patient was aphonic. Laryngoscopic examination showed that vocal chords were normal and the aphonia functional.

BLOOD:- Erythrocytes 5,900,000. Hb.85%.
All muscles reacted normally to faradism. No reaction of degeneration. The urine was 'defective in nitrogen to an extraordinary degree and creatin was in excess' (Prof.E. Cathcart.)
Wassermann reaction of blood negative.

CEREBRO/

CEREBRO-SPINAL FLUID:- Clear. Pressure normal. Cell count 14. Small lymphocytes. Protein tests negative.
Wassermann reaction C.S.F. positive.
Colloidal gold reaction:- 3 3 4 2 2 1 0 0 0 0 0.

COMMENT:- It will be noted that in this case the positive Wassermann reaction in the cerebro-spinal fluid was supported by a luetic colloidal gold reaction and pleocytosis.

On reviewing the cases investigated in the course of this research, one cannot fail to be impressed by the necessity for the serological investigation of blood and cerebro-spinal fluid in all cases of nervous disease and in such investigation the test which would appear to be of the most value to the clinician is the Wassermann reaction. The routine application of this test reveals the very large part played by syphilis in the production of nervous disease and the study of individual cases recorded in the preceding pages will serve as examples of the protean manifestations of the ravages of the spirochaeta pallida.

It is desired to emphasize that no Wassermann reaction has been obtained which, in the light of the co-existing cerebro-spinal fluid picture and other clinical and therapeutical evidence, could be regarded as anomalous. The value of the so-called provocative action of Neo-salvarsan in inducing a positive Wassermann reaction in cases of latent syphilis in which the reaction had previously been negative, would appear to be very doubtful though occasionally cases on the border line between

'negative'/

'negative' and 'positive' may be encountered and such cases might erroneously appear to support the provocative theory. The statement has recently been made by Strickler[73] and his co-workers that the routine administration of neo-salvarsan to non-syphilitic patients will induce a positive result to the Wassermann test. Their observations were made on a series of 24 cases of skin diseases in which there was no history of syphilitic infection and in which prior to treatment the Wassermann reaction was negative. They state that in 66% of these cases under Salvarsan treatment a positive Wassermann reaction was obtained.

The results obtained in this research do not support these observations for in no case of non-syphilitic disease has a positive Wassermann reaction developed during Salvarsan treatment. As regards the colloidal gold test, there is little known as to the real nature of the reaction. From a consideration of the results of this research it would appear that the colloidal gold reaction has no definite relationship to the Wassermann reaction, that it is not specific in the sense that the Wassermann reaction is specific, though like the Wassermann reaction it would appear to depend on some quality of the globulin fraction. The opinion has, however, been formed that the test is of undoubted value to the clinician as it would seem to indicate the first definite involvement of the central nervous system

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in organic diseases and it is especially hoped that we may have, in the colloidal gold reaction, a method for differentiating between early disseminated sclerosis and functional diseases of the nervous system. The results obtained have been referred to in detail but attention is drawn to the fact that the reaction is as constantly positive in disseminated sclerosis as in syphilis and that a 'paretic' curve may be encountered in the former disease - Such a curve is still stated in current literature to be pathognomonic of general paralysis of the insane.

SUMMARY:-(1) The cerebro-spinal fluid picture in disseminated sclerosis is as follows:- A normal cell count, a negative Wassermann reaction, a luetic or paretic reaction to colloidal gold and, in most cases (83%) a normal protein content.

(2) The absence of a positive Wassermann reaction in the great majority of cases, and the absence of pleocytosis are in accordance with the view that this disease is not of syphilitic origin.

(3) On the supposition that the origin might be spirochaetal, treatment was carried out by spirochaeticidal drugs. In practically every case under treatment modifications towards a negative result of the colloidal gold reaction were noted. As regards clinical effect of such/

such treatment, though no marked improvement resulted in advanced cases of the disease prolonged treatment produced amelioration of early cases and in some instances the results were marked.

(4) With reference to early diagnosis emphasis is laid on a history of transient diplopia, precipitancy of micturition, nocturnal seminal emissions and also on the detection of slight retro-bulbar neuritis, loss of the abdominal reflex and on the cerebro-spinal fluid picture.

(5) It would appear that there is clinical and serological evidence to justify energetic anti-specific treatment of cases of neuro-syphilis at every stage of the infection.

CONCLUSION:

The present nomenclature of nervous diseases, depending as it does largely on an anatomical basis, is unsatisfactory and a classification on aetiological lines would clear up much of the existing confusion.

It is hoped that as a result of this investigation, early diagnosis and prompt and prolonged treatment may arrest the further progress of cases of disseminated sclerosis.

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