A CLINICAL AND EXPERIMENTAL INVESTIGATION INTO VARIOUS ASPECTS OF DISSEMINATED SCLEROSIS.

THESIS PRESENTED FOR THE DEGREE OF M.D. IN THE UNIVERSITY OF GLASGOW

by

JOHN M. SUTHERLAND, M.B., Ch.B.

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I

INTRODUCTION.

1. The Present Investigation.

This Thesis is based on work done, during the past three years, on the subject of disseminated sclerosis. The primary object was to attempt an investigation into the aetiology of the disease.

A study of clinical histories, and of the literature, suggested the possibility that in disseminated sclerosis there is a very considerable rural incidence. Statistical analysis of a series of 389 cases of disseminated sclerosis was therefore undertaken with a view to establishing this observation. This series consists partly of cases seen in private by Dr. D.K.Adams, and partly of cases admitted to Dr. Adams' Medical Unit at the Western Infirmary, Glasgow. The opportunity was also taken of assessing the importance of other factors reputed to be of aetiological significance.

Resulting from this, a hypothesis was formulated concerning the aetiology of the disease. In an attempt to test this hypothesis, experimental work has been performed on sheep, using disseminated sclerosis material as inoculum. In addition the hypothesis that a relationship exists between brucellosis and disseminated sclerosis has been subjected to experimental test.

As a basis for other investigations, done concurrently with that outlined above, the statistical analysis was extended to cover

symptomatology, serology and treatment. The work now reported thus embraces the pathogenesis, clinical features, serology and treatment of disseminated sclerosis.

It was apparent from the outset that the prospective programme necessitated the assistance and co-operation of others. Steps were therefore taken to establish a friendly liaison with a veterinary research unit. In addition advice was obtained in planning the statistical investigation and in interpreting the results of this. Due acknowledgement will be made to them, and to Dr. Douglas K. Adams, Western Infirmary, Glasgow, under whose general supervision this investigation has been undertaken.

2. Historical Note.

Cruveilhier is credited with being the first to describe disseminated sclerosis in the literature. In his "Anatomie Pathologique", published between 1835 and 1842, he depicted the disease as it was seen in the pons, medulla and spinal cord of four patients. The morbid appearances of the disease are also recorded by Carswell in his "Illustrations of the Elementary Forms of Disease", published in 1838.

The first clinical study is reputed to be that of Frerichs in 1849. Firth (1948), however, has pointed out that Sir Augustus D'Este clearly recorded the course of the disease, as it affected himself, from 1825, when the initial complaint of dimness of vision occurred, to 1848, when he died. Frerich's work was amplified by

his pupil Valentiner, who, in 1856, reported a series of cases, It was not, however, until the works of Charcot (1877) and his school were published, that the disease became widely known.

The authoritative histological studies of Siemerling and Raecke (1914), and the monumental work of Dawson (1916), placed the pathology of disseminated sclerosis on a sound basis. The view that disseminated sclerosis, as judged by its histology, is a distinct pathological entity, has not been contradicted, despite recent evidence that demyelination may be produced by a variety of different agents (e.g. Hurst and Cooke, 1942; Morrison, 1946; Wolf, Kabat and Bezer, 1947).

II

THE AETIOLOGY OF DISSEMINATED SCLEROSIS.

Numerous theories and a vast literature exist on the aetiology of disseminated sclerosis. These have recently been critically reviewed by Reubi (1947). The cause of the disease remains unknown but the present writer subscribes to the view expressed by McAlpine (1946) that there is increasing evidence in support of the infective nature of the disease. Demyelination may be produced by a variety of means, yet it is generally accepted that, as judged by its histology, disseminated sclerosis is a distinct pathological entity. Further, the hypothesis, as expressed by Steiner (1941), that disseminated sclerosis is an "aetiologically uniform infectious disease" has never been disproved.

1. Review of Theories of Aetiology.

The following theories of aetiology will be briefly discussed:-

(a) The Infective Theory.

(b) The Role of Allergy.

(c) The Vascular Theory.

(d) The Toxic Theory.

(e) The Ferment Theory.

(a) The Infective Theory. With regard to the infective nature of disseminated sclerosis two main schools of thought exist. The one, that disseminated sclerosis is due to the activity of a spirochaete; the other that a neurotrophic virus is responsible.

A relationship between disseminated sclerosis and an infective agent was first propounded by Pierre Marie (1891). That this agent might be a spirochaete was suggested by Buzzard (1911). This view has been supported particularly by the work of Kuhn and Steiner (1917), by Marinesco (1919), and by Adams, Blacklock, Dunlop and Scott (1924). On clinical, serological and perhaps on therapeutic grounds, there is nothing incompatible with the theory that disseminated sclerosis results from the activity of a spirochaete. On the other hand, such a microorganism has never been cultured from disseminated sclerosis material. In explanation, it may be that the microorganism is present only in very small numbers, or present technical methods may be insufficiently sensitive to demonstrate its presence. Steiner (1941), however, reports the presence of extra cellular spirochaetes (spirochaeta myelophthora) in 11 out of 49 cases of disseminated sclerosis (22.4%). In addition, the presence of intracellular debris, like that seen in other proven spirochaetal diseases, was demonstrated. The silver reduction method employed by Steiner, and other technical points may explain the discrepancy between the results of this study and those of other workers. In this connection, it may be noted that Browning (1924), records that it is frequently a matter of difficulty

to demonstrate the presence of spirochaeta pallida in the brains of general paralytics.

Bulloch (Gye)(1913), appears to have been one of the first workers to implicate a filter passing virus. He produced paresis associated with spinal cord changes in rabbits, by injecting them with cerebrospinal fluid obtained from a case of disseminated sclerosis. Recently, the Russian workers Margulis, Soloviev and Schubladze (1946), isolated viruses of identical strain from two cases of acute disseminated encephalomyelitis. Virus neutralising experiments, using sera obtained from cases of acute disseminated encephalomyelitis and disseminated sclerosis, suggest that both these diseases result from infection with the same virus. The importance of these findings is obvious. Repetition and extension of this work is indicated.

(b) The Role of Allergy. In many instances, various workers have failed to transmit disseminated sclerosis from man to animals. This fact may be explained by the theory that in the pathogenesis of disseminated sclerosis allergy plays a part. The scarcity of spirochaetes in the brains of certain cases of general paralysis has been mentioned, and Browning (1924), points out that there is no constant relationship between the number of spirochaetes and the severity of the disease process in this condition. He suggests that in syphilis there is a balance between immunity phenomena and allergy. Gowers (1903), expressed the view that "different as the two processes (syphilis and disseminated sclerosis) are in their

immediate pathology, they may possess some common relations in nature or causation". It is not impossible that a common factor in the pathogenesis of both conditions is allergy.

Baer and Sulzberger (1939), investigated the incidence of atopic hypersensitivity in 30 cases of disseminated sclerosis. A positive history, a positive skin test, or both, occurred in 10 (33%) of these cases. Although this figure is not significantly greater than the incidence in the general population, it does not exclude the possibility that some other form of allergy may play a part. In McAlpine's Series (1946), approximately 6% of patients gave a history of asthma, hay fever, or urticaria. Kammer & Karnosh (1947) reviewed the relationship of the arthus phenomenon and disordered clotting mechanism to demyelinating diseases. Three of their twelve cases had urticaria or contact dermatitis.

It is the opinion of Kennedy (1938), that the clinical events in disseminated sclerosis resemble the manifestations of localised allergic oedema of the central nervous system. Similarly, Ferraro(1944) considers the demyelinating diseases to be an expression of an allergic reaction in nerve tissue. He further believes that unification of the demyelinating group of diseases can be accomplished on this basis. It is suggested by Ferraro that once the initial pathological process is established, additional factors such as the possible development of antigens from the white or from the grey matter may play a part in the disease process. That antigenic substances can be derived from myelin sheaths has been established

by the work of Bailey and Gardner (1940), whilst Plaut (1928), demonstrated that the nervous system can produce all the usual antibodies. The production of acute disseminated encephalomyelitis in the rhesus monkey, following the injection of brain emulsions, was considered by Kabat, Wolf and Bezer (1947), to be due to the antibody so produced reacting with the tissues of the central nervous system.

There is, thus, a body of opinion which favours the conception that allergy plays a part in disseminated sclerosis. Further reference will be made to this aspect in later sections.

(c) The Vascular Theory. In America, the work of Putnam (1935, 1937, 1941), has focussed attention on the possibility that thrombosis in the venules of the central nervous system may be the essential feature of the disease. Although vascular occlusion may result in demyelination, Dawson (1916) did not consider venous thrombosis to be a characteristic feature in the histology of disseminated sclerosis. Further, in a recent study, Dow and Bergland (1942) failed to find evidence of vascular occlusion. A vascular aetiology is also postulated by Scheinker (1949) who, however, differs from Putnam in that he considers vasoconstriction in the central nervous system to be the essential feature.

On general principles, the sudden onset of initial symptoms favours a vascular event. Further, since allergy may play a part of aetiological significance, the changes which occur in the coagulation time of the blood in allergic conditions may predispose to vascular occlusion. I, personally, have been impressed with the

occurrence of vasomotor phenomena in the extremities of cases of disseminated sclerosis. It is not impossible that similar changes may occur in the central nervous system. Whether or not this might favour venous thrombosis is problematical. On the evidence available, although vascular phenomena may occur in the pathogenesis of disseminated sclerosis, it would seem unlikely that this is the essential feature in the aetiology.

(d) The Toxic Theory. At various times, toxic substances such as lead, arsenic, and carbon monoxide have been implicated as the cause of disseminated sclerosis. Cone, Russel and Harwood (1934), suggested that lead was the aetiological agent in cases of the exacerbating and remitting type. Boshes (1935), however, further investigating this possibility, concluded that there was no adequate proof for, and ample evidence against, such a theory.

Toxic substances may, however, produce demyelination in the central nervous system. Thus it was demonstrated by Hurst (1944), that demyelination could be produced by the administration to monkeys of potassium cyanide and sodium azide and, further, that the changes in the central nervous system varied in site and character with the dose given.

The possibility that lead may play an aetiological role has been revived by the suggestion that lead may interfere with the absorption or utilisation of copper in the disease of sheep known as swayback. The report of Campbell and his colleagues (1947), has focussed attention on the possible relationship between this disease and disseminated sclerosis.

(e) The Ferment Theory. The presence of a myelin splitting ferment in the blood has been postulated by Brickner (1930), Crandall and Cherry (1932), and by Brickner, Watters, Wexler and Soltz (1936). Lafontaine (1948), as a result of experimental work, came to the conclusion that the tissue fluids - serum, plasma, cerebrospinal fluid and urine, of patients suffering from disseminated sclerosis contain myelinolytic substances capable of destroying myelin and of hydrolysing certain lipids. This activity is present to a less degree in normal subjects. In disseminated sclerosis it varies with the phase of the disease; the activity appears to be greater during exacerbations than remissions.

Thus there is no uniformity of opinion regarding the aetiology of disseminated sclerosis. It is apparent that demyelination may result from several causes. Similarly, a clinical syndrome compatible with disseminated sclerosis may result from more than one aetological factor. Gowers, for example, stressed the difficulty in differentiating between certain cases of neurosyphilis and disseminated sclerosis. Dawson (1916), however, was of the opinion that disseminated sclerosis is due to a specific morbid agent and this view is still widely held. It is possible that whereas the disease known as disseminated sclerosis is a pathological entity, the clinical syndrome which we term disseminated sclerosis may be due to multiple causes.

2. A Conception of the Disease Process.

The writer's conception of the disease process is outlined diagrammatically in diagram 1.

This scheme will now be amplified.

The Causal Agent of Disseminated Sclerosis. This aspect will be referred to more fully in the next section. It may however, be reiterated that the infective nature of the disease is adhered to. It is further suggested that the causal agent may be as ubiquitous as the tubercle bacillus. It is probable that, as in syphilis, disease of the nervous system due to the causal agent of disseminated sclerosis is relatively infrequent compared with infection of the nervous system by it.

Transmission of the Infective Agent to Humans. The importance of detecting the mode of transmission of the disease to the individual has been stressed by Adams (1923). McAlpine (1946), refers to the possibility of a cutaneous entry, and Adams and Sutherland (1948) suggest that by analogy with neurosyphilis, the primary inoculation may be through the skin. In this connection, it is interesting to note that Steiner (1918), implicated a tick. He found evidence of contact with ticks in 21 out of 43 cases, while this was present in only 10% of a control series.

It may be observed that whereas the bite of the adult tick is generally readily remembered, the nymphal form of the tick is of insignificant size. There is, however, conclusive evidence that at this immature stage of its life history, the sheep tick

(ixodes ricinus) can transmit the neurotrophic virus of the disease in animals known as louping ill.

The Infected Person. Assuming infection of an individual with the causal agent of disseminated sclerosis, the future outcome depends largely on the type of individual so affected. Natural resistance to the invading microorganism may be high. Such non-allergic insensitiveness or hyposensitiveness results in absolute protection of the individual.

On the other hand, inoculation into a susceptible person may occur with resulting invasion of the central nervous system. Consequent upon this, a variable degree of damage will be inflicted on the nervous system. At the same time the occurrence of immunity reactions greatly reduces the numbers of infecting microorganisms. The central nervous system is now allergised. With regard to the nature of the allergen three possibilities exist:-

(a) The antigen may be the infecting microorganism or its toxin.

(b) The products resulting from the initial damage inflicted by the microorganism on the nervous system may act as antigen or hapten. This concept of auto-allergisation is referred to by Urbach and Gottlieb (1946). It involves the alteration of autogenous material within the body by autolytic, inflammatory, or other processes. As a result the antigenous material loses its biochemical identity and becomes foreign to the body. This foreign material will act as an antigen or hapten. The observation of

Bailey and Gardner (1940), that antigenic substances may indeed be derived from myelin sheaths has already been mentioned.

(c) A combination of factors referred to under (a) and (b) may be the basis of the allergisation.

Whatever the true nature of the allergen, reaction between antigen and antibody may result in one of three possibilities:-

(1) A state of immunity may develop. This is a special form of allergic hypersensitiveness and is characterised by the total or relative absence of reactivity to the introduction of foreign substances. With reference to disseminated sclerosis, it is suggested that this state of immunity may obtain in cases in which the initial manifestation is followed by a prolonged remission, as in the following case:-

> Case 58/M/30 Male aged 31.
> At the age of 11 years, and subsequent to a farming holiday, retrobulbar neuritis developed in one eye. A complete symptomatic remission ensued until he was 31 years of age, when he commenced to drag his right foot. Clinical examination disclosed the presence of signs referable to lesions of pyramidal tracts and posterior columns.

It is suggested that subsequent to the initial manifestation of retrobulbar neuritis, a state of immunity developed which held in check the progress of the disease for 20 years. It is equally conceivable that such immunity may last 40 years, or indeed a lifetime.

(2) An excessive reaction of defence may occur. As in

anaphylaxis, this might be of such violence that the consequences may be deleterious to part or all of the organism. In disseminated sclerosis this severe constitutional reaction may result in death or in recovery. The following case exemplifies this concept:-

Case 22/M/20.
This patient, now a solicitor, was first examined by Dr. D.K.Adams in April 1929. He then gave a history of a three weeks illness which commenced with weakness in the muscles of mastication. This was followed by rapidly progressing spastic paraplegia, staggering gait and diplopia. It is perhaps of interest to note that in July and August of the previous year the patient had spent a holiday on a sheep farm. During the course of assisting to "dip" sheep he had been bitten repeatedly by sheep ticks.

On examination in 1929, the patient was bedridden and unable to use his legs. Clinical evidence of bilateral pyramidal tract damage was elicited. Ankle clonus was extreme. The abdominal reflexes were not elicited.

He was considered to be an acute case of disseminated sclerosis. This opinion was shared by six other hospital physicians.

He was treated with protein shock therapy and organic arsenic intravenously. Subsequently arsenic was administered orally over the next 10 years.

This patient was kind enough to permit me to examine him in 1948. He was then subjectively and objectively well. The only abnormal features detected were easily exhausted abdominal reflexes and exaggerated knee jerks.

If this was not a case of disseminated sclerosis, the question remains from what other illness was the patient suffering? The only other reasonable possibility is acute disseminated encephalomyelitis of unknown aetiology. As already mentioned, the work of Margulis, Soloviev and Shubladze (1946) suggests that both acute disseminated encephalomyelitis and disseminated sclerosis result from

infection with the same agent. Similarly, Cournand (1930), and Marburg (1942), believe that they are identical diseases. Adie (1929) was of the opinion that "disseminated sclerosis is probably due to a virus belonging to the same group as those that cause diffuse and disseminated encephalitis....." In connection with another similar demyelinating disease, Brain (1929) considered that the difference between disseminated sclerosis and neuromyelitis optica might lie not in the virus but in the degree of immunity evoked in the host.

It is suggested that this patient was indeed suffering from disseminated sclerosis and that an intense immunity reaction was evoked as a result of which the patient recovered and is well 20 years later. It is worthy of note that recovery coincided with the treatment already referred to, the abdominal reflexes returning within 3 weeks of commencing protein shock and arsenic.

(3) The third possibility is that a condition approaching allergic equilibrium may ensue. In this state, a balance obtains between the antigen and the circulating antibodies. When this balance is equipoised, disseminated sclerosis is spoken of as being in a stage of remission, whilst upset of the balance by exogenous or endogenous factors, results in an exacerbation of the disease process. It is believed that treatment can stimulate the production of circulating

antibodies and thus assist in achieving allergic equilibrium. One means of doing this is by administering T.A.B. vaccine intravenously. MacKenzie and Fruehbauer (1927), demonstrated that rabbits sensitised to egg white after a while show no trace of circulating antibodies to egg white. These will, however, immediately reappear after the injection of a typhoid vaccine. This is an example of a specifically conditioned organism being stimulated by non-specific influences to produce specific antibodies (Urbach and Gottlieb, 1946). With regard to human disease, it is suggested that the following case of disseminated sclerosis exemplifies this concept:-

Case 10/M/43 Male aged 32.
Following a 6 weeks history of hesitancy of micturition later accompanied by weakness of left arm and leg, this patient was diagnosed on clinical and serological grounds in June 1943, as a case of disseminated sclerosis. The colloidal gold test furnished a paretic curve. The Wassermann reaction was negative in blood and cerebrospinal fluid. He was treated with a course of protein shock and organic arsenic. Symptomatic improvement was accompanied by progressive flattening of the colloidal gold curve. In September 1943, the colloidal gold test was reported as being negative. This remission was maintained until November 1946, when he experienced transient dimness of vision in one eye during an attack of "influenza". This was followed by paraesthesia affecting both feet. He was readmitted to hospital in January 1947. The colloidal gold test gave a strong first zone precipitation (4444321000). He was treated with a course of T.A.B. intravenously. Symptomatic improvement again ensued and in February 1947, the colloidal gold curve was 1111000000. In March 1947 a further slight exacerbation responded rapidly to two protein shocks. In September 1947, a similar response was achieved after one shock. The patient has since remained well.

Two criticisms can be directed against the hypothesis formulated in connection with the above case. The one being that spontaneous alterations in the colloidal gold reaction occur; the other that the patient's symptoms were largely psychogenic and that they responded to the powerful "persuasion" of protein shock therapy. Although such criticism is well founded, it is felt that the combination of symptomatic and serological improvement is not without significance. Future investigations may show that protein shock, by stimulating antibody production, is of service in initiating remissions in disseminated sclerosis.

In concluding this section, it must be emphasised that this concept of the disease process in disseminated sclerosis is purely hypothetical. The theory would seem, however, to fit the known facts. Further evidence compatible with this infective-allergic process will be adduced in later sections.

3. The Causative Agent.

In this section the work done by the author and his colleagues in attempting to establish the nature of the causative agent will be reviewed. The infective nature of the disease is adhered to.

(a) The Relationship between Disseminated Sclerosis and Rural Exposure. Recent literature emphasises the possible relationship between disseminated sclerosis and agricultural exposure. In particular, sheep have been implicated. (Campbell and his associates

1947; Lhermitte 1947; Dean 1949; Shield 1947). Articles to this effect, however, have been published for well over a quarter of a century. (Morawitz 1904; Steiner 1918; Dreyfus 1921; Adams 1923 and 1927; Wilson 1927). Reference to this aspect has been made in the textbooks of Kinnier Wilson (1940) and of Boyd (1944).

The working hypothesis was formulated that infection with the causative agent of disseminated sclerosis is influenced by rural or agricultural exposure. It is obvious that if this view should prove correct the field of search for the infective agent would be materially reduced.

The first step designed to test this hypothesis was a study of the occupational incidence of disseminated sclerosis. Table 1 records the occupations in 173 male cases of the disease. It would appear that occupation plays no significant role in the aetiology of disseminated sclerosis. This view coincides with that of Bramwell (1917)(1), Brain (1930) and (1947), Adie (1932), Wilson (1940), McAlpine (1946), and Walshe (1947). In contrast to the occupational incidence we have been impressed by the fact that a history of exposure to rural conditions is an almost constant finding in cases of disseminated sclerosis seen by us. From Table 2 it will be observed that many patients have lived in the country, and further, that the majority have at one time or another been in the country. A note of caution must be struck in connection with the statistical evaluation of occupational incidence and

exposure to rural conditions. For example, we have found that the occupation of a patient has not always been that which he is following at the time of seeking treatment for disseminated sclerosis. Again, a short holiday in the country, perhaps several years previously, may be readily forgotten by a patient. We would, therefore, suggest that occupation is significant only in so far as it brings a person into contact with conditions obtaining in country districts. Exposure to rural conditions, rather than agricultural employment or rural residence, is necessary for exposure to the causative agent of the disease. Such a hypothesis, however, demands an explanation of the fact that more people do not develop disseminated sclerosis since the vast majority of the population have at sometime been exposed to conditions obtaining in country districts. We would suggest that the explanation may lie in one or more of the following:-

1. Only certain districts may harbour the causative agent. It is well known that disseminated sclerosis has a clearly defined geographical incidence. (Bing, 1932, Sallstrom, 1942). We further believe that disseminated sclerosis has, in a given country, a district incidence. Thus Bing found the incidence in North Switzerland to be four times as great as in South Switzerland. Similarly the high incidence of the disease in the region of the great lakes of North America is well known. In England, Wilson (1927), in a statistical study found that the death rate was much higher

in some counties compared with others. We are of the opinion that in Scotland, disseminated sclerosis has a definite district incidence. In some areas the disease is common; in others it is seldom if ever encountered. It has not yet been found possible to undertake an accurate investigation on this subject. I believe, however, that this will prove a helpful and interesting study. As an example, it may be mentioned that whereas in Caithness the disease is uncommon, in Ayrshire it is frequently encountered. Similarly I have learned that in 25 years, only two cases of disseminated sclerosis have occurred in a practice embracing Loch Lomondside and the Drymen district, whilst in a Peebles practice the disease is prevalent. On this subject, Gray (1947), has informed me that of seven cases of disseminated sclerosis occurring in a practice, five of them came from one small district. To the best of my knowledge none of these cases is genetically related.

2. Andrews (1948), points out that no mere contact of virus and host is enough to produce overt infection. He considers that many virus infections may normally be subclinical or latent. It has already been suggested that in some instances infection with the causative agent of disseminated sclerosis may be

compatible with perfect health and a normal life whilst in others, subsequent to the initial manifestation, the disease may be asymptomatic.

3. Following on this, the development of clinical disseminated sclerosis may depend on personal susceptibility, predisposing factors, or exposure to an overwhelming infection. Although lacking statistical proof, it was felt that the evidence available warranted the investigation being carried a stage further. This embraced a consideration of factors peculiar to rural districts which might be responsible for harbouring, transmitting, or predisposing to infection with the infective agent.

Burnet (1945), has suggested that most of the obvious virus diseases of man are of relatively recent origin and that they are originally contracted from some animal. Although we would hesitate at this stage to implicate a virus as the causative agent of disseminated sclerosis, it would appear reasonable to suppose that this disease is caused by some closely allied organism. We have, therefore, proceeded on the assumption that an animal, or animals, might prove to be the natural reservoir of the disease. Sheep and cattle, being essentially peculiar to rural areas, were considered first.

A questionnaire was sent to 79 hospital cases of disseminated sclerosis, regarding their association with sheep or cattle. Twenty-one patients failed to reply. Of the remaining 58, 25 cases

admitted to association with sheep or cattle or both. In 33 instances a negative reply to this question was obtained. Statistically this result is inconclusive and the large percentage of cases which failed to reply render the investigation inadequate. Such an inconclusive and inadequate statistical investigation was not, however, permitted to negative clinical impressions resulting from experience with cases such as the examples given below. It must be stressed that the following cases are only representative of numerous similar ones.

Case 66/F/20 Female aged 33.
Always lived in the country and married a farmer. 15 years previous to examination she suffered from retrobulbar neuritis in one eye. After a short interval, the second eye became similarly affected. A 14 year remission was broken by the onset of weakness of both legs followed by defective bladder control and tremor of arms. Clinical examination divulged the presence of scattered lesions in the C.N.S. The case was considered to be one of disseminated sclerosis.

Case 62/F/30 Female aged 38 years.
One year after a holiday spent on a dairy farm the patient complained of loss of power in her legs. This was followed 3 years later by diplopia and severe vertigo. On examination there was evidence of pyramidal tract, posterior column and cerebellar lesions. It is interesting to note that this patient attributed her illness to farm residence. The diagnosis was disseminated sclerosis.

Case 54/M/30 Male aged 42.
This was an advanced case of disseminated sclerosis. Until three years prior to the onset of the disease, he had lived on a farm in Ireland, in which horses and cows predominated. Trauma to the back resulting from a fall appears to have been a precipitating factor in this case.

Case 55/M/30 Male aged 27.
Nine months prior to onset of disease he had spent one month on holiday on a croft. Five months later a severe fall was followed immediately by weakness in both legs. This was later accompanied by precipitancy and incontinence of urine.

On examination he was found to have a bilateral extensor plantar response, absent abdominal reflexes, defective posterior column function and pallor of the temporal half of the right disc. The diagnosis of disseminated sclerosis was made on these findings.

Case 57/M/30 Male aged 29.
This patient was found to be suffering from retrobulbar neuritis of unknown aetiology. Objectively, no sign of deranged function of the nervous system was elicited except a slight degree of ataxia when performing the finger to nose test. His vacations were always spent on a mixed farm. This was considered to be a case of retrobulbar neuritis due to the causal agent of disseminated sclerosis.

Case 40/F/40 Female aged 27.
One month before examination, whilst living on a cattle farm the patient developed a febrile illness. This was accompanied by weakness and stiffness of the left leg which has persisted since this time. Clinical and serological examination was compatible with the diagnosis of disseminated sclerosis.

Case 27/M/40 Male aged 31.
Seven years previously this patient, a sheep farmer, suffered from retrobulbar neuritis affecting his left eye. Subsequently his right leg became weak, and bouts of paraesthesiae in legs have been experienced. Evidence of organic pyramidal tract damage was detected on clinical examination. This finding associated with the history of retrobulbar neuritis was compatible with a diagnosis of disseminated sclerosis.

It was therefore a clinical impression, supported by a study of the literature and not disproved by statistical investigation, which rendered desirable an investigation into certain diseases of sheep and cattle.

(b) Diseases of Sheep. The diseases of sheep considered in this connection were louping ill, scrapie and swayback.

Louping ill. is a virus disease affecting principally sheep. The disease is transmitted to this animal by the sheep tick - Ixodes

ricinus - in both its nymphal and adult forms. In the sheep, infection with the virus results in a meningo encephalitis. It is interesting to note that the pathology of the experimentally produced illness varies in the sheep, pig and mouse, and that in the naturally acquired disease, great variations in the intensity of lesions occur. Gordon (1934) reported the comparative aspects of louping ill in sheep and poliomyelitis in man. He pointed out the apparent anomaly that a bloodsucking arachnid has the role of transmitting a neurotrophic virus. This is explained by the fact that the virus multiplies in the blood stream before invading the central nervous system. MacLeod and Gordon (1932), have observed that in the absence of an independent febrile illness (tick borne fever - Gordon, Brownlee, Wilson and MacLeod, 1932) the typical nervous symptoms of louping ill are unlikely to develop.

The virus of louping ill can infect humans. In them it produces a clinical picture resembling tuberculous meningitis or encephalitis, with recovery, (Rivers and Schwentker, 1934). More recently, Davison, Neulbauer and Hurst (1948), and Lawson and his associates (1949), have reported cases of meningo-encephalitis in man due to this cause. It was, therefore, unlikely that the virus of louping ill could be directly implicated in connection with the aetiology of disseminated sclerosis. In the course of the present work, it has been learned that human infection with louping ill in veterinary laboratory workers is not uncommon. The manifestations vary greatly in severity and this disease may account for some

unexplained pyrexial illnesses in agricultural workers whose occupations expose them to being bitten by the sheep tick.

Scrapie was investigated in collaboration with veterinary colleagues. This virus disease of sheep is characterised pathologically by vacuolation of nerve cells in the medulla, pons, midbrain and spinal column (Brownlee, 1940; Holman and Pattison 1943). It has been described as a subacute polio-myelo-encephalitis. The clinical aspects of scrapie, as described by Greig (1940), have several points in common with disseminated sclerosis. Thus in scrapie the infection may remain latent for prolonged periods. There is a marked geographical and breed incidence. In many instances pregnancy and parturition have been known to precipitate the manifestations of the disease. With regard to symptomatology, paralysis of limbs, disturbance of sphincter control, and changes of temperament are common to both diseases. The pruritis which occurs in scrapie where there is no skin lesion may be analagous to the paraesthesiae so commonly complained of in disseminated sclerosis. Lange's colloidal gold test has been performed on the cerebrospinal fluid of seven sheep suffering from scrapie, and thirteen normal sheep. In the cerebrospinal fluid of the scrapie cases, precipitation of the gold sol occurred, and was found to be maximal with cerebrospinal fluid dilutions of 1/40, 1/80 and 1/160. In one case, light blue ("4") precipitation was obtained; in two, blue ("3") precipitation occurred; in the remaining four fluids the maximum degree of precipitation was lilac ("2"). The curve obtained tends

to be midzone in type.

Examples:- (1) 1123432000 - 0

(2) 1133211000 - 0

(3) 1233210000 - 0

(4) 1233210000 - 0

In the control series of thirteen normal sheep, the colloidal gold results differed considerably from the above. In nine of these fluids, the gold sol was not precipitated beyond the degree dark red ("1"). In the remainder, lilac ("2") was the maximum degree of precipitation, and in three of these only one tube (Tube 3 - cerebrospinal fluid dilution 1/40) was so affected. In no instance, therefore, did a normal cerebrospinal fluid cause precipitation of the gold sol beyond the degree lilac ("2"). Although no conclusion of significance can be drawn from this investigation, it is of interest to note that an organic nervous disease of sheep, due to a virus, has certain clinical and serological similarities to disseminated sclerosis in man. The pathological changes would appear to be quite distinct. We would emphasise, however, that as stressed by Blacklock (1923), the same known infective agent may produce different types of pathological change in animals of different species. This is well exemplified by the virus of louping ill, which, as already mentioned, occasions a different pathological picture in the sheep, pig and the mouse.

Swayback. The report by Campbell and his associates (1947), on the incidence of disseminated sclerosis in research workers on

swayback in sheep has focussed attention on this disease. Swayback is a disease of young lambs and is characterised by diffuse, symmetrical demyelination of the cerebrum with secondary degeneration of the motor tracts. Its resemblance to Schilder's disease in man was the subject of a paper by Innes and Shearer (1940). The disease has not been transmitted experimentally. It is related in some way to defective mineral metabolism. In particular, copper has been implicated and although this trace element does not appear to be deficient in the pastures, its administration to the pregnant ewe prevents the appearance of swayback in the lamb.

Trace elements may be classified into those which are essential for the maintenance of health, e.g. iodine, copper, cobalt and manganese; and secondly, toxic trace elements, e.g. fluorine and molybdenum. These, by appearing in soils, pastures or drinking water, may damage plant or animal life. It does not follow, however, that if an essential element is present in the soil it is necessarily available to plants and animals. For example, it is known that manganese exists in the soil in at least two forms of which only one is available. The cause of swayback is unknown. It is possible that it is due to an infective agent conditioned by a relative or absolute deficiency in available copper. Some toxic element may be present in the soil which can compete with copper in plant or animal metabolism. With regard to disseminated sclerosis, Mandelbrote and his co-workers (1948) discovered no change in the blood and liver

copper levels in disseminated sclerosis, as compared with normal individuals.

(c) The Inoculation of Sheep. As mentioned in a recent paper (Adams and Sutherland, 1948) a logical approach to the problem would appear to lie in attempting to produce a known pathology in sheep by inoculating them with material from a suitable case of disseminated sclerosis. This reverse experiment was also mentioned by Campbell and by McLusky in a discussion on the association between swayback and disseminated sclerosis (Proceedings of the Association of Physicians of Great Britain and Ireland, 1947). If a known pathological picture could be produced in sheep subsequent to inoculating them with disseminated sclerosis material, and if this disease could be transferred from sheep to sheep, the net round the infective agent of disseminated sclerosis would indeed be drawn closer. The discovery of the nature of the invader, its culture, the further inoculation of animals and further culture, would then be indicated. Remaining, however, would be the important questions of the mode of transmission of the disease to humans, the prevention of this, and the evolution of specific therapy.

In collaboration with Dr. D.R.Wilson of the Animal Diseases Research Association, Moredun Institute, Edinburgh, inoculation of sheep with blood and cerebrospinal fluid from cases of disseminated sclerosis was performed. A full account of this

will be published jointly in the future. The experiment will now be briefly reported.

The Cases of disseminated sclerosis chosen: Because of the belief that in established cases of disseminated sclerosis immunity reactions destroy large numbers of the infecting microorganisms, it was decided to utilise early cases of the disease. It was considered that only in such cases would the causal agent be present in significant numbers. I am pleased to acknowledge the co-operation of Dr. Douglas K. Adams, Dr. J.B.Gaylor and Dr. J.Dixon who furnished me with three cases suitable for this purpose. These cases diagnosed on clinical and serological grounds as suffering from early disseminated sclerosis are now described:-

S.M.Female aged 40, Victoria Infirmary:
Dimness of vision in the right eye was experienced in 1947. This was of sudden onset and persisted for several days. She subsequently remained well until seven days previous to present examination, when she became incontinent of urine. This was associated with frequency of micturition and was later accompanied by paraesthesiae, weakness of legs, and tremor of the left arm. Clinical examination disclosed the presence of signs referable to dysfunction of both pyramidal tracts, both dorsal columns and the left lobe of the cerebellum. On ophthalmoscopic examination the temporal half of the right optic disc showed a pathological degree of pallor.

Lumbar puncture; a clear fluid was obtained under an average pressure. There was no evidence of block in the subarachnoid space. Six lymphocytes were present per c.mm. The protein content was reported as being 43 mg %; the chlorides 707 mg %; the sugar 43 mg %. The colloidal gold test furnished the following curve:- 1333300000. The Wassermann reactions of the blood and cerebrospinal fluid were negative.

H.B. Female aged 24, Victoria Infirmary:
Three weeks before admission the patient experienced double vision. This was followed by vertigo, and one week before admission she complained that the left side of her face felt "dead".

On examination there was a slight degree of bilateral external strabismus. Horizontal and vertical nystagmus was elicited, and tests of cerebellar function were inadequately performed on each side. The abdominal reflexes were not elicited and both plantar responses were strongly extensor. The knee jerks were overactive and unequal. No sensory loss was detected. The patient was facile, euphoric and emotional.

Examination of the cerebrospinal fluid furnished the following findings: the fluid was obtained under average pressure and there was no evidence of spinal block. Cells, 2 cmm; protein, 42 mg %; chlorides, 765 mg %; sugar, 51 mg %. The colloidal gold and Wassermann reactions were negative. The Wassermann reaction of the blood was also negative.

T.K. Male, aged 27, Western Infirmary:
Was admitted from Dr. J.B.Gaylor's neurological clinic as a case of disseminated sclerosis. He complained of weakness in both arms and impaired sensation in the right hand, of 3 weeks' duration. He further stated that his right leg became readily fatigued on walking. A history of loss of vision in his left eye one year previously was obtained. This was of sudden onset, and after persisting for some four weeks the sight gradually returned. This patient's mother came from a farming family and he himself had spent many holidays on farms. He had also been billeted on a farm in Ireland whilst serving in the R.A.F.

Examination disclosed no abnormality of cranial nerves. The pupils were unequal and the optic fundi appeared normal. Bilateral intention tremor and horizontal nystagmus were elicited. The knee jerks were overactive and unequal, the right being more active than the left. The abdominal reflexes were readily exhausted on each side. The right plantar response was extensor, the left flexor. Slight impairment of dorsal column function was found in both arms and legs.

X-ray examination of skull, spine and chest revealed no abnormal features.

The cerebrospinal fluid obtained on lumbar puncture was clear and under average pressure. Queckenstedt's test revealed no evidence of spinal block. The cell count was 7 lymphocytes per cmm. No increase in protein

was detected by either Pandy's or Ross Jones' tests. The colloidal gold test furnished the following curve - 2233110000. The Wassermann reaction was negative in both blood and cerebrospinal fluid.

The Technique of Inoculation. This was discussed with my co-worker, Dr. D.R.Wilson, of the Moredun Institute, Edinburgh. The advice of Professor Carl Browning of the Westerm Infirmary, Glasgow, of Professor J. Blacklock then of the Royal Infirmary, Glasgow, of Dr. D.K.Adams, Western Infirmary, and of Dr. Kyles, Western Infirmary was sought and freely given. I am indebted to these authorities for their co-operation.

As a result of these discussions and from a study of the literature, it was decided:-

(1) to inoculate sheep with blood and cerebrospinal fluid from the three cases of disseminated sclerosis;

(2) to inoculate the animals intracerebrally and also into the sciatic nerve.

Intracerebral inoculation was desirable as a means of bringing the causal agent into direct contact with the tissues of the central nervous system. Further, it seemed that such a technique would reduce the incubation period to a minimum. The monkey inoculated intracerebrally by Steiner (1919), however, showed no symptoms for eleven months after inoculation, when it developed transient paresis in the lower limbs.

Inoculation into the sciatic nerve was advised by Professor Blacklock. Margulis, Soloviev and Shubladze (1946) found

inoculation into the sciatic nerve successful in transmitting acute disseminated encephalomyelitis to rabbits.

The Sheep. A number of lambs were procured by Dr. Wilson of the Moredun Institute. They appeared to be in every way normal and healthy. The cerebrospinal fluid from six specimen lambs was examined with negative results. In particular, the colloidal gold reaction was normal. In no case did precipitation beyond the degree dark red ("1") occur. It was decided to inoculate six of these sheep and retain a further two as controls.

Collection of Blood and Cerebrospinal Fluid. Blood was obtained by venepuncture and cerebrospinal fluid by lumbar puncture from the three cases of disseminated sclerosis. A scrupulously aseptic technique was employed, and the blood and fluid were withdrawn into containers which had previously been autoclaved. These containers were immediately sealed by heat.

Heparin was chosen as the most satisfactory anti-coagulant for this purpose. "Liquemin" (Roche) was employed, 0.2c.c. of this preparation being used for every 5 c.c. of blood withdrawn.

Approximately 15 c.c. of blood and 15 c.c. of cerebrospinal fluid was obtained from each of the three cases of disseminated sclerosis. These specimens were divided into two equal parts, thus making a total of twelve samples. Three samples of blood and three of cerebrospinal fluid were placed in a container at 0°c, and the other six in a container at 37° c. This precaution was taken because of the uncertainty as to the optimum temperature

at which the potential infective agent in the blood and cerebrospinal fluid should be transported to Edinburgh.

Immediately after the last withdrawal, the specimens of blood and cerebrospinal fluid were taken by road to the Moredun Institute, Edinburgh. There the specimens at 0°c were slowly thawed to blood temperature. The six samples of blood were then intermixed, as were the six samples of cerebrospinal fluid.

The Inoculation. On 24th November, 1948, some three hours after withdrawal, six lambs were inoculated with blood or cerebrospinal fluid from the three cases of disseminated sclerosis. A further two lambs were used as controls. The inoculations were performed by Dr. D.R.Wilson, assisted by his staff. Pentothal anaesthesia was employed.

Three sheep were inoculated with the mixture of cerebrospinal fluids, 1 c.c. being injected intracerebrally, and 0.2 c.c. into the sciatic nerve. In two animals the mixture of bloods was inoculated intracerebrally and into the sciatic nerve, using the same amounts as for the cerebrospinal fluid. The remaining lamb was inoculated with 1 c.c. of blood intracerebrally only.

The eight sheep were thereafter carefully segregated from all other animals. Those inoculated showed no immediate ill effects apart from some lameness due to the operation wound performed to expose the sciatic nerve. This soon wore off.

Follow-up Investigation. Some four months subsequent to inoculation (7th April 1949), cysternal puncture was performed by

Dr. Wilson on the eight sheep. The colloidal gold test was performed on the cerebrospinal fluids so obtained. Precipitation of the gold sol exceeded dark red ("1") in only one instance, viz:- 1122000000. The result of the colloidal gold test on this sheep prior to inoculation was 1110000000. The results so obtained must therefore be regarded as being negative.

Following cysternal puncture, which was performed under pentothal anaesthesia, one lamb was accidentally suffocated. The brain and spinal cord were carefully removed from this animal for histological examination. Sections were prepared from the cerebrum, cerebellum, medulla and cord. These were stained by haemalum and eosin, and by Weigert's method. In addition Gram stains were performed. The appearances were those of a meningo-encephalitis. The lesions predominated in the cerebrum but were also present in medulla, cerebellum and cord. Marked vascular cuffing was seen. The cells taking part in this were both lymphocytes and polymorphonuclears. Gram stain disclosed no pyogenic microorganisms, and no spirochaetes were seen on appropriate examination. The sections stained by Weigert's method failed to reveal any evidence of demyelination. The picture was thus one of inflammation of meninges and nervous tissue of subacute type.

Of the six sheep inoculated, only three are now alive. One animal was killed on 18th November, 1949, and another on 3rd December, 1949. In both instances the general condition of

the sheep deteriorated without any apparent cause. They were humanely destroyed at the onset of what would have proved to have been terminal pneumonia. In neither case was there evidence of paresis or of other involvement of the central nervous system. The brain and cord of each animal was removed and subjected to histological examination which, however, failed to reveal any notable abnormality. The two control sheep and the remaining three inoculated ones are at present in good health. Micro-photographs which demonstrate the histological picture obtained will be found in the appendix.

In only one instance, therefore, were significant changes found in the nervous system of the three inoculated sheep which died. In this instance no known pathology was reproduced. It must be appreciated, however, that only serial sections could absolutely exclude pathological changes, and isolated lesions in the central nervous system of the inoculated animals could be overlooked by the methods of examination at our disposal.

(d) Disease of Cattle - Brucellosis. It was observed that a considerable number of patients suffering from disseminated sclerosis who were farmers, denied having had any association with sheep. They were cattle or dairy farmers. Almost invariably a history was obtained of epidemic abortion among their stock. The following case exemplifies this:-

R.M.Male aged 46.
This cattle and dairy farmer had never worked with sheep. His stock suffered severely from epidemic

abortion in 1929 and 1934.

in 1930 he observed that he was losing the hair from his right leg and subsequently from his left leg. Eleven years later, in 1941, his left leg became weak and stiff. Later his right leg became similarly affected to a lesser degree. In 1947, paraesthesiae was experienced in his left hand and in both lower limbs. In 1948 hesitancy of micturition developed.

Clinical examination revealed a spastic paraplegia with bilateral extensor plantar responses. The knee jerks were exaggerated and the abdominal reflexes were not elicited. Vibration sense was greatly diminished in both legs. Cerebellar tests were not performed efficiently with the left arm. The Wassermann reaction of the blood and cerebrospinal fluid was negative. Fractional test meal disclosed the presence of free hydrochloric acid. The colloidal gold test resulted in a low first zone curve.

The case was considered to be one of disseminated sclerosis.

It is, however, not surprising that cattle farmers should give a history of contagious abortion in their animals. Such a history would probably be obtained from the majority of cattle or dairy farmers in this country, as the average percentage of cows infected with the causal agent of contagious abortion is not less than 20%, and probably nearer 30%. (Stableforth 1934). The incidence of the disease, according to this author appears to be increasing.

Other factors, however, which rendered an investigation into disease of cattle desirable were:-

(1) cattle constitute one of the factors which were considered to be essentially peculiar to rural areas.

(2) A small and admittedly uncontrolled investigation was undertaken into the relative incidence of disseminated sclerosis and certain disease of sheep in the Isle of Islay. Of the three diseases of sheep under consideration it would appear that only louping ill occurs on the island. Swayback and scrapie are unknown. Several cases of disseminated sclerosis whose homes are in Islay have been examined, and it would appear that, whilst not extremely prevalent, the disease is by no means unknown in this locality. I have subsequently learned that epidemic abortion in cattle is very widespread in Islay (Hepburn, 1949), and that several cases of undulant fever have been diagnosed in humans.

(3) In certain countries such as Denmark, disseminated sclerosis is prevalent. The sheep population is small in Denmark, dairy and cattle farming being the main form of husbandry in the rural areas.

For these reasons it was considered desirable to consider the disease of cattle known as epidemic abortion (contagious abortion, Bang's disease), from the point of view of a possible relationship to disseminated sclerosis.

Approximately 85% to 90% of abortions in cattle are of the epidemic or contagious variety (Fitch & Boyd, 1940; Stableforth 1934).

The causative agent of this disease is the Brucella abortus which, as already mentioned, infects some 20% - 30% of cows in this country. It has long been recognised that Brucella abortus is often present in the milk drawn from apparently healthy cows (Schroeder & Cotton, 1916; Cooledge, 1916).

Three varieties of Brucella exist, the bovine type (Br. abortus), the caprine type (Br. melitensis), and the porcine type (Br. suis). These varieties are morphologically and in most biological respects indistinguishable. The brucella microorganisms are short gram negative cocco-bacilli. They have a considerable viability outside the body, and their presence in pastures, dust, dung etc., has been repeatedly noted. Br. melitensis can be cultured reasonably readily under ordinary conditions and is found in blood culture in a high percentage of cases. On the other hand, Br. abortus is difficult to grow, and when first isolated will only do so in an atmosphere containing some 10% of carbon dioxide. This accounts for the infrequency with which this strain has been isolated from the blood (Dible and Davie, 1939). All strains grow best on blood, or preferably liver, agar. The brucella micro-organisms are killed by pasteurisation.

Brucellosis, as already indicated, may affect cattle, goats and swine. In these animals abortion is the main manifestation of the disease. Sheep may be affected by Br. abortus, but the prevalence appears to be unknown (Fitch and Boyd, 1940).

The horse is probably more susceptible to Br. abortus than the sheep. In the former the structures principally affected are muscles, joints and tendons, whilst in the sheep abortion is the usual outcome. Taylor (1939) examined sera from 957 apparently healthy horses for agglutinins to Br. abortus. Agglutinins were detected in 188 horses (19.6%) in a serum dilution of 1 : 10, in 21 (2.1%) in a dilution of 1:20, and in 19 (1.9%) in a dilution of 1:40 or more. Thus, as in the cow, and possibly other animals, infection with Br. abortus in the horse may be unaccompanied by clinical signs.

Treatment of epidemic abortion is, in the main, prophylactic. This is accomplished by inoculation of the young cow with the live microorganisms. Dead vaccines have unfortunately proved unreliable. It is claimed however, that the strain at present used, of American origin, is avirulent. Despite the lack of virulence it evokes the production of antibodies against virulent strains of Br. abortus. Previous to the use of this strain, although the inoculated cattle were protected from epidemic abortion, the virulent organisms in many instances were subsequently excreted in the milk of the cow.

Infection with the Brucella group of microorganisms in man results typically in undulant fever. This illness is characterised by alternating pyrexial and apyrexial phases, associated with severe sweats, and commonly with arthritis and bronchitis. Not infrequently symptoms referable to the nervous

system occur (Harries & Mitman, 1940). It is widely recognised, however, that Brucella infection may occur in so mild a form as to produce no clinical evidence. Thus Fitch and Boyd (1940) records that 0.5 - 2% of the population have brucella agglutinins in the blood. In a population receiving unpasteurised milk, or in individuals who have been on an intensive milk diet, this percentage rises to between 5% and 10% (Dible & Davie, 1939).

Humans are susceptible to infection by the three varieties of Brucella in varying degree. Thus Elder (1946), observes that man is very susceptible to melitensis infection, and that Br. suis is more pathogenic for man than Br. abortus. Infection may occur by drinking infected milk or handling infected meat (Fitch and Boyd 1940). There is evidence that in animals, infection may occur via the conjunctivae or through the broken or intact skin (Stableforth 1934). Dible & Davie (1939) state that occasionally the infection may be transmitted by biting insects.

With special reference to the neurological manifestations of brucellosis in the human subject, infection with Br. abortus may cause depression, irritability, delirium, neuralgia and neuritis (Harries and Mitman, 1940). Brain (1947), observes that meningitis and myelitis may result from infection with this microorganism. The occurrence of transient sensory and motor disturbances in 10 cases of brucellosis is recorded by Roger (1931), and Beriel, Barbier and Lambert (1932) refer to disseminated sclerosis occurring during the course of a case of brucella

infection. Roger, Paillas and Marcorelles (1941), reported a case of neuromyelitis optica in which there was a brucella agglutination titre of 1:800 in the cerebrospinal fluid. A similar association was previously reported by McCullagh and Clodfelter (1937). In a series of 10 patients with chronic brucellosis, Apter, Halstead, Essele and McCullough (1948) found evidence of organic brain damage in 7, and in one of these cases definite neurological signs were present. It is interesting to note that one of Dean's (1948) "doubtful cases" of disseminated sclerosis was described as "a case of focal demyelination following brucellosis".

The incidence of symptoms referable to disease of the nervous system in a series of 560 cases of chronic brucellosis was the subject of a study by Kyger and Haden (1948). They found that 28 of these cases displayed definite sensory and motor changes, or lesions of the 2nd, 6th or 8th cranial nerves. In two further cases the fully developed picture of disseminated sclerosis was present. As a result of this study these authors formulated the hypothesis that disseminated sclerosis might be a central nervous system manifestation of chronic brucellosis. This theory was tested in 118 cases of disseminated sclerosis by performing skin tests, and blood agglutination reactions, for brucella infection. Compared with a control series of 98 cases, they found a high degree of cutaneous reactivity to brucella antigen in the 118 cases of disseminated sclerosis. These workers concluded that the

pathological features and geographical incidence of disseminated sclerosis and brucellosis were not incompatible with some relationship.

This brief survey indicates that:-

(1) Brucellosis in man may be associated with evidence of organic nervous disease.

(2) The lesions may occur in the coverings of the nervous system, and in the nervous system itself they may be central or peripheral.

(3) The clinical picture may be that of disseminated sclerosis or of a closely allied condition.

As a result, it was decided to investigate the possible relationship between disseminated sclerosis and brucellosis in Scotland. The cutaneous reactivity of a series of disseminated sclerosis patients to brucellin is at present being assessed. Brucellin is an antigen prepared from Br. abortus and Br. melitensis. In addition agglutination reactions against Br. abortus and Br. melitensis are performed using blood and cerebrospinal fluid obtained from these cases. A control series was subjected to similar investigations. This series was sub-divided into:-

(1) Patients who consumed 1 pint or more of milk per day. These were generally peptic ulcer cases.

(2) Cases with a neurological disease other than disseminated sclerosis.

(3) Country dwellers suffering from miscellaneous diseases, other than disseminated sclerosis.

Apart from investigating a relationship which might exist between disseminated sclerosis and brucellosis, it is hoped that further light might be thrown on both the neurological manifestations of brucella infection, and also the incidence of subclinical brucella infection in the West of Scotland. If the results obtained from this investigation in Scotland should prove to be not dissimilar from those reported by Kyger and Haden (1948), in America, their conclusion that some relationship may exist between disseminated sclerosis and brucellosis would be strengthened, and would point the way to future studies. Such a relationship would explain:-

(1) The rural incidence of disseminated sclerosis. Milk injested in rural areas is generally not pasteurised. Further, cutaneous infection or infection from biting insects would be more likely to occur.

(2) The occurrence of disseminated sclerosis in patients who give no history of rural association. Infection under these circumstances is most likely to result from drinking non-pasteurised milk.

(3) The influenzal illness which frequently ushers in disseminated sclerosis would be ascribed to a pyrexial phase of undulant fever.

On completion this investigation will be the subject of a joint report. The results so far indicate that positive brucellin skin tests occur more frequently in cases of disseminated sclerosis than in other neurological conditions. On the other hand,

agglutination reactions have not been more frequently positive in the blood and cerebrospinal fluid of disseminated sclerosis cases in comparison with the control series. It is suggested, however, that certain cases clinically indistinguishable from disseminated sclerosis may be due to brucellosis. It is not yet possible to say whether or not the serology of the two conditions is also identical.

(e) Equine Encephalomyelitis. Equine encephalomyelitis came under consideration but it was not found possible to undertake any investigation on this subject. The disease is caused by a virus which evokes in the horse, calf, sheep and dog an intense encephalomyelitis. The histological picture produced is that of degeneration of nerve cells, cellular infiltrations, with early microglial proliferation, and perivascular cuffing with polymorphonuclear and mononuclear cells in varying proportions. The lesions are widespread but are most marked in the cerebral cortex, thalamus and hypothalamus. Meningeal infiltration occurs secondary. (Hurst, 1934).

It is of some interest to note, in view of the histological picture described in connection with the sheep inoculated with disseminated sclerosis material, that this virus disease of the nervous system is associated with perivascular cuffing with polymorphonuclear cells. Other neurotrophic virus diseases, which show polymorphonuclear infiltrations, are anterior poliomyelitis and louping ill. The proportion of polymorphonuclear leucocytes present

in comparison with the numbers of lymphocytes or plasma cells, is probably indicative of the acute nature of the process.

(f) The Mode of Transmission of the Causative Agent. In commenting on the mode of transmission of disseminated sclerosis to the individual, mention has already been made of the possibility of cutaneous entry. In this connection Steiner (1918), implicated a tick. Horan and his associates (1944), reporting a case of encephalomyelitis, associated with an infected laceration of a finger, consider that the causative agent entered by the skin.

The following case of fulminating disseminated sclerosis or encephalomyelitis also exemplifies the possibility of cutaneous entry, and is a further example that infection may occur through the agency of a vector:-

> A.E.Male, aged 27.
> This patient gave a history of being bitten by an insect on the right side of his neck, when in North Africa. Within a short period of time he was admitted to hospital and diagnosed as encephalitis. On examination many months later he was found to have diplopia associated with paresis of his left arm and leg. In addition there was evidence of eighth nerve involvement.

That an insect may in certain instances be the vector of the causal agent of disseminated sclerosis is also suggested by the following cases:-

> H.P.Male, aged 60.
> In 1920, this patient complained of paraesthesiae affecting his shoulder region. This was followed two years later by weakness of both legs. In 1923 his speech became slurred, his gait ataxic, and his legs progressively weaker. In 1924, he was examined by Dr.D.K.Adams, and diagnosed as a case of disseminated sclerosis.
>
> In 1924, his cat developed paralysis of the hind quarters, and was destroyed. The patient attributed this

disease in the cat to the fact that the animal was in the habit of killing and eating flies which invaded the house from a stable midden in the vicinity.

In view of the fact that at this time Dr. Adams and his collaborators were carrying out their inoculation experiments on rabbits, it is a pity that the destruction of the animal prevented comparative histological studies being made using the cat's central nervous system.

J.J. Female aged 41.
In the summer of 1932, whilst spending a holiday on a sheep farm, this patient received an insect bite on the anterior aspect of the leg. A vesicle developed over the site of the lesion; this eventually discharged a yellow fluid. Some six weeks after this incident, the patient developed double vision. This was of sudden onset and persisted for several days. A remission ensued until 1946, when she complained of paraesthesiae in arms and legs and ataxia on walking. Shortly afterwards she observed that her right hand was tremulous on performing fine movements, and a few weeks later her left foot began to drag. Since this time her condition has progressively deteriorated.

Clinical examination disclosed the presence of a spastic paraplegia. There was in addition evidence of posterior column and cerebellar damage. The left leg showed obvious vasomotor disturbance. The Wassermann reaction of the blood and cerebrospinal fluid was negative. The colloidal gold test furnished the following curve:- 1123210000.

She was therefore diagnosed on clinical and serological grounds as a case of disseminated sclerosis. It will be observed that her illness coincided with a holiday on a sheep farm, and commenced within a few weeks of being bitten by an insect.

4. The Sex Incidence.

In this series of 389 cases of disseminated sclerosis, the sex incidence is in accordance with the views previously expressed

by Wilson (1940), and by Brain (1947), that in this country female cases slightly predominate. Of the 389 cases, 216 (55.5%) were females, and 173 (44.5%) were males. In a series of 200 cases, Bramwell (1917) obtained identical figures, whilst Adie (1932) found the female incidence in a series of 188 cases to be 58%. On the continent of Europe, and elsewhere, the sex incidence in most reported series has been approximately equal or has shown a slight male predominance.

Table 3 demonstrates that the sex incidence has not changed in any significant way over the past 25 years.

5. The Age Incidence.

The age incidence is tabulated in Table 4. The age was calculated from the date of onset of the first symptom. Some 70% of cases occurred in the third and fourth decades of life. In less than 10% of cases did the disease occur under 20 years of age. It is equally uncommon for the first symptom to appear after the age of 45 years.

Male cases were found to predominate at the extremes of the age incidence. With these exceptions more female than male cases occur, the sex incidence, however, being almost equal in the age group 30 - 34 years. These findings are recorded in Table 5 and are also presented in Diagram II.

In view of the fact that the sex incidence of a series would seem to depend on the age groups from which the patients are drawn, it is desirable when reviewing this matter to consider the age and

sex incidence in relation to each other.

Adie (1932) records the age of onset as being in the third or fourth decade in 74.5% of cases, whilst Brain (1947) states that in two thirds of all cases the disease begins between 20 and 40 years of age. These figures approximate closely to those obtained in the present series.

The two youngest cases in the series are briefly reported:-

J. MacM., Male.
This patient suffered from retrobulbar neuritis at the age of eleven years. After a long remission further symptoms developed, and at the age of 31 years he was found to be suffering from fully established disseminated sclerosis.

N.K. Female.
At the age of 14 years this patient experienced paraesthesiae affecting one arm and leg. This was followed by severe dysmenorrhoea, and within 2 years there was clinical evidence of bilateral pyramidal tract lesions and a unilateral third nerve palsy. She was diagnosed on clinical and serological grounds as disseminated sclerosis.

Kinnier Wilson (1940), reviewing 1107 cases from eight series, records the onset of disseminated sclerosis as being below ten years of age in 25 cases (2.2%). Macek (1948), has recently reported the disease occurring in a 7 year old child.

The oldest age of onset in the present series was 59 years. This case is now reported:-

J.K. Female, aged 63.
At 59 years of age this patient developed weakness in both legs. This symptom was accompanied by derangement of bladder control. When she was 62 years the left arm became weak. Clinical examination and serological investigations were compatible with the diagnosis of disseminated sclerosis.

Although relatively uncommon after the age of 45 years, Kinnier Wilson (1940), in the series of 1107 cases, records the onset of disseminated sclerosis as occurring in 47 cases (4.2%) between the ages of 51 and 60 years. In three instances (0.3%) the age at onset of the disease was over 60 years.

The possibility that the age of onset of disseminated sclerosis might be increasing was reviewed. The age incidence in male cases has not materially altered. With regard to the female series there is a slight tendency for the age of onset to increase.

6. Familial Incidence.

In this series the occurrence of the disease in more than one member of a family has been exceptional. This was also the experience of Risien Russell (1911), Bramwell (1917)(1), Adams (1923) and Wilson (1940). On the other hand, Curtius (1933) found more than one case of disseminated sclerosis in 6 out of 56 families investigated. McAlpine (1946) reports a familial incidence of 5% in a series of 143 cases, whilst Brain (1947) considers that some 5 - 10% of cases of disseminated sclerosis have a near relative similarly affected.

Although exceptional, it is apparent that multiple cases of disseminated sclerosis may occur in a family. It is possible that this may be due to hereditary influences. A second possibility however, is that mutual infection or a common environment may be responsible. Ruedin (1939), investigating cases of disseminated

sclerosis in siblings and in twins, considers that the disease is caused by environmental factors. Such a contention is strengthened by the observation of Campbell (1947), who records an outbreak of disseminated sclerosis affecting a number of girls in a certain village. Similarly, I have learned of this illness occurring in three girl friends who were not genetically related. The fact, as already mentioned, that disseminated sclerosis has a certain district incidence also supports the view that environmental factors may be more important than hereditary ones.

The difficulty in assessing the respective importance of these two factors is exemplified by the following case:-

> J.D. Male, aged 22.
> This patient was diagnosed in 1948, on clinical and serological grounds, as suffering from disseminated sclerosis. His occupation was that of farmer. The patient's fater and his uncle, who were also farmers in the same district, had died some time previously from disseminated sclerosis. In addition, a cousin of the patient who lives on an adjoining farm is probably also suffering from this illness.

This series of 4 cases shows common familial and occupational factors. Maier (1947) reports the occurrence of disseminated sclerosis in a mother, son and daughter. These cases, clinically typical, were confirmed by post mortem examination. Such examples of familial disseminated sclerosis do not, however, afford proof that genetic influences play any major role in the etiology of the disease. It is conceivable that environmental factors play at least an equally important part.

7. Predisposing Factors.

In 127 cases (36.5%), one or other of four factors preceded the first symptom of disseminated sclerosis by a short period of time. In no instance did this exceed six months. By so doing they might reasonably be regarded as predisposing to the illness. These factors were febrile illness (14.4%), trauma (10.5%), pregnancy (4.5%), and emotional upset (2.8%).

(a) Infection. A relationship between disseminated sclerosis and infection has been noted by many workers. Head (1920) observed that disseminated sclerosis not unusually begins with short attacks of what is called "influenza". Bramwell (1917)(1), found this relationship in 28 of his 200 cases (14%). Wilson (1940) and McAlpine (1946) suggest 5% as the possible figure. As a transitory febrile illness may be readily forgotten by the patient, the value of statistical evidence on this aspect is problematical. Brain (1947) grants that such an illness may reasonably be regarded as a predisposing factor, but considers that the cause of the pyrexial reaction is unknown. Collier and Adie (1934) emphasised the possibility that in some cases this reaction may be a febrile phase of disseminated sclerosis itself.

It seems probable that in phases of activity disseminated sclerosis is a febrile illness. This view is supported by the fact that in several instances elevation of the blood sedimentation rate was found. In these cases the increased rate of sedimentation could not be explained on the basis of intercurrent infection.

The following cases are examples of the relationship between disseminated sclerosis and a febrile illness:-

M. MacW. Female aged 42.
This case was found to be suffering from organic spastic paraplegia with defective vibration and postural sensibility associated with loss of pain sensation over the left side of the face. A history was obtained that twenty two years previously she had suffered from a "feverish cold" for a few days. Immediately subsequent to this she experienced a dead feeling on the left side of her face and a sensation of numbness in the left arm. The arm returned to normal within a few days, but the numb sensation in her face remained. After a remission of fifteen years weakness of the left hand was experienced. Since this time gradual deterioration in her condition occurred. She was diagnosed as a case of disseminated sclerosis.

A.L. Male aged 49.
This patient gave a history of weakness of legs, coldness of feet, paraesthesiae of right arm and frequency of micturition. These symptoms had developed over the previous two years. An attack of "influenza" two years previously was followed by weakness of his right foot. Some months later a second attack of "influenza" resulted in deterioration of this complaint. Since this time he has become gradually worse, and on clinical examination evidence was found of scattered lesions in the central nervous system.

H.E. Female aged 27.
Whilst working on a cattle farm, this patient developed what was diagnosed at that time as "acute rheumatism". Within four weeks of the onset of this febrile illness she experienced weakness of her left leg and a tendency to fall to the right. On examination the knee jerks were unequal, the abdominal reflexes absent, and the plantar responses extensor. Serological investigation was compatible with the clinical diagnosis of disseminated sclerosis.

(b) Trauma. Forty one (10.5%) of the 389 cases gave a history of either accidental or surgical trauma occurring shortly before the first manifestation of disseminated sclerosis. In a further

considerable number of cases a history of trauma preceding an exacerbation was obtained. This relationship may be illustrated by reference to two typical examples:-

A.L. Female aged 16.
Within a week of being knocked down by a motor car weakness in both legs was complained of. Subsequently frequency of micturition and paraesthesiae of the right leg developed. On examination her speech was found to be slurred, the tendon reflexes were over active, the abdominal reflexes were absent, and a bilateral extensor plantar response was obtained. Lateral nystagmus was elicited and both arms displayed intention tremor. These symptoms and signs suggested the diagnosis of disseminated sclerosis.

W.H. Male aged 51.
Fifteen years previous to examination this patient developed symptoms which were then diagnosed as being due to disseminated sclerosis. A more or less complete remission ensued until he met with a severe accident. This was immediately followed by an exacerbation. He complained of weakness of legs associated with precipitancy and frequent retention of micturition. There was clinical evidence of bilateral pyramidal tract damage.

The predisposing influence of trauma is noted amongst others by Marie (1895) and by Adams, Blacklock, Dunlop and Scott (1924). It appears to exist in 5 - 10% of cases of disseminated sclerosis (Brain, 1930 and 1947). Thus Bramwell (1917)(1) noted the influence of trauma in 17 (8.5%) of 200 cases, Von Hoesslin (1934) in 59 (11.4%) of 516 cases, and McAlpine (1946) in 8 (5.6%) of 142 cases. Recently Parmeggiani (1947) published a historical survey of this problem. It would appear to be still impossible to make a definite statement as to the position of trauma in the aetiology of the disease. Scheinker (1949) has shown that various factors, among them trauma, may result in a

vasoparalytic reaction in the vessels of the central nervous system. The rapidity with which symptoms may follow trauma supports such a vascular hypothesis. On the other hand, Browning and MacKenzie (1924), observing that the existence of latent periods in disease is not peculiar to syphilis, consider that trauma may give rise to disturbed relations between the patient and organisms which have already been present for some time in the body without causing an active lesion. It is possible that in disseminated sclerosis trauma may act by adversely influencing the antigen - antibody balance mechanism in the central nervous system. Klauder (1947), investigating the relationship of trauma to herpes zoster has afforded some evidence that trauma may light up a latent virus infection.

(c) Pregnancy. The first symptoms of disseminated sclerosis occurred after childbirth in 19 (8.8%) of the 216 female cases. Many authors have referred to the deleterious effect pregnancy and parturition have on this illness. Mention of this is made by Gowers(1903). Risien Russell (1911) observed that pregnancy or parturition may be responsible for relapses or more rapid progress of the disease, and stated that the first symptoms of the malady are not infrequently observed in these instances. The National Multiple Sclerosis Society (1947) consider that the onset of the disease or a relapse is precipitated in about 40% of female patients who become pregnant. Walshe (1947), referring to the

possible ill effects of pregnancy on disseminated sclerosis, considers that it is not uniformly deleterious, whilst Wilson (1940) emphasises the difficulty of establishing a causal nixus between the two. The weight of evidence favours the view that pregnancy occurring in a case of disseminated sclerosis should be regarded as a grave complication of that illness.

Mention has already been made of the finding that at the extremes of age incidence male cases predominate. It is suggested that the predisposing factors of pregnancy during the child bearing era may be responsible for the fact that female cases predominate in the age group 20 - 45 years. The following cases are reported to exemplify these views:-

Mrs. D. (68/F/20) aged 49.
This patient gave a history of disseminated sclerosis of over 20 years duration. The symptoms were mainly confined to the legs and arms and on examination there was clinical evidence of pyramidal tract damage and cerebellar involvement. During this time, only two exacerbations had occurred; the first nine years before the present examination when, following on the birth of her first child, her condition greatly deteriorated. The second exacerbation took place five years later when her second child was born.

Mrs. C. (46/F/30) aged 33.
This patient was in good health until the puerperium following the birth of her first child. She then complained of weakness affecting both legs. This was followed by weakness of her right arm. On examination she was found to have a spastic paraplegia. The tendon reflexes were over sensitive, the abdominal reflexes were absent and a bilateral extensor plantar response was obtained. The right arm showed intention tremor.

Mrs. A. (65/F/30) aged 34.
This patient gave a five years history of weakness and

stiffness of the legs. These symptoms commenced in the puerperium. During the ensuing five years remissions and exacerbations had occurred. The arm reflexes were found to be unequal, the knee jerks overactive and the abdominal reflexes absent. Ankle clonus was elicited and the plantar responses were extensor. There was bilateral intention tremor. The temporal half of the right optic disc was pathologically pale.

With regard to trauma as a predisposing factor, the fallacy in logic of "post hoc ergo propter hoc" has been held to explain this relationship. In addition the criticism has also been made that the nervous disease occasioned the trauma, and not vice versa. It is obviously difficult to entertain this latter argument with regard to the relationship between pregnancy and disseminated sclerosis.

(d) Emotional Upset. An emotional upset such as grief, worry or fright, preceded the onset of disseminated sclerosis by a short period in eleven cases (2.8%). This relationship has been referred to by Risien Russell (1911), Bramwell (1917)(1), McAlpine (1946), and by the National Multiple Sclerosis Society (1947). Adams and Sutherland (1948) have stressed that fright has activated the most fulminating cases in their experience. Emotional trauma may act by "accentuating or evoking phenomena previously existing", (Risien Russell, 1911), or "by reducing resistance" (Wilson, 1940). It is not improbable that an intense emotional reaction may produce stimulation of the sympathetic nervous system resulting in localised vascular phenomena.

In this connection three cases are reported:-

M.J. Female aged 44.
This patient was found to be suffering from a chronic progressive type of disseminated sclerosis. The onset of the disease occurred 20 years previously with weakness in the left leg. The condition remained more or less stationary until the death of her mother twelve years later. Immediately subsequent to this she developed weakness in the right leg, diplopia and hesitancy of micturition. On examination there was marked euthoria. Signs were elicited referable to lesions in the pyramidal tracts, posterior columns, and cerebellum.

C.D. Female aged 45.
Immediately following the "blitz" on Greenock, this patient developed weakness of both legs, slurring speech, frequency of micturition, and incontinence of faeces. There was clinical evidence of cerebellar and pyramidal tract damage.

W.L. Male aged 26.
Whilst driving an army vehicle this patient experienced a severe emotional reaction resulting from a bomb exploding on the road immediately in front of him. He sustained a minor shrapnel wound of his right leg. Whilst in hospital with this, he lost the power in both legs, and for one week had retention of urine. His condition subsequently deteriorated and within four years he was completely helpless. Clinical examination and serological investigations were compatible with the diagnosis of disseminated sclerosis.

III

THE SYMPTOMATOLOGY OF DISSEMINATED SCLEROSIS.

1. The Importance of Early Diagnosis.

The diagnosis of disseminated sclerosis at an early stage is important from the point of view of treatment. This aspect will be stressed in a future publication by the present author in association with colleagues. If therapeutic measures are to benefit the patient they must be employed before erreparable damage has been inflicted on the central nervous system. This will be equally true if and when the causal agent is known and specific treatment is available for its eradication. The most satisfactory standard of diagnosis will entail recognition of the disease at a monosymptomatic stage.

This standard cannot be achieved however, until disseminated sclerosis is made known to the general public. It is surprising how infrequently the patient communicates the first symptom to his doctor. Unless the lay public are taught to appreciate the potential significance of such symptoms as temporary weakness in a limb, transient dimness of vision, or diplopia, the latter part of Buzzard's (1897) criticism "the full grown disease is frequently not recognised, the infant disease practically never"must

remain justified.

Early diagnosis depends on a proper appreciation of the disease process. I should like to stress the concept that in its early stages disseminated sclerosis is a functional nervous disorder. It was emphasised by Head (1920) that "all disease of the nervous system manifests itself in loss of function". "Functional" must not be regarded as the antithesis of "organic". Neither is it a euphemism for "hysterical". Experience has shown that certain signs depend, commonly, on the destruction of particular parts of the nervous system. It must be appreciated, however, that these are, per se, signs of deranged function. In the early stages of disseminated sclerosis they may not be proof of irreversible changes in the central nervous system. Since it is, perhaps, only at this stage that complete cure can be hoped for, the disastrous policy of waiting for multiple signs and symptoms to become apparent is at once obvious.

As emphasised by Adie (1932), the onset of disseminated sclerosis is sudden, if by "onset" the appearance of the earliest symptom is referred to. The first symptom is generally referable to a single lesion in the white matter of the central nervous system. In the majority of cases, the initial symptom after persisting for a variable time disappears. This is followed by a more or less complete remission during which time the patient feels in normal health.

2. The Initial Symptoms.

An appreciation of those symptoms which suggest the onset of disseminated sclerosis is of fundamental importance. The earliest manifestations in 389 cases of the disease are recorded in Table 6. From this table it is apparent that the common early symptoms are weakness in one or more limbs (51.4%), visual upset (26.8%), paraesthesiae (8.7%), vertigo (3.8%), and upset of micturition (2.8%). One or other of these symptoms was the earliest manifestation of disseminated sclerosis in 93.5% of cases. These figures differ in no significant manner from those obtained by other workers.

Emphasis has rightly been placed on those initial symptoms which occur most commonly, and by so doing to some extent suggest the diagnosis. It should be stressed, however, that in some 5% of cases the first symptom may not in itself be suggestive of the onset of disseminated sclerosis. Thus, we have encountered as the first manifestation of the disease, mental confusion, pain in back, pain in legs (each 3 cases, 0.8%), epileptiform attacks, facial paralysis, loss of sensation over side of face, dysarthria, and staggering gait (each 2 cases, 0.5%). In one case weakness of mastication was the initial symptom.

The following initial symptoms will be discussed in more detail:-

Paresis of limbs. Some 50% of cases of disseminated sclerosis will present paresis of one or more limbs as the earliest

manifestation of the disease. It is important to recognise that this symptom is frequently transient. Examination of the central nervous system should be undertaken in any young patient who complains of weakness or stiffness in a limb and in whom no other cause is apparent. Reviewing the results in four series of cases, totalling 539 patients, Kinnier Wilson (1940) found "motor weakness, fatigue etc." as a first symptom in 46.2%, whilst Russell, Brain (1946), in 100 consecutive patients reported that 5 0% showed "weakness or loss of control over limbs" as the first symptom. In the latter series involvement of both lower limbs was more common than weakness affecting one lower limb in the proportion of 18% to 14%. In the present series of 389 cases, both lower limbs were involved simultaneously in 22.9%, and one lower limb in 17.7%. The frequency with which the lower limbs are involved in comparison with the upper is worthy of note. Also of interest is the fact that I have found the most frequently affected limbs are those on the right side of the body.

Visual upset. Diplopia or transient unilateral impairment of vision accounted for some 25% of initial symptoms. Kinnier Wilson analysing 539 cases, furnished 14.3% as the figure for "ocular and visual trouble". Brain (1946) found these symptoms to obtain in 29% of a series of 100 consecutive patients.

Further reference should be made to the occurrence of acute retrobulbar neuritis in disseminated sclerosis. Owing to the long remission which may follow transient dimness or loss of vision,

the accuracy of statistical evidence on the subsequent development of disseminated sclerosis after retrobulbar neuritis is difficult to assess. Gunn (1904) found that of 233 cases of primary retrobulbar neuritis, 51 (21.9%) were due to disseminated sclerosis. Marburg (1920) reported that 14 (58.3%) out of 24 cases of retrobulbar neuritis subsequently developed disseminated sclerosis. Weill (1923) investigated neurologically 22 cases of retrobulbar neuritis; of these 12 were found to be suffering from disseminated sclerosis, and 5 subsequently developed the disease. Adie (1932) examined 70 cases of acute retrobulbar neuritis within one or two weeks of onset. He found 31.3% to be suffering from disseminated sclerosis; in 41.8% the diagnosis was probably disseminated sclerosis; in 26.8% there was no other suspicious symptom and no definite sign of organic nervous disease. Adams (1927) stressed the importance of "so called idiopathic retrobulbar neuritis" as a potential early manifestation of disseminated sclerosis, whilst Adie (1929) emphasised that "there is only one known, proved, common cause of this condition and that is disseminated sclerosis". I would emphasise that although not every case of retrobulbar neuritis need necessarily proceed to clinically recognisable disseminated sclerosis, it is probable that almost every case of otherwise idiopathic retrobulbar neuritis is due to the causal agent of this disease. This view receives the support of Steiner (1941), who observes, "if syphilis can be excluded in a young patient with monosymptomatic retrobulbar neuritis....a diagnosis of multiple sclerosis should then be considered".

Paraesthesiae. A sensation of numbness, tingling, or pins and needles occurred as a first symptom in approximately 10% of cases. The incidence of this symptom is variously recorded as occurring in 22.8% of cases (Kinnier Wilson, 1940), and in 11% (Brain, 1946). It is probable that the incidence of this symptom as a first manifestation of the disease is more frequent than these figures suggest. The transient nature of the initial symptom, and the fact that paraesthesiae causes but little disability may well result in it being ignored by patients.

Vertigo. This constituted the initial symptom in some 4% of cases. It was noted in 9% of patients in Kinnier Wilson's (1940) review and in 2% of Brain's (1946) series. It is therefore important not to dismiss a case of vertigo in a young adult as being probably hysterical in origin. It has been stressed by Kinnier Wilson that there is a "predisseminated type" where symptoms are chiefly, if not solely, subjective.

Upset of Micturition. In some 3% of cases the first symptom of disseminated sclerosis was referable to urinary bladder dysfunction. The impression was gained that this constituted a much more frequent mode of onset than the result of this analysis would suggest. Thus Sir Henry Head is reputed to have regarded disorders of micturition as being one of the most common initial symptoms of disseminated sclerosis. Kinnier Wilson (1940) reports its occurrence in 9.3% of cases. I would emphasise, however, that we have found this symptom to occur very frequently in the later stages

of the disease. This fact will be discussed later. The significance of incontinence or precipitancy of micturition in a young adult is so well known as to render further discussion unnecessary.

Epilepsy. An epileptic attack was the first symptom in 2 cases (0.5%). Wilson and MacBride (1925) collected 8 cases from the literature and added a further 7 which had been personally observed. It would therefore appear reasonable to consider disseminated sclerosis when attempting to determine the cause of epilepsy commencing for the first time in a young adult.

Symptoms referable to Cranial Nerve Lesions. Excluding the second, third, fourth and sixth cranial nerves, it is uncommon for the first symptom of disseminated sclerosis to result from dysfunction of one of the cranial nerves. Loss of sensation over one side of the face, difficulty in chewing, facial paralysis, and deafness have, however, been encountered. In our experience deafness has been a rare manifestation of the disease. Von Leden and Horton (1948) however, found changes in auditory acuity in 43% of established cases of disseminated sclerosis, compared with 18% of a control series. In the majority of instances, disturbance of auditory nerve function was objective and not subjective. This finding is compatible with the view that deafness as an initial symptom is uncommon.

Pain. Spontaneous pain is not frequently encountered as an initial symptom of disseminated sclerosis. In the present series pain in the legs occurred in 0.8% of cases, and pain in the back in a further

0.8%. Brain (1930) has stressed the risk of overlooking the significance of this system. Headache was not encountered as an initial symptom but did occur in the later stages of the disease.

3. The Relationship of Certain Factors to Initial Symptoms.

The relationship of various factors to the first symptom of disseminated sclerosis was studied and is now reported:-

(a) Occupation. The occupation of the patient and his mode of life is known to exert an influence on the manifestations of organic nervous disease. This fact has been noted by Edinger; and Williamson (1908) observed that in tabes dorsalis leg symptoms predominated in cases in which occupational overstrain of leg muscles occurred. Similarly arm ataxia was observed in a case whose occupation subjected him to great overstrain of his arms, and, in other cases in which occupational overstrain of the eyes obtained, optic atrophy developed. Further in connection with the manifestations of amyotrophic lateral sclerosis, Brain (1947) records "it is an old observation that weakness or wasting may first appear in the muscles which are used most by the patient in his occupation".

An attempt was made to classify the occupations of the 389 patients in the present series into 6 categories, but, with the exception of brain workers, difficulty was experienced in obtaining

clear cut divisions. The general picture obtained, however, did not disagree with the views outlined above with regard to neurosyphilis and amyotrophic lateral sclerosis. It is worthy of note that the clearly defined group of brain workers showed the highest incidence of retrobulbar neuritis.

A study of initial symptoms in farmers showed no significant variation when compared with the onset of the disease in the majority of patients.

(b) Sex of the Patient. Table 7 records the sex of the patient in relation to the initial symptoms of the disease. It will be seen that the incidence of paresis is remarkably constant in the two sexes. Visual manifestations and paraesthesiae appeared to occur more frequently in female cases, whereas disorders of micturition, vertigo and miscellaneous symptoms predominate in male cases. With regard to this, it may be that the more varies occupational stress to which the male is subject, renders more vulnerable through fatigue, certain parts of the nervous system.

(c) Age of the Patient. The effect of the patient's age on the initial symptomatology was studied and the results obtained are recorded in Table 8. The incidence of motor weakness increases in the older age groups. On the other hand visual symptoms tend to occur most often in younger patients. With these exceptions the age of the patient does not materially influence the initial symptomatology.

4. The Symptomatology of Established Disseminated Sclerosis.

The symptoms complained of by 389 cases of disseminated sclerosis on presenting for treatment are listed in Table 9. Paresis of a limb or limbs occurred in 368 cases (94.6%). This demonstrates the predominating tendency for disseminated sclerosis to occasion varying degrees of motor helplessness. In comparison, it will be seen that symptoms referable to retrobulbar neuritis occur relatively infrequently after the disease is established. This has also been the experience of Adie (1932). Blindness or dimness of vision occurred in the initial stage of the disease in 54 cases (13.9%) and was complained of on presenting for treatment in 57 (14.7%).

A noticeable feature is the increased incidence of disorders of micturition. Symptoms of urinary bladder dysfunction occurred as an initial symptom in 11 cases (2.8%), whereas on presenting for treatment disorders of micturition were complained of by 173 cases (44.5%). The symptoms of urinary bladder dysfunctions have been analysed further. In the hospital series of 79 cases, 34 (43.0%) complained of an upset of micturition on presenting for treatment. Table 10 lists the various types of urinary bladder symptoms complained of. It will be seen that frequency and precipitancy of micturition occurred most commonly, (11 cases, 13.9%). Incontinence of urine was comparitively rare, (1 case, 1.3%).

5. Physical Signs in Disseminated Sclerosis.

It would seem reasonable to suppose that in the early stages of disseminated sclerosis signs, which by custom we speak of as being "organic", are minimal. As previously emphasised, however, these signs are in reality evidence of disturbed function and not of structural changes. The physical findings which will be referred to are based largely on the result of examination of cases in the hospital series. The majority of these patients complained of more than one symptom. We are of the opinion that the physical signs which will be described occur frequently and are of the same significance in the earlier, monosymptomatic phase, of the disease.

(a) The Mental State of the Patient. In all phases of disseminated sclerosis hysterical symptoms frequently coexist with symptoms which result from organic dysfunction of the central nervous system. Appreciation of this fact is of great importance because, having found evidence of hysteria, the true significance of organic symptoms and signs may be overlooked. The difficulty in distinguishing early disseminated sclerosis from hysteria was stressed by Buzzard (1897) in the following words, "in its infancy.....the name given to disseminated sclerosis is hysteria". Brain (1930) has observed that hysterical symptoms occur more often with disseminated sclerosis than with other organic diseases of the nervous system, whilst Langworthy (1948) has expressed the

view that the existence of evidence of organic disease of the nervous system, emotional immaturity, and a hysterical personality, are characteristic features of disseminated sclerosis.

Cottrell and Wilson (1926), stressed as being of diagnostic importance the triad of change in prevailing emotional disposition, change in emotional expression and control, and change in sense of physical well being. The mental condition obtaining in 389 cases of disseminated sclerosis is described in Table 11. Since this aspect of investigation was done in retrospect, it is felt that only limited significance should be placed on the results obtained. In contrast the 100 consecutive patients which comprised Cottrell and Wilson's series showed a very much higher incidence of emotional abnormality. These authors regard the changes described by them as being direct results of the disease process, whereas Langworthy (1948) suggests that neurotic difficulties form the basis of vascular changes in the brain which in turn lead to organic changes in the central nervous system. The underlying cause of the hysterical and emotional abnormalities remains unknown; their occurrence is however a feature, and probably a common one, of disseminated sclerosis.

(b) Neurovascular Phenomena. I have been impressed with the fact that vasomotor symptoms are common in patients suffering from disseminated sclerosis. Thus, cold hands and feet, acroparaesthesiae and chilblains are frequently encountered. Erythromelalgia was encountered in one case. Purves Stewart (1945) observes that this

condition may be one of the earliest signs of organic spinal cord disease such as disseminated sclerosis. It has also been observed by us that weakness in a limb is often associated with a lowered skin temperature in that limb. It is possible that cutaneous angioneurosis may be an expression of "the soil" which predisposes to the development of disseminated sclerosis. Vasomotor instability of the extremities in this disease is referred to by Langworthy (1948), MacIntyre (1949), and by Aring (1949).

(c) The Eyes. It has been found that three ocular signs have an important diagnostic value in disseminated sclerosis. This triad consists of imbalance of the ocular muscles, mydriasis, and hippus.

The ocular imbalance does not amount to strabismus which in our experience is infrequent; it rather consists of a somewhat dissociated action of the extrinsic muscles of the eyes.

The pupils are generally larger than the average. In only 5 cases (6.3%) of the hospital series were the pupils myotic. Associated with this is the fact that the pupils are unduly mobile. The reaction to light is generally brisk. In only 2 cases (2.5%) was the light reflex absent. Similarly, the reaction of the pupil to near vision was found to be brisk in 74 cases (93.7%). The occasional occurrence of paralysis of accommodation has been referred to by Kinnier Wilson (1940), and was observed in 3 cases (3.8%) of the hospital series. In no instance were the requirements of the Argyll-Robertson pupil fulfilled. Recently, however, Rougues, Voisin and Pautrat (1948) have reported a definite case of

disseminated sclerosis in which the Argyll-Robertson sign, without dilation of the pupils, was present.

In a considerable number of cases the phenomenon of hippus was observed. Lagrange and Marquezy (1924) have referred to the occurrence of hippus in disseminated sclerosis, but it is felt that this sign is not accorded sufficient importance in textbooks or in teaching.

Gowers emphasised the difficulty in distinguishing between certain cases of disseminated sclerosis and neurosyphilis. It is suggested that the association of ocular imbalance, mydriasis, and hippus in disseminated sclerosis is of considerable importance in the differential diagnosis of these two conditions.

Table 12 records the occurrence of nystagmus together with the other components of the triad of Charcot in the hospital series. The full triad occurred in only 12 cases (15.1%). In comparison, however, the components of the triad occurred singly or in various combinations in 49 patients (61.7%). Greve (1947), in a study of 600 nervous cases has shown that nystagmus and nystagmoid jerks are common in disseminated sclerosis, occurring in 47 out of 50 cases of this disease. It would appear, however, that oculogyric instability is equally common in other diseases of the nervous system.

The characteristic ophthalmoscopic picture is that of pathological pallor of the temporal half of the optic nerve head. Such was found in 13 (16.5%) of the 79 hospital cases. This figure

is very low compared with that of "over 50%" suggested by Brain (1947). It does, however, closely approximate to the incidence of symptoms referable to retrobulbar neuritis which occurred in 13.9% of the total series as a first symptom. Further, it is our experience, as was that of Adie (1932), that retrobulbar neuritis occurs relatively infrequently after the disease is established. In the present series therefore, pathological temporal pallor of the optic disc was not present in a high proportion of cases; the absence of this feature should in no way invalidate the diagnosis. Simarro, Lloberas and Ribas (1948), studied the fundus oculi in 865 nervous patients including 31 sure and 5 doubtful cases of disseminated sclerosis. The results obtained were compared with those from a control series of patients who were not suffering from a nervous illness. A higher proportion of cases of temporal pallor of the disc was present in the non-neurological cases than in those with disseminated sclerosis. It should therefore be emphasised that pathological temporal pallor of the optic disc is frequently not present in cases of disseminated sclerosis and further that temporal pallor of the disc is not uncommon in individuals who are not suffering from disease of the central nervous system.

(d) The Tendon Reflexes. Of the various tendon reflexes particular diagnostic importance attaches to the knee jerks. These were regarded as normal in only 7 (8.9%) of the hospital series. The knee jerks were unequal in 36 patients (45.5%), and were

exaggerated in a further 36 instances (45.5%). In no patient in this series were the knee jerks abolished.

(e) The Abdominal Skin Reflexes. In the diagnosis of disseminated sclerosis the importance of the abdominal skin reflexes is evident from the fact that they were abnormal in 77 patients (97.4%) in the hospital series. They were present normally in only 2 instances. In 69 cases (87.3%) there was bilateral loss of the reflex; in 3 (3.8%), unilateral loss was reported, and in 5 (6.3%) the abdominal reflex was regarded as being readily exhausted.

The importance of absent abdominal reflexes was noted by Risien Russell (1911). Strumpell is quoted by him as finding them absent in 67% of 24 cases of disseminated sclerosis compared with 13.5% in 185 persons with normal nervous systems. In Probst's series, quoted by Russell, the abdominal reflex was absent in 73% of cases. "The almost constant absence" of this reflex was emphasised by Adams (1921). Kinnier Wilson (1940) considered that suspicion of disseminated sclerosis should be attached to a case in which the abdominal reflex can be tired. Similarly, Purves Stewart (1945) stresses the significance of absence or diminution of the reflex on one or both sides. Further, it is suggested that disseminated sclerosis should be suspected in a young patient whose abdominal reflexes do not share in the over activity of the knee jerks, should this latter abnormality be present.

Bohmig (1922), analysing 155 cases, considered that the addition of any single nervous physical sign to the combination of spastic phenomena in the lower limbs and the loss of the abdominal reflexes, justifies the diagnosis of disseminated sclerosis, syphilis being excluded. This view is undoubtedly correct. It must be emphasised however, that spastic phenomena in the legs is not essential to the diagnosis. In a young adult, the presence of a sign or symptom referable to a lesion in the white matter, associated with any of the abnormalities of the abdominal skin reflex mentioned above, should arouse suspicion of disseminated sclerosis. Wartenberg (1944) considers that the abdominal muscle reflex was of value in detecting a pyramidal tract lesion "much earlier, better and more surely" than the loss of the abdominal skin reflex. Such a view may be acceptable if significance be restricted to the loss of the skin reflex. If, however, the importance of the other abnormalities of the skin reflex be appreciated, it is felt that in disseminated sclerosis at any rate, this reflex is at least of equal value in the early recognition of disturbed pyramidal tract function.

The abdominal skin reflex was abnormal in several instances in which the plantar response was either equivocal or flexor. On the other hand, in no instance was an extensor plantar response associated with normal abdominal skin reflexes.

(f) The Plantar Response. Pyramidal tract dysfunction was suggested by an extensor plantar response (Babinski phenomenon) on

one or both sides in 66 cases (83.5%). In 5 instances (6.3%), the response was flexor and in a further 8 (10.1%) an equivocal result was obtained.

Thus in only 2 cases (2.5%) of the 79 hospital patients no evidence of pyramidal tract damage was elicited from examination of the abdominal or plantar reflexes.

I have been impressed with the value of Chaddocks Test. In several instances in which the plantar response was equivocal this test furnished evidence of pyramidal tract dysfunction.

(g) The Adductor Spasm of the Legs. The presence of spasm of the adductor muscles of the legs is indicative of loss of normal upper motor neuron function. This sign is considered to be an early manifestation of spastic phenomena in the lower limbs and as such it constitutes one of Bohmig's criteria for the diagnosis of disseminated sclerosis.

(h) Sensory Changes. Signs referable to dysfunction of the posterior columns occurred in 37 cases (46.8%) of the hospital series. In this connection impaired vibration sensibility was found to be the earliest manifestation of dorsal column involvement. Loss of spinothalmic tract function was unusual and was elicited in only 3 patients (3.8%).

(i) The Blood Pressure. During the routine examination of patients with disseminated sclerosis, the impression was gained that arterial hypotension was a feature of the disease. This has also been suggested by Scheinker (1949), who reported that in

a series of 40 cases systolic and diastolic blood pressure readings were below normal values in the large majority of cases. The experience however, of MacIntyre (1949), is not in accordance with this view. This authority has stated that more than 50% of cases have a normal blood pressure.

An investigation into this question was considered to be both interesting and important. In a series of 54 cases, the average systolic blood pressure was 122.8 mm. of mercury, and the average diastolic pressure 77.3 mm. The average findings in the several age groups are recorded in Table 13, and the frequency distributions of systolic and diastolic pressures in Table 14. It will be seen that in 5 cases (9.3%), the systolic pressure was over 140 mm. and that in 2 (3.7%) a reading in excess of 160 mm. was obtained.

Alvarez (1923), has reported that 22% of healthy males between the ages of 16 and 40 years have a systolic blood pressure exceeding 140 mm. Diehl & Sutherland (1925) put this figure at 9%. MacKinlay & Walker (1935), reviewed the blood pressure findings in 566 fit males. The average findings in this series and in the present series of cases of disseminated sclerosis are summarised for the purpose of comparison in Table 15. It would seem from this table that the blood pressure in patients with disseminated sclerosis does tend to be lower than in healthy individuals. It must be pointed out, however, that the MacKinlay & Walker series was made up entirely of male cases.

On the other hand, whereas in this series the average age was just over 23 years, almost 50% of the disseminated sclerosis patients were over 40 years of age at the time the blood pressure recordings were made. Oliver (1916) considers that if the average systolic blood pressure at the age of 20 years is taken to be 120 mm., the expected increase in systolic blood pressure is 1 mm. for every 2 years of life thereafter. Presented graphically this increase would be represented by a straight line rising from 120 mm. at the age of 20, to 135 mm. at the age of 50. A similar graph showing the systolic blood pressure in the present series of disseminated sclerosis patients, between the age group "under 20" to the age group "50 and over" would run at a lower level.

As will be seen from MacKinlay & Walker's study, the blood pressure in healthy cases is subject to wide variations. It is therefore incorrect to suggest disseminated sclerosis is characterised by blood pressure readings below "normal values", and equally incorrect to state that "more than 50% of cases" have a "normal blood pressure". The present small series of cases suggests, however, that in disseminated sclerosis the blood pressure values are predominantly at the lower end of a table showing the frequency distribution of blood pressures.

With regard to the practical value of this suggestion, it is apparent that a considerable degree of arterial hypertension would militate against a diagnosis of disseminated sclerosis.

Should hypertension be present, the possiblity of arterio-sclerosis of the spinal arteries must be considered. It is recognised that a clinical picture resembling the "spinal" form of disseminated sclerosis may result from this condition (Adams 1921).

More hypothetical is the possibility that the finding of low blood pressure readings in disseminated sclerosis is added evidence in favour of the allergic nature of the disease. Kahn (1924) has shown that hypotension is common in allergic states. Urbach & Gottlieb (1946) quote this observation but also suggest that autoendogenous allergens may in some instances cause arterial hypertension. It is interesting to speculate on whether the rare occurrence of hypertension in disseminated sclerosis may also be due to this mechanism.

It has been observed that interruption of the antero-lateral tracts of the spinal cord results in a fall in blood pressure. Sorgo (1948) succeeded in lowering the blood pressure in patients with severe hypertension by surgical interruption of these tracts. It is possible that this mechanism may operate in producing hypotension in disseminated sclerosis. Should this be so, it follows that other diseases of the nervous system characterised by a similar anatomical involvement of the cord should also be associated with this tendency to low blood pressure.

Moruzzi (1940) has attributed to the paleocerebellum autonomic effects such as an influence on blood pressure. The chief connection of the paleocerebellum is from the spinal cord

via the dorsal and ventral spino-cerebellar tracts. It is therefore possible that a lesion situated in the lateral aspect of the spinal cord or in the cerebellum might result in abnormalities of blood pressure.

(j) Fractional Test Meal. Brain (1947) quotes Dattner (1937) as reporting a high incidence of gastric hypochlorhydria or achlorhydria in disseminated sclerosis. This has not been our experience. In 64 cases of the disease a fractional test meal was performed and the results are now presented in Table 16. Of these 57 (89.1%) had free hydrochloric acid in the gastric juice. Achlorhydria was reported in 7 instances (10.9%). On no occasion were steps taken to ascertain whether or not the achlorhydria was histamine fast. In those cases in which free hydrochloric acid was present the fractional test meal generally revealed an average percentage of free hydrochloric acid. In only a few instances was the percentage of free hydrochloric acid higher than the average; in an almost equal number the percentage was below average.

Although the figures quoted above are too small to have statistical significance they suggest that the fractional test meal has no positive value in the diagnosis of disseminated sclerosis. The finding of achlorhydria is not common and indeed the presence of this feature would make it imperative to exclude sub-acute combined degeneration of the cord by other means.

IV

THE CEREBROSPINAL FLUID IN DISSEMINATED SCLEROSIS.

1. The Value of Lumbar Puncture.

It is considered that lumbar puncture is of very considerable diagnostic value in disseminated sclerosis. In a disease with protean manifestations absolute accuracy of diagnosis is hardly possible. An investigation which is of assistance in this respect is obviously of value. Walshe (1949), however, has stated that purely clinical investigation was usually all that was necessary to diagnose disseminated sclerosis. Whilst agreeing that laboratory and serological tests must always be subsidiary to clinical findings, it is felt that the diagnosis of the underlying pathology is often extremely difficult in a monosymptomatic case presenting with an unusual symptom. Adams (1921) has stated that the recognition of the disease presents little difficulty if the diagnosis be limited to cases in which spastic paraplegia, intention tremor, nystagmus, scanning speech and primary optic atrophy can be demonstrated. It is in the earlier stages of the disease that lumbar puncture is of value. This view is shared by Brain (1930), who regards examination of the cerebrospinal

fluid as being an important part in the investigation of a case of disseminated sclerosis.

2. The Disadvantages of Lumbar Puncture.

Two main disadvantages of lumbar puncture in disseminated sclerosis cases appear to exist:-

(a) It is suggested that an exacerbation of the disease may result from this manoeuvre.

(b) Following lumbar puncture the patient may suffer from headaches of varying intensity and duration.

With regard to the effect of lumbar puncture on the course of the disease, Brain (1930) quotes the results of Bohmig's investigations on this subject. In this series, 38% of cases displayed new symptoms within two or three weeks after the lumbar puncture. In 11 cases those symptoms involved the lower limbs, in 4 paresis of the external rectus occurred, and in a further 2 facial paralysis developed. Pappenheim (1925) discusses the occasional occurrence of "transient disturbances of the cranial nerves" in, apparently, a variety of diseases after lumbar puncture. This author also notes the occurrence of ill after-effects in early cases of syphilis in which there were no objective neurological signs. He further observes that repeated punctures favour the development of untoward effects "which sometimes make their typical appearance when the punctures have been unsuccessful". More recently, the National Multiple Sclerosis Society have stated

that sometimes even such trifling trauma as lumbar puncture or venipuncture may appear to precipitate attacks, whilst Walshe (1949) states that "lumbar puncture.....might exacerbate symptoms in this malady...."

Such has not been our experience. In a very considerable number of cases of disseminated sclerosis I, personally, can not recall a single instance in which either a new symptom appeared or an exacerbation of existing symptoms occurred following lumbar puncture within a short period of time. It should perhaps be observed, however, that treatment was instituted within a few days of the puncture being performed. Whether or not this fact is of significance, is difficult to say. In the present state of our knowledge it is possible that exacerbations of the disease process following lumbar puncture might be examples of "post hoc" and not of "propter hoc".

On the other hand, headaches have been a frequent and troublesome feature following lumbar puncture in cases of disseminated sclerosis. It is our impression that this complication occurs more frequently in patients with this disease than in those suffering from other diseases of the nervous system. Intolerance to lumbar puncture in cases of disseminated sclerosis has also been noted by Simek (1948). Merritt and Fremont Smith (1937) consider that post puncture symptoms (headache, vomiting, stiffness of the neck and pyrexia up to 102° F.) occur in between 15% and 40% of lumbar punctures in

patients suffering from a variety of diseases. The increased susceptibility of cases suffering from disseminated sclerosis to post puncture headaches, and if possible the prevention of this, is the subject of a future investigation.

At present it would not seem justifiable on the grounds of isolated instances, to warn against the use of a helpful diagnostic technique, and particularly one which is of service in diagnosing disseminated sclerosis at an early stage.

3. Changes in the Cerebrospinal Fluid.

A valuable survey of this subject has been made by Merritt (1934). In this study the findings in 100 cases of disseminated sclerosis are recorded and those in 968 cases previously reported in the literature are summarised.

(a) Pressure; cells; protein. With reference to the pressure of cerebrospinal fluid, the cell count, and the protein content, the results obtained by the present writer are not at variance with those contained in many articles on this subject, (e.g. Ayer & Foster, 1922; Adams, 1923; Merritt, 1934; Merritt & Fremont-Smith, 1937). The pressure was generally found to be within average limits. Whereas in normal fluids I have found the cell count most frequently to be zero, in disseminated sclerosis the average pleocytosis is in the region of 4 to 6 cells/c.mm; only in exceptional occasions was a cell count in excess of 15 - 20 cells/c.mm encountered. The protein content was estimated

in each case by Pandys and by Ross Jones' tests. A weakly positive reaction was not infrequently encountered with the former; a positive Ross Jones' test was less common. Such results coincide with Merritts (1934) experience that the average protein content in disseminated sclerosis was in the region of 43 m.g. per 100 c.c.

It is thus apparent that a slight pleocytosis associated with a weakly positive protein test is compatible with a clinical diagnosis of disseminated sclerosis. On the other hand, a fluid normal in these respects does not exclude this possibility.

(b) The Wassermann Reaction. Standard textbooks nearly all adhere to the view that the Wassermann reaction in disseminated sclerosis is negative. Further, Brain (1930), and Merritt & Fremont-Smith (1937), support this opinion, whilst Merritt (1934) observes that a positive Wassermann in the cerebrospinal fluid is considered as excluding the diagnosis of disseminated sclerosis.

In our experience the result of the Wassermann reaction of the blood has been uniformly negative. On the other hand, as will be seen from Table 17, this reaction in the cerebrospinal fluid was negative in only 46 out of 79 cases of disseminated sclerosis (58.2%). In 5 cases (6.3%) the reaction was not performed. Thus in 28 cases (35.5%) the Wassermann reaction in the cerebrospinal fluid was reported as being "suspicious", "very weak positive", or "weak positive". Excluding the 19 (24.1%) "suspicious" cases, a weak or very weak positive

Wassermann reaction was obtained in 9 (11.4%) instances.

That disseminated sclerosis may be associated with a positive Wassermann reaction is reported by Adams (1921, 1923, 1936), and by Perdrau and Stebbing (1921). Greenfield & Carmichael (1925) observe that although a positive Wassermann reaction should always throw doubt on the diagnosis, several cases classed as disseminated sclerosis are reported in the literature in spite of the discovery of a positive Wassermann reaction in the cerebrospinal fluid. More recently, Trolle (1944) reported 250 (5.51%) unspecific Wassermann reactions in 4,541 case records. Of these 264 were absolutely certain cases of disseminated sclerosis, and in this group 24 unspecific reactions occurred (9.09%). It will be observed that this figure approximates to that of 11.4% recorded above for "very weak positive" or "weak positive" Wassermann reactions in the present series. Trolle notes that "strong reactions" (i.e. nonspecific) are relatively more frequent in cases of disseminated sclerosis than in other neurological cases.

Four possibilities exist to explain the occurrence of positive Wassermann reactions in the cerebrospinal fluids of cases of disseminated sclerosis:-

1. That syphilis plays an aetiological role in disseminated sclerosis.
2. That the two diseases - disseminated sclerosis and syphilis - may exist simultaneously.

3. That in these instances the disease from which the patient is suffering is syphilis and not disseminated sclerosis.

4. That a positive Wassermann reaction occurring in the circumstances under discussion is not evidence of syphilitic infection.

It is believed that this last explanation is the correct one. Browning and MacKenzie (1924), emphasising that the Wassermann reaction is essentially quantitative in character, considered that this implies there will always be a frontier region of doubtful or suspicious reactions. He also pointed out that in certain instances these reactions do not afford evidence of syphilitic disease.

It must therefore be concluded that reactions such as "weak positive" do not in any way imply that syphilis plays a part in the aetiology of disseminated sclerosis. It is interesting, however, to speculate why "frontier region" results are so frequently obtained in disseminated sclerosis. Such results constitute another instance of the parallelism which exists between neurosyphilis on the one hand and disseminated sclerosis on the other.

(c) The Colloidal Gold Test. Introduced by Lange in 1912 as a test for neurosyphilis, Miller, Brush, Hammers and Felton (1915) showed that the colloidal gold test furnished "paretic" and "luetic" reactions in other illnesses, and notably in disseminated sclerosis.

In this country the pioneer work of Cruikshank (1920) and of Adams (1921 and 1923) proved that this test yielded positive results in disseminated sclerosis almost as frequently as in neurosyphilis. The colloidal gold reaction is now regarded as being a serological test of proved value and, as emphasised by the National Multiple Sclerosis Society (1947), it should always be performed in suspected cases of disseminated sclerosis. Attempts to change the nomenclature with regard to the types of reaction obtained have, in the main, proved unsuccessful. Provided that no aetiological significance be accorded the terms "paretic" and "luetic", they may be used synonymously with the more recent expressions "first zone" and "mid zone" respectively.

Adams (1921), in a series of 41 cases of disseminated sclerosis, reported that all save 2 gave a paretic or luetic type of colloidal gold reaction. Brain (1930), quoting the results obtained by Ayer & Foster, notes that a paretic curve was obtained in about half the cases, and some other abnormality in a further quarter, in a series of 33 patients furnishing 42 specimens of cerebrospinal fluid. Analysing the colloidal gold reaction in 142 fluids from 100 cases, Merritt (1934) found a first zone curve in 33% and a mid zone in 17%. "Slight abnormality" occurred in 25% and in a further 25% the reaction was negative. Merritt and Fremont-Smith's (1937) figures were first zone 25%, mid zone 22%, and slight abnormality

24%. It would therefore appear that a positive result to the colloidal gold reaction may be expected in some 70 - 75% of cases.

The results obtained in the present investigation which comprised 79 cases of disseminated sclerosis are recorded in Table 18. In this series "lilac" (2) precipitation was regarded as positive, and according to the dilution of cerebrospinal fluid at which precipitation occurred, the result obtained was described as paretic (first zone) or luetic (mid zone). "Dark red" (1) precipitation was regarded as being negative. It will be seen from Table 18 that in approximately 70% of cases a positive result was obtained.

The diagnostic importance of the colloidal gold reaction is emphasised by Lange and Harris (1949). These authors consider that if a positive gold reaction is correlated with the clinical data the differentiation of disseminated sclerosis from the other two clinical syndromes - chronic neurovirus infection and parenchymatous neurosyphilis - which may give a similar type of gold curve, offers no difficulty as a rule.

It must be appreciated, however, that the gold test per se, has no specific diagnostic import. It would appear to indicate some abnormality in the protein content of the fluid (Merritt & Fremont-Smith, 1937). The mechanism of the reaction is still imperfectly understood. Cruickshank (1920) considered that the reacting substance resided in the globulin fraction.

A positive colloidal gold test bears no relationship to the total protein but positive results do appear to be roughly related to the albumin-globulin ratio (Merritt & Fremont-Smith 1937), in so far as the globulin fraction is most active in the precipitation of the colloidal solution whilst the albumin fraction exerts a protective influence. Lange (1945), however, reporting an analysis of the reactions between the gold sol and isolated protein fractions, considers that the albumin-globulin ratio has little or no effect. MacLagan (1946), however, suggests that positive results to the test depend on a relative increase in the gamma globulin concentration, whilst alpha and beta globulins and albumin have an inhibitory effect. He suggests that although alterations in all four fractions may be important, probably the most important single factor is variation in the gamma globulin content. He stresses that an increase in this fraction is known to occur in neurosyphilis and in disseminated sclerosis, the two diseases in which the test has been particularly applied.

(d) Comparison of the Results of Wassermann Reaction and Colloidal Gold Test. The results of the Wassermann reaction and the colloidal gold test in 79 cases of disseminated sclerosis have been compared. The results obtained are to be found in Table 19. Of the 17 cases with a negative colloidal gold, the Wassermann reaction in 4 (23.5%) was either "suspiciously positive" or "very weakly positive". In no instance was the Wassermann reaction reported as being "weakly positive". In

33 cases with a paretic colloidal gold reaction, the Wassermann reaction was altered in 13 (39.4%), and of these one was considered to be "weakly positive". A "frontier zone" Wassermann reaction was reported in 10 (47.6%) of the 21 fluids furnishing a luetic colloidal gold test, and of these the Wassermann reaction was considered to be "weakly positive" in one instance (4.8%). Thus, only in fluids in which a positive colloidal gold curve was obtained was the Wassermann reaction reported as being "weak positive". Further, the percentage of other doubtful Wassermann reactions is much smaller in fluids in which the colloidal gold was negative compared with fluids in which a positive gold test occurred. This is, of course, in accordance with the observation made by Cruickshank (1920) that the globulin fraction had the precipitating power of the original spinal fluid and also gave a positive Wassermann reaction. It would, however, seem incompatible with this view that a negative colloidal gold test may in some instances be associated with a doubtfully positive Wassermann reaction. Such an association may be explained by the fact that a slow complement may furnish a suspicious Wassermann reaction and a relatively insensitive gold, a negative colloidal gold result.

It is suggested that the occurrence of doubtfully positive and weakly positive Wassermann reactions is not without significance in respect of the allergic factor which is considered to be of aetiological significance in disseminated sclerosis.

This it would appear to be the consensus of opinion that the Wassermann reaction "is based on a specific process, i.e. on an underlying antigen-antibody reaction" (Urbach & Gottlieb, 1946). It is also perhaps worthy of note that antibodies consist of modified serum globulins. The importance of the globulin fraction in causing precipitation of colloidal gold has already been discussed.

(e) Relationship of Patients' Age to Serological Picture. The relationship between the patients' age and the serological picture was investigated; the results obtained are recorded in Table 20. As already seen from Table 18, the colloidal gold reaction was negative in some 20 - 30% of cases. The present investigation shows that the colloidal gold test is most frequently positive in the 30 - 39 years age group. In this age group, a positive result was obtained in 24 instances (77.4%). A positive result was also frequently encountered in patients between the ages of 20 and 29 years. In this age group 20 cases (68.9) gave a positive gold reaction. The results obtained indicate that the colloidal gold test is less frequently positive under 20 years and over 40 years. The two cases in the over 50 years age group both furnished a positive gold test but no significance can be attached to this in view of the small number of cases involved.

The Wassermann reaction, as previously mentioned, was "altered" in 28 (33.5%) of the 79 cases. With regard to this

test the 30 to 39 years age group again furnished the highest percentage of abnormal fluids. Of the 31 cases of this group, 15 (48.4%) displayed some abnormality in the Wassermann reaction performed on the cerebrospinal fluid. These results may be summarised in approximate figures, thus:-

	under 20yrs.		20-29yrs.		30-39yrs.		40-49yrs.		50+ yrs.	
	No.	%	No.	%	No.	%	No.	%	No.	%
Positive colloidal gold	2	40	20	69	24	77	6	50	2	100
Altered W.R.	1	20	8	28	15	48	4	33	-	-

Thus, with regard to both the colloidal gold test and the Wassermann reaction, the highest incidence of positive reactions in the cerebrospinal fluid occur in the age group 30-39 years. In the present state of our knowledge, the reason for this is uncertain. Should these tests depend in some way on an antigen-antibody reaction, it is possible that at this age group such a reaction is more intense than at others. Below 30 years of age the activity of the disease process, by being more marked, may result in a weaker form of antigen-antibody reaction; above 40 years of age a tendency may exist for the disease process to "burn itself out".

(f) The Cerebrospinal Fluid Findings in Patients with Disseminated Sclerosis from Rural Areas. It was considered possible that country dwellers might suffer from a disease which, although clinically identical with disseminated sclerosis, was aetiologically and perhaps serologically distinct. It was

therefore considered important to relate the serological picture to country associations. This investigation unfortunately has to some extent been invalidated by the number of cases which did not reply to the questionnaire sent them regarding their association with country districts. The results of this investigation are tabulated in Table 21.

In this table, serological results obtained in cases derived from predominantly rural areas are compared with the results obtained on investigating the cerebrospinal fluid of town dwellers. It will be seen that the nature of the results does not vary in any significant manner in the two groups of patients. Indeed, a characteristic serological picture was found to occur slightly more often in the patients whose homes were in the country. It is therefore unlikely that we are dealing with two separate disease entities - disseminated sclerosis on the one hand, and a disseminated sclerosis-like clinical syndrome on the other.

This review indicates that suspicion of disseminated sclerosis should be entertained in a patient who complains of severe lumbar puncture sequelae and whose cerebrospinal fluid shows a slight pleocytosis, a high average protein content, a first or mid zone colloidal gold reaction and a non-specific, weakly positive Wassermann reaction. Any or all of the above abnormalities may occur in other conditions. Examination of the cerebrospinal fluid should therefore be regarded as playing

an important subsidiary part in the diagnosis of disseminated sclerosis. One of its main functions is in distinguishing early disseminated sclerosis from hysteria. For this reason we feel justified in regarding precipitation of the gold sol to the degree "lilac" (2) as being abnormal, provided that significance is accorded this change only when it occurs in combination with clinical signs or symptoms suggestive of dysfunction of the nervous system.

In concluding this section it should be mentioned that Steiner (1935) evolved a complement fixation test for disseminated sclerosis. The technique of this reaction appears to resemble that of the Wassermann reaction. Steiner found positive reactions to this test in a high percentage of cases. Positive reactions were particularly common in young cases, in early ones, or during an exacerbation of the disease. The occurrence of positive results to such a test furnishes further support in favour of the allergic nature of the disease.

V

THE PROGNOSIS.

It is a matter of extreme difficulty to formulate the prognosis in any given case of disseminated sclerosis. The available literature on this subject is scanty and tends to suggest only a general picture of the natural history in typical cases of the disease. It has been pointed out by Adams (1936) that the classical picture of disseminated sclerosis accounts for only a certain proportion of cases, and "formes frustes" are constantly encountered. Thus, not only classical cases, but also aberant forms of disseminated sclerosis must be considered in this connection.

1. Duration of the Disease.

The duration of disseminated sclerosis varies within wide limits. Brain (1930), for example, notes the duration as varying from a few months to 20 or 30 years. The average duration of the disease in a series of 170 fatal and non-fatal cases was found by Bramwell (1917) to be 12 years and one month. It is interesting to compare the duration of the disease as reported by Bramwell (1917)(2), and by Muller (1949).

The results of these authors' investigations are tabulated below:-

Total Series.

Duration of Illness.	Bramwell (1917)	Muller (1949)
	170 cases	810 cases
	106 dead	190 dead.
More than 10 years	50.6%	63%
More than 20 years	14.7%	22%

Series of Fatal Cases.

Duration of Illness.	Bramwell (1917)	Muller (1949)
	106 cases	190 cases
Under 5 years	21.6%	6%
Under 20 years	86.7%	34%

Consideration of this summary suggests that the disease now lasts longer than was supposed 32 years ago. This possibility was mentioned by Wilson (1927) who studied the death rate in disseminated sclerosis at different ages, and is in accordance with the view expressed by MacIntyre & MacIntyre (1943), that the prognosis on the whole is considerably better than one has been led to believe. It is possible that the character of the disease is changing and that, like rheumatic fever, it has now assumed a less virulent form. This suggestion would account to some extent for the increased prevalence of the disease. Thus, Williamson (1908) observed that disseminated sclerosis was not a common disease, even in hospital practice.

In comparison, Walshe (1947) considers it to be one of the most common organic nervous diseases, taking numerical precedence over neurosyphilis.

Certain factors which might exert an influence on the progress of the disease were investigated. This was done by relating such factors to the duration of the period which elapsed before the patient sought treatment. It was recognised that in some instances this period would refer to the rate of progress of the disease rather than to absolute latency of infection. It was considered, however, to constitute a reasonable basis for the investigation. It was hoped that information might be obtained which would assist in estimating the prognosis in a given case, particularly after a mono-symptomatic diagnosis. The factors so considered were the sex and age of the patient, the onset of the disease, and the initial symptom.

2. The Relationship of the Sex of the Patient to the Progress of the Disease.

The relationship of the sex of the patient to the duration of the period before treatment was required is shown in Table 22. Of the 216 female cases 115 (53.3%) required treatment within 5 years of onset, 80 (37.0%) within 5 to 15 years of onset, and 21 (9.7%) after 15 years or more from the initial symptom. With regard to the male series of 173 cases, the corresponding figures are 113 (65.3%) within 5 years, 50 (28.9%)

within 5 to 15 years, and 10 (5.8%) over 15 years.

It would thus appear that a more prolonged remission following the first symptom occurs in female patients in comparison with males.

3. The Relationship Between the Age of the Patient and the Progress of the Disease.

Table 23 relates the age of the patient at the onset of the disease to the duration of the period before the patient required treatment. This table demonstrates that adolescent patients tend to have a more prolonged remission than cases in which the disease first appears in later life. Thus, in the under 20 years age group of 27 cases, 6 (22.3%) had a latent period exceeding 15 years after the onset of the disease. This is the highest percentage of cases showing such a prolonged remission. Similarly, the age group 20 to 24 years tended to have longer periods of latency than subsequent age groups. In comparison the older age groups generally required treatment within 5 to 10 years of the initial symptom developing. This view differs from that expressed by Adams (1936), and Thygesen (1947) who were of the opinion that the prognosis was less favourable in young patients. The long latency of infection following initial symptoms in young patients may result from the fact that visual symptoms occur most frequently in the younger age groups. Mention has already been made of this fact, and

Muller (1949) has observed that the best prognosis accompanies initial symptoms referable to cranial nerve lesions or paraesthesiae.

4. The Relationship of Mode of Onset to Progress of the Disease.

The fact that a fulminating onset may be followed by almost complete clinical recovery has already been discussed. It is sufficient to reiterate that if the patient survives the initial severe illness, the prognosis is on the whole better than in cases in which the onset has been less acute.

Mention has also been made in a previous section on the relationship which exists between the onset of disseminated sclerosis and a febrile illness.

By analogy with syphilis it was considered that a febrile onset in disseminated sclerosis might be associated with long latency of infection subsequent to the initial manifestation. In this respect Mattauschek & Pilcz (1913) noted that of those syphilitics who soon after infection suffered from a febrile disease, the development of general paralysis was rare compared with the incidence of this condition in syphilitics in whom no intercurrent infection occurred. Similarly, Browning & MacKenzie (1924) observed that the course of syphilitic infection may be modified by an intercurrent infection.

Table 24 records the effect of a febrile onset on the subsequent course of the disease. The results obtained suggest

that a febrile onset does not materially influence the subsequent course of the disease with regard to latency of infection or progression of the disease process. Of the 56 cases which gave a history of febrile onset 13 (23.2%) presented for treatment within one year of the disease, and 35 (62.5%) within 5 years. In the 293 cases in which no history of febrile illness was obtained, the corresponding figures were 56 (19.1%) and 173 (59%). It must be appreciated, however, that this investigation does not take into account cases with a febrile onset which, perhaps, never presented for treatment. This investigation of necessity has been restricted to those cases with a febrile onset which ultimately required treatment. It is not impossible that a proportion of cases were protected from further manifestations of the disease by a febrile onset. Indeed, a febrile illness, by occurring shortly after infection with the causative agent, may have protected the patient from any clinical manifestation of disseminated sclerosis.

5. The Relationship of Initial Symptoms to the Progress of the Disease.

Adie (1932) observed that very long remissions "up to 20 years or more" are not uncommon in cases in which retrobulbar neuritis was the first symptom. He considered, however, that similar remissions were not common after other modes of onset. This question was investigated by relating initial manifestations

to the duration of the period before the patient reported for treatment, and the results obtained are tabulated in Table 25.

Regardless of the initial symptom, 58.6% of patients presented for treatment within 5 years of the onset of the disease. In comparison 80% of patients with miscellaneous symptoms, 73.3% with vertigo, 62% with paresis, 53% with paraesthesiae, 52% with diplopia, 46.5% with dimness or loss of vision, and 36.4% with upset of micturition as the first symptom, required treatment within 5 years of the onset. The number of cases with initial symptoms of vertigo or upset of micturition are too few to be statistically significant. A latent period of 15 years or more followed the first symptom in 31 cases (7.9%). The only initial symptoms to be followed by a latent period of such duration were dimness or loss of vision in one eye in 8 cases (14.8%), paresis in 19 (9.5%), paraesthesiae in 3 (8.8%) and diplopia in 1 (2%). It would therefore be reasonable to suppose that, since these symptoms may be followed by such a long latent period, in some instances they may be the sole manifestation of disseminated sclerosis in a lifetime. Adie (1929) suggested in connection with retrobulbar neuritis, "if a remission should last for 24 years, why not 54?". This contention was strengthened by a further observation made in the following year (Adie 1930), "now 47 years is the longest interval on record".

6. Other Factors.

The bad effect on prognosis of such factors as trauma, emotional upset and pregnancy has already been discussed in a previous section. The effect of treatment as this influences the course of the disease will be considered later. It is recognised that the serological picture is of no value in assessing the prognosis in a given case. The recent report by Thygesen (1949) is in support of this view, and my own experience has indicated that changes in the cerebrospinal fluid bear no relation to the activity or otherwise of the disease process.

The results of the present investigation suggest that as previously mentioned the prognosis in disseminated sclerosis is very much better than was once supposed. Not only is this true in established cases but it is also suggested that following certain initial symptoms the disease may remain latent for an indefinite period; in some instances this period may amount to a lifetime. Thus, following a monosymptomatic diagnosis of disseminated sclerosis the prognosis should not be regarded as being one of unmitigated gloom.

In conclusion, a study of the literature and the results of the present investigation suggests that the following factors should be considered in attempting to assess the prognosis in a case of disseminated sclerosis. These are presented in tabular form as follows:-

Factors which tend to influence the course of the disease:-

	Improved Prognosis.	More Guarded Prognosis.
1.	Onset in adolescence (under 20 years to 24 years) and over 45 years.	1. Intermediate age groups (25 years to 45 years)
2.	Female cases (provided pregnancy is avoided).	2. Male cases. Pregnancy in female cases.
3.	Fulminating onset, provided patient survives initial severe illness.	3. There is a risk of death in the acute stage of a fulminating onset; an insidious form of onset is generally associated with a progressive course.
4.	"Febrile onset" of doubtful significance.	4. "Influenzal" illness frequently associated with onset or exacerbation of disease.
5.	————	5. Pregnancy, trauma and emotional upset tend to cause an exacerbation.
6.	Prolonged remissions frequently follow initial symptoms of retrobulbar neuritis, motor weakness in a limb, paraesthesiae and diplopia.	6. Prolonged remissions not common after other initial symptoms.
7.	No exacerbation within 1 year of first symptom.	7. Exacerbation within one year of onset.

VI

THE TREATMENT OF DISSEMINATED SCLEROSIS.

1. Introduction.

A vast literature exists on the therapeutic measures which have been used in the treatment of disseminated sclerosis. This subject has been extensively reviewed by Brickner (1936), and more recently by Reubi (1947). It has been stated that the multiplicity of treatments which exist suggests that none has proved completely satisfactory. Indeed, the view has been expressed by MacIntyre (1949) that no type of treatment advocated at present is of any value and that the only form of therapy is supportive and symptomatic. Many other authorities, however, consider that this is too extreme a view and certainly personal experience does not support such therapeutic nihilism.

Owing to the spontaneous variations in symptoms and signs which characterise the course of disseminated sclerosis, the difficulty in assessing the value of any particular treatment has frequently been commented on. For example, Adie (1932) has observed "functional recovery from the severest manifestations may occur and.....all physical signs including extensor plantar responses may disappear.....all the subjective and objective

improvements that have been recorded as evidence of the efficacy of special treatment are common in the natural course of the disease".

Reference has been made by Adams and his associates (1924) to a further factor which must be considered in estimating the response to a particular form of treatment. This is "how far is recovery possible? i.e. how much permanent damage has already been done?". In this connection the futility of ascribing to a therapeutic agent the property of restoring the function of irreparably damaged central neurones is obvious. Buzzard (1911) has observed that irreparable damage may occur in the axis cylinders in cases of disseminated sclerosis, and Putnam & Alexander (1947) have reported on the loss of axis cylinders in sclerotic plaques.

In estimating the results of treatment a further danger must be emphasised. As mentioned in a previous section symptoms due to deranged function are frequently associated with those arising from a psychogenic basis. A favourable response to therapy might be wrongly regarded as efficacy of a particular treatment whereas, in truth, only the hysterical element is responding to suggestion and kindly interest.

The correct view to take is that expressed by Charcot (1877) who urged physicians to take advantage of the spontaneous tendency to remissions which characterise disseminated sclerosis. The criterion of successful treatment should be, therefore, the

promotion of remissions, and, as emphasised by Putnam (1939) "the prevention of relapses". This standard of judgement would involve the detection of a further spread of the disease to some portion of the central nervous system not previously involved. Such an event would indicate therapeutic failure.

Adequate treatment should therefore -

(a) induce a remission of the disease process;

(b) prevent a relapse or progression of the disease occurring in the future;

(c) improve symptoms resulting from a functional impairment of central neurones;

(d) improve symptoms which are psychogenic in origin;

(e) afford symptomatic relief to the patient.

In the following pages current therapeutic measures will be briefly reviewed and subsequently the results of various forms of therapy carried out personally will be reported.

2. Review of Current Therapeutics.

(a) Treatments Based on Theories of Aetiology.

The Infective Theory. Marie (1895) advised "...the administration of drugs suitable on the one hand to the sclerotic, on the other to the infective element of the disease". For this latter mercury was advised "....on account of its disinfecting properties ....." Adams, Blacklock, Dunlop and Scott (1924) considered

that "the supreme object of treatment must be towards the eradication of the infective agent in the earliest stages of the disease...."

To accomplish this eradication of the infective agent arsenic has been the most popular remedy. The value of this form of therapy has been referred to by Adams (1923), and Wilson (1940) observed that its use can still be recommended. Treatment by organic arsenic appears to have been suggested first by Buzzard (1911), and Adams (1921) reported that in many instances clinical improvement following the use of organic arsenic was accompanied by modifications of the colloidal gold curve towards normality. The beneficial effect of drugs of the salvarsan series has been reported by, amongst others, Johnson (1923), Schacherl (1924), Adams, Blacklock, Dunlop and Scott (1924), Osnato (1928), Collier and Adie (1934) and Wilson (1940). Brain (1930), however, in his critical review, observes that the organic compounds of arsenic are the most popular therapeutic agents but considers there is no general agreement as to their value. He stresses the fact that this is in contrast to the status of arsenicals in the treatment of neurosyphilis, and concludes that they probably have no specific action on the cause of disseminated sclerosis. Such a view is shared by Walshe (1947), whilst Putnam (1939) reported no success with this form of treatment. Reubi (1947)(2) lists arsenic as an ineffective measure.

Fever therapy has been employed by many workers. The most popular form of this treatment is protein shock induced by the intravenous injection of typhoid vaccine. The rationale of pyretotherapy is not clearly understood and reference will be made to it again in subsequent sections. With regard to the infective nature of the disease it is suggested that the induction of fever may create conditions inimical to the survival of an infecting microorganism. It is well known by research workers that there are optimal temperatures for the development of certain viruses in chick embryos. It is also recognised that fever therapy may light up a latent infection with the herpes simplex virus so that it becomes clinically manifest. In view of the phenomenon of "virus interference" this occurrence is of considerable interest. By "virus interference" is meant the ability of certain viruses to interfere with the multiplication of other immunologically unrelated viruses in the same susceptible host. Antibody apparently plays no part in this reaction and it has been suggested that the two viruses have to compete for some common factor either on the cell surface or within the cell. Findlay (1948) quotes a number of examples of virus interference in relation to both plant and animal viruses. It would appear, however, that this conception is not a new one. Thus, it has been known for over 150 years that the occurrence of herpes febrilis was of good prognostic

significance in acute infections, and Naegeli (1935) reported that the same holds true in the fever therapy of neurosyphilis. According to this author fever therapy in neurosyphilis is only a secondary factor. Its importance lies in the activation of the primary curative factor, the herpetic virus.

The value of pyrexial therapy has been noted by MacBride & Carmichael (1924), Adams (1936), Bennett & Lewis (1940), and Wilson (1940). On the other hand, Putnam (1939) appears to have had no success with this form of treatment, and Walshe (1947) observes that pyrexial therapy is not free from the danger of provoking an exacerbation. Reubi (1947)(2) considers pyretotherapy to be ineffective, and the National Multiple Sclerosis Society (1947) regards fever treatment with disfavour. MacIntyre (1949) condemns the use of typhoid vaccine treatment in retrobulbar neuritis. Two schools of thought thus exist. It is impossible to disregard the experience of those authorities who favour this form of treatment. Similarly, the views of those who have criticised fever therapy must be held in respect. Such bald statements as "it may confidently be stated that fever and vaccine therapy are useless", as recently published by an anonymous writer should not, however, be accorded serious contemplation. The employment of fever therapy would appear to be attended by beneficial results, particularly in early cases (Bennett & Lewis, 1940) and "in cases that progress steadily and rapidly" (Brain, 1947).

The value of malaria therapy in disseminated sclerosis has been observed by several workers. This form of treatment was suggested by Wagner-Jauregg in 1887 for general paralysis, and in 1924 this author reported that almost 100% of remissions could be obtained in early cases of this disease. Rudolf (1927) considered that malaria therapy promotes full remissions in approximately 33% of cases of general paralysis and partial remissions in a further 25% of cases. This form of treatment, either alone or together with penicillin is the treatment of choice for general paralysis at the present time (Nicol, 1946; Reynolds, Mohr and Moore, 1946).

With regard to the use of therapeutic malaria in disseminated sclerosis, Pilcz (1923), Grosz (1924), Dreyfus & Hanau (1926), and Dreyfus & Mayer (1929) have accorded it varying degrees of commendation, whilst Wilson (1940) observes that "malaria has been tried with satisfactory issue".

The mode of action of malaria therapy is uncertain. It probably exerts a beneficial effect in the same way as does protein shock. Rudolf (1927), reviewing this problem, refers to the leucocytosis, the psychological effect, the high temperature, the metabolic changes, the formation of antibody and the vasodilation which follow a malarial paroxysm. Bruetsch (1949) considers that the effect in general paralysis is only in minor degree due to the rise in temperature. He considers the principal factor to be an increased activity of

the reticulo-endothelial system which produces and stimulates macrophages and immunity reactions. Bercovitz (1924) reported on the relative incidence of malaria and neurosyphilis in Hainau, China. It was estimated that 90% of the population had malaria and between 50 and 60% had syphilis. It was, however, a striking fact that in eight years no case of G.P.I. had been seen and only a few cases of tabes dorsalis. Various explanations exist to explain this occurrence, but it is possible that malaria either in an active or in a latent form may prevent the development of neurosyphilis. Similarly, it may be noted that in areas where malaria is endemic, disseminated sclerosis is rare or does not occur.

With the exception of T.A.B., vaccine therapy appears to have fallen from favour. A further exception to this statement is the specific vaccine therapy of Margulis and his associates (1946). These workers prepared a vaccine from the cerebral substance of albino mice and guinea-pigs which had been inoculated with the strain of virus they believe to be the cause of acute disseminated encephalomyelitis and disseminated sclerosis. Benefit appears to have been derived from this treatment in a proportion of cases, and a considerable increase of antibodies in the blood of patients so treated was demonstrated.

Marie (1895) was the first to suggest vaccine therapy. He stated "I have little doubt that by the employment of such

a substance as the vaccine matter of Pasteur or lymph of Koch, the evolution of insular sclerosis will some day be rendered absolutely impossible".

A similar line of treatment using the serum of non-progressive cases of disseminated sclerosis was reported by Dumas and Foix (1924). Laignel-Lavastine and Koressios (1928) and (1929) recommended the use of the serum of rabbits inoculated with patients' blood, whilst Ortoph (1932) has reported on the effects of administering, by intramuscular injection, the patient's own blood. More recently Stransky (1949) reviewing the results of donor-blood treatment of disseminated sclerosis, reports two cases of disseminated sclerosis in which syphilis developed. Both these cases showed considerable improvement. This result is considered to be due to the combined effects of haemotherapy and the syphilitic antibodies. It should be noted, however, that both these cases received arsenical therapy for the syphilitic infection. It is not impossible that this may also have played a beneficial role.

In view of the suggested relationship between swayback in sheep and disseminated sclerosis in man, Campbell and his coOworkers (1947) employed copper sulphate in the treatment of the latter disease, but apparently without success. Copper sulphate is a gastric irritant and its use is attended by the dangers inescapable from the use of any heavy metal, including, apparently, hepatic damage. In a later communication

Campbell (1948) reported on the use of an organic copper compound "cuprelone". Whilst less toxic that the inorganic salt, its use in disseminated sclerosis has been disappointing. Dean (1949) has also advocated copper therapy. In the present state of our knowledge, and, in view both of the results obtained and of the toxic effects of copper treatment, its use at present does not seem justifiable.

MacIntyre (1949) has stated that penicillin is of no value in the treatment of disseminated sclerosis. Previously Fleming (1946) had observed that "nervous degenerations e.g. disseminated sclerosis, do not respond to penicillin". Rimbaud (1946) however, reports the case of a man aged 30 years with pyramido-cerebellar disturbance associated with nystagmus and diplopia of short duration. In this case penicillin therapy was followed by a surprisingly rapid regression. Similarly, Oravec (1948) has reported a case of encephalomyelitis presumably due to a virus in which improvement and subsequently complete recovery followed the use of penicillin. Finally, a well known authority on disseminated sclerosis in a personal communication to Dr. D.K.Adams in 1948, informed us that in his experience encouraging results have followed treatment of disseminated sclerosis with a high total dosage of penicillin combined with injections of bismuth.

Penicillin therapy in disseminated sclerosis is rational from two points of view:-

Firstly its efficacy in the treatment of neurosyphilis is widely recognised (Fleming 1946; Nicol 1946; Martin 1948). Wilson (1940) has observed that most treatments for disseminated sclerosis are replicas of those used in neurosyphilis, and Buzzard (1911) stated in connection with the use of organic arsenic ".....what is efficient in the one case (neurosyphilis) might prove equally so in the other (disseminated sclerosis". The value of arsenic in the treatment of disseminated sclerosis has already been referred to. On these grounds penicillin therapy is at least worthy of a reasonable trial. It must be emphasised that penicillin can not be expected to restore the function of irreparably damaged central neurones. Secondly, it is not irrational to employ penicillin on the assumption that disseminated sclerosis is due to a virus, since certain viruses have been found to react to antibiotics (Findlay, 1948). Thus penicillin may cure vaccinia in the rabbit. Sulphonamides, on the other hand, apart from controlling secondary bacterial microorganisms are without effect in disease due to the pox virus, and pure penicillin was also found to be devoid of action. It would therefore appear that an impurity present in commercial penicillin is responsible for the anti-viral action rather than penicillin itself.

I have been unable to trace any reference to the use of the newer antibiotics in the treatment of disseminated sclerosis. Should, however, the suggested relationship between disseminated

sclerosis and brucellosis be significant, the results of treatment with aureomycin (Galpine 1949), and with chloramphenicol (Parke Davis & Co., 1949; Walley & Cooper, 1949) would be of interest. Aureomycin has also been shown to be effective in certain virus diseases. Further developments in this field may yield an antibiotic with a wide anti-viral action.

The Allergic Theory. Various treatments exist which either by design or by accident may interrupt the allergic cycle presumed to exist in disseminated sclerosis. Thus certain treatments based on the infective nature of the disease may well exert an anti-allergic action. For example, vaccine therapy, malaria therapy and haemotherapy may stimulate the production of antibodies. In addition, more specific anti-allergic measures have been employed such as the administration of histamine, histamine conjugates and anti-histamine drugs.

Treatment with histamine will receive only brief mention under the present heading since most authors share the view that its action is vascular rather than anti-allergic. There is little doubt, however, that histamine is intimately connected with allergic phenomena (Urbach & Gottlieb, 1946) and it has been shown that although not antigenic, the administration of histamine may produce a resistance of the body to its action. In this way the body may be protected from the effect of histamine liberated as a result of antigen-antibody reactions. Thus, Abramson (1948) has reported favourably on the results of

histamine applied by iontophoresis in patients with disseminated sclerosis.

The central nervous system, however, has never been shown to contain histamine. Further, there is a tendency at present to implicate acetyl choline as the chemical factor which mediates allergy. In support of this view it is pointed out that probably all allergic manifestations can be reproduced by stimulation of the parasympathetic nerves with this substance. The use of histamine will be discussed further under the vascular theory of aetiology.

Although not itself antigenic, histamine can, however, act as a hapten. That is, if histamine is coupled with a protein an antigen is produced the specificity of which is at least patially determined by the histamine content (Fell, Rodney, and Marshall, 1943; Cohen and Friedman, 1948). The use of such a preparation is suggested by Ferraro (1944), and Reubi (1947)(2) considers that limited benefit may be derived from anti-allergic measures. This author particularly recommends the new antihistamine drugs such as antistin.

The Vascular Theory. Treatments based on this theory depend on whether it is believed that the primary factor is vasoconstriction (Scheinker 1949), or an increased coaguability of the blood (Putnam 1935, 1937).

Both drugs have been used and operative procedures devised to relieve the vasoconstriction which is stated to

exist in the central nervous system of patients suffering from disseminated sclerosis. With regard to drugs, histamine is the most powerful vasodilating agent available for increasing the blood supply to the central nervous system. Thus Horton and his associates (1944) report satisfactory results with daily intra-venous administration of histamine in 24 acute cases of disseminated sclerosis and 78 chronic ones. These workers concluded that histamine therapy is an adequate and highly satisfactory substitute for the methods of treatment employed formerly, notably typhoid vaccine. Similarly, in a series of 124 cases treated with intravenous histamine and intramuscular d-tubocurarine, Jonez (1948) reported extremely satisfactory results. It is of interest to note that nearly all the cases in this series had some form of allergic sensitivity. On the other hand Riser, Dardenne, Pigassou and Monnier (1949) found only temporary improvement in a small series of cases, whilst MacIntyre (1949) considered the results of this form of treatment to be indifferent in a series of 30 cases.

Vasodilation of the vessels in the central nervous system may also be produced by protein shock. It has been suggested that protein shock therapy inactivates the sympathetic nervous system thus permitting of vasodilation of the vasculature of the central nervous system.

Vasodilator drugs which can be given orally are aminophyllin, syntropan and papaverine hydrochloride. Their use,

however, in this connection is still in the experimental stage. They may be given combined with daily intravenous histamine treatment.

A further medical method of producing vasodilation is by the use of tetraethyl ammonium chloride (Etamon). This preparation given parenterally by either intravenous or intramuscular injection partially blocks the transmission of both sympathetic and parasympathetic motor impulses through autonomic ganglia. The block of sympathetic stimuli relieves vasospasm and results in an increased blood supply to the affected part. The use of tetraethyl ammonium chloride in a series of 14 cases of disseminated sclerosis is reported by Bell, Williams and Karnosh (1948). Remissions of acute recent symptoms were obtained but those present for over six months were not affected.

Nicotinic acid has been used to promote vasodilation and increased blood supply to the brain and spinal cord. Moore (1940) comments favourably on its use and has shown that the cerebrospinal fluid pressure increases during the period of flushing of the skin. Further, nicotinic acid was seen to dilate the blood vessels and to occasion increased capillary filling in the brain and spinal cord of the cat. This author is of the opinion that the results obtained with nicotinic acid are similar to those resulting from fever therapy or sympathectomy, but without the difficulties, complications and

and dangers incident to those measures. More recently, Pero (1946) reported this hyperaemic activity of nicotinic acid in 30 cases suffering from chronic diseases of the nervous system. Sodium nicotinate was administered by the subarachnoid route and good results were reported in four out of six cases of disseminated sclerosis included in this series.

A surgical approach to the relief of vasospasm in the central nervous system is the operation of cervico-dorsal sympathectomy, (Royle, 1933; Wetherell, 1934, 1935). Although encouraging results were reported, this treatment now appears to have been abandoned. Either the late results were such that continuance of this treatment was not justified, or the sequelae of the operation, as distinct from the effect on the nervous system, deprived the treatment from true benefit to the patient.

Anticoagulant therapy is based on the hypothesis that in disseminated sclerosis an increased coagubility of the blood is responsible for thrombus formation in the venules of the central nervous system. Many authors have suggested that such an alteration in the coagubility of the blood may be an expression of allergy (e.g. Putnam, 1941; Kammer & Karnosh, 1947). Opinions appear to differ, however, as to whether the blood coagulation time is shortened or prolonged in allergic diseases, whilst in anaphylactic shock there is known to be a decreased coagubility of the blood due probably to the presence of heparin in the blood stream, liberated, presumably, from the liver (Urbach & Gottlieb, 1946).

Putnam, Chiavacci, Hoff and Weitzen (1947), report the administration of dicoumarol to 74 cases of disseminated sclerosis. They reviewed the results of this treatment in 43 cases treated for longer than six months. These 43 cases were subdivided into two groups. In group A (27 patients) the disease was of remittent form, and in group B (16 patients) the condition was progressive. In group A, 23 patients remained unchanged during treatment; in 4, relapses occurred. In group B, 7 cases remained static, whilst in 9 the treatment was regarded as having been without effect. Previously, Reese (1944) had treated a smaller series of 28 cases for shorter periods up to six months. The results obtained were disappointing. Kammer & Karnosh, (1947), treated 12 cases of disseminated sclerosis with dicoumarol for an average duration of 42 days. Subjective improvement occurred in 10 cases, and in an equal number objective improvement was noted. Lesny and Polacek (1949) have reported their experience of heparin and dicoumarin. Improvement was obtained in 22 cases in a series of 27 using heparin, and in 34 in a series of 40 patients using a dicoumarin preparation. Reubi (1947)(2), however, regards coagulation inhibitors as being ineffective in the treatment of disseminated sclerosis, and MacIntyre (1949) considers that claims for this form of therapy should be suspended until observations have been extended over a longer period.

Should venous thrombosis be an essential factor in the pathogenesis of the disease, a tendency to this is presumably a permanent feature. It follows, therefore, that coagulation-inhibitor therapy should be continued for the remainder of the patient's life. A further and a more serious disadvantage of anti-coagulant treatment, particularly with dicoumarol, is the tendency to haemorrhage which may prove fatal. Prevention of this complication entails the regular estimation of the prothrombin time.

The Ferment Theory. Treatments designed to inactivate the myelin splitting ferment said to be present in excess in the tissue fluids of cases of disseminated sclerosis have achieved considerable popularity. Quinine is regarded as being the most efficacious means of inactivating this ferment (Brickner 1932, 1935). Other antimyelolytic factors are Vitamin B.1 (Aneurin) and heat. MacIntyre (1949) reports the use of quinine hydrochloride, Vitamin B.1, and liver. Liver is administered because of its reputed action in aiding metabolism of myelin. Goodall and Slater (1931) and Gowlland (1935), had previously suggested liver therapy in disseminated sclerosis. Adams (1936), however, considered that liver therapy could not be regarded as being in any way specific or "indeed of much real value".

Lafontaine (1948) made the observation that lipolytic activity could be inhibited by heat. It is possible that the value of pyretoytherapy may at least in part be due to this action.

However strong the theoretical grounds for using antimyelolytic drugs, it is probable that no specific attribute can be accorded the lipase inhibitors such as quinine. This view is in accordance with those expressed by MacIntyre and MacIntyre (1943) and by Reubi (1947).

(b) Other Forms of Treatment.

Vitamins. Vitamins have been extensively used in the treatment of disseminated sclerosis. Reference has already been made to the vasodilating properties of nicotinic acid. Aneurin has achieved certain popularity on the grounds that it, like quinine, inhibits lipolytic activity and, perhaps, along with other members of the B. complex contained in liver it may aid in the metabolism of myelin. Moore (1940) recommended the use ofVitamin B.1, on the basis that deprivation results in a disturbance of the normal metabolism of carbohydrate in the central nervous system, leading to an accumulation of pyruvic acid. He suggested that such a deviation from the normal produces physiological and pathological changes in nerve tissue. A further action of Vitamin B.1, may be its curare-like action which was observed by Pick and Unna (1945) when the drug was given in excessive doses.

The National Multiple Sclerosis Society (1947) consider that vitamins have no specific effect on the course of the disease in well nourished patients. Subclinical avitaminosis B. is, however, a common condition particularly when the requirements

of the vitamin are increased by a compulsory high carbohydrate intake diet. Vitamin B. may therefore be employed on the assumption that it protects the nervous system from damage resulting from a subclinical deficiency. In a nervous system which is already the seat of a disease process, the results of such deficiency may predispose to further spread of this process.

Williams (1947) advocated the intravenous administration of Vitamin C, together with a diet rich in this vitamin and the parenteral administration of liver extract. This author found subnormal levels of Vitamin C in the blood in 17 patients before treatment commenced. Over a seven year period a relapse occurred in only one case who, incidentally, had failed to carry out dietary instructions on his discharge from hospital. Williams does not regard disseminated sclerosis as being a Vitamin C deficiency disease. He suggests, however, that a deficiency of ascorbic acid permits an easy invasion of the nervous system. It is pointed out that citrus fruits are rare in Scandinavia where disseminated sclerosis is common compared with Mediterranean countries where the incidence of the disease is extremely low.

It is reasonable to employ vitamins when there is the slightest suspicion that a deficiency exists, partly for reasons already described in connection with Vitamin B.1, and partly because it is important "to maintain nutrition at a high standard" (Risien Russell, 1911). Putnam (1939) reported

subjective improvement in some patients treated with vitamins but no protection was afforded them against relapses, whilst Reubi (1947) considers dietetic measures, including massive doses of vitamins, to be ineffective. It is interesting to observe that Vitamin C is known to have a beneficial effect in allergic diseases. The use of alphatocopherol (Vitamin E) will be referred to later.

Potassium Iodide. The use of potassium iodide was recommended by Marie (1895) as being suitable for the sclerotic element of the disease. Collier and Adie (1934) consider this substance to be of great service. Although neither specific nor curative - as in neurosyphilis, so in disseminated sclerosis - potassium iodide has still a place in therapeutics.

Curare and curare-like drugs. Curare in the form of a crude extract or as a crystalline alkaloid, d-tubocurarine chloride, has been used in an attempt to relieve muscle spasm in disseminated sclerosis. For this purpose it is best administered intra-muscularly as an oil-wax suspension. It appears to act by preventing acetylcholine from exerting its normal effect on voluntary muscle. It has also been suggested, however, that relief of spasticity in certain instances is due to a central effect (Pick and Unna, 1945). Curare may liberate histamine. This was reported by Grob, Lilienthal and Harvey (1947). Although this liberation of histamine followed intra-arterial injection, it is possible that a similar occurrence may take

place after intramuscular administration of curare. In certain subjects, suffering from disseminated sclerosis, treatment with curare therefore may be attended by a beneficial effect due on the one hand to relief of spasticity and on the other to vasodilation consequent on histamine liberation.

Apart from relieving spasticity and preventing contractures Schlesinger (1946) observed that curare administration may relieve tremor in some cases. Jonez (1948) reports favourably on the combined use of d-tubocurarine in oil and wax and histamine. Other investigators have, however, reported disappointing results (Cooper & Hoen, 1948; Clarke and Hotston, 1948).

It would appear that the main use of curare in oil is in permitting the patient to derive maximum benefit from physiotherapy. Untoward results are uncommon and Jonez (1948) administered twenty thousand doses without a single undesirable reaction. In view, however, of occasional idiosyncrasy to the drug (Gray and Halton, 1948), the initial dose should be a small one and prostigmine should be available to combat any complications which may occur.

Myanesin is a pure crystalline synthetic substance and produces muscular relaxation by diminishing the reflex activity of the spinal cord (Marston, 1948). Its efficacy as a relaxant in anaesthesiae has been commented on by Davison (1948.)

Schlesinger and his associates (1948) reviewed the use of myanesin in various conditions and reported that intravenous administration of the drug was attended by relief of spasticity due to lesions of the brain and spinal cord. This therapeutic effect, however, lasted for only a short time after the injection of the drug was discontinued and he placed no reliance on oral administration. In the opinion of Berger and Schwartz (1948), however, myanesin is effective when given by mouth. In their experience exaggerated reflexes due to spastic paralysis are reduced to normal without affecting normal reflexes. Considerable recovery of voluntary movement was obtained in hemiplegics, and various forms of tremor were improved. Reported toxic effects after intravenous administration include haemoglobinuria and venous thrombosis. The tendency to nausea reported by Schlesinger (1948) was not a feature in Berger and Schwartz's cases, some of which were treated continuously for five weeks without the occurrence of side effects.

Prostigmin is a synthetic physostigmine analogue. It apparently acts by protecting acetyl choline from destruction by choline esterase. It therefore exerts an indirect cholinergic effect on all structures innervated by cholinergic fibres. Prostigmin and curare have, therefore, antagonistic actions on the motor end-plate. Berman (1948), however, suggests that curare and prostigmin act synergistically on the central

nervous system. The use of prostigmin in disseminated sclerosis is recommended by Scheinker (1949), on the basis that in this disease there is a "myasthenia like fatiguability of muscles". MacIntyre (1949), however, considers it to be of no value in disseminated sclerosis, and Aring (1949) suggests that prostigmin in this disease can only have a psychotherapeutic effect.

Fatiguability of muscles is a feature of disseminated sclerosis and a frequent complaint is "after walking for a certain distance my leg commences to drag". Further, peripheral circulatory disorders, which, as already noted, are frequently encountered in disseminated sclerosis, have benefited from the administration of prostigmin. This drug may, therefore, have a use in the symptomatic treatment of disseminated sclerosis. Undesirable side effects can be controlled by the concurrent administration of atropine.

(c) Symptomatic Treatment. The value of physiotherapy has been commented on by most authorities including Risien Russell (1911), who stated "massage with passive movements at the various joints is of undoubted value in lessening the tendency to permanent contracture and to spasmodic rigidity". In similar terms Jeliffe and White (1923) remarked on the beneficial results of physiotherapy whilst Collier and Adie (1934) observed that "training exercises will usually improve the ataxy of the legs". More recently, the National Multiple

Sclerosis Society (1947) remark on the value of massage, hydrotherapy and exercises, passive and active, in the treatment of disabilities resulting from disseminated sclerosis. The value of curare and similar drugs in unmasking latent muscle power, and thus permitting the patient to derive maximum benefit from physiotherapy, has already been mentioned.

The use of ultra violet light may be mentioned under the heading 'physiotherapy'. Livet (1926) reported its use in 11 cases, but the results obtained were unimpressive. In moderate dosage it may, however, benefit some cases by its general tonic action. Further, by increasing the activity of the reticulo-endothelial system with a resulting non-specific increase in antibodies, irradiation treatment exerts an anti-allergic influence (Urbach and Gottlieb, 1946). Similarly, the use of X-ray therapy (Herman, 1931) may be compared with foreign protein therapy. X-ray therapy results in slight damage to tissues and the breakdown products so formed act as antigens.

Of great importance in the treatment of disseminated sclerosis is what is termed by the National Multiple Sclerosis Society (1947) "moral building", and by MacIntyre (1939) as "supportive treatment". This consists essentially of sympathetic understanding of the problems confronting each individual patient, and advice and help in solving them. This aspect will receive further mention in the next section.

3. Personal Experience in the Treatment of Disseminated Sclerosis.

The several aspects considered in this section will be discussed under the following five main headings:-

(a) Preventive Treatment.

(b) Active Treatment.

(c) Ancillary Treatment.

(d) Symptomatic Treatment.

(e) Supportive Treatment.

(a) Preventive Treatment. True prophylaxis can not be achieved until more is know of the infective agent and the mode of its transmission to the individual. Relative prophylaxis, however, can be obtained by guarding the patient against predisposing factors. The relationship of trauma, pregnancy, infection, emotional upset, exhaustion and exposure to the onset and course of the disease has already been discussed. Avoidance, when at all possible, of such predisposing factors is of obvious importance.

Climate would appear to exert some influence. Thus, a damp climate seems to be less favourable than a dry one to the course of the disease. Some support for this suggestion is forthcoming from a consideration of the world incidence of disseminated sclerosis. Thus in Europe a high incidence of the disease occurs in damp Northern European countries compared with dry Mediterranean ones. Similarly on the American Continent

the greatest incidence of the disease appears to be in those regions which have a considerable rainfall. For example, the disease is relatively more common along the northern Atlantic coast and in the Great Lakes area, than in the southern States of America or in South America. It is an uncommon disease in the African Continent and is almost non-existent in China and Japan. Further evidence in support of this hypothesis lies in the observation made by the National Multiple Sclerosis Society (1947) that patients who move from a cold damp climate into a mild dry one are often relatively free from acute relapses. I, personally, have been impressed with the fact that many patients suffering from disseminated sclerosis state that their condition is worse in cold, damp weather. When the district incidence in Scotland is investigated in a future study, it will be of interest to equate the incidence of the disease with the annual rainfall in various areas.

It is of interest to note, in connection with the allergic theory of aetiology, that climatic conditions exert an influence on allergic manifestations. Thus, it is stated that areas situated along the seashore and therefore damp, as well as moors and a clay soil, favour the development of allergy. It has also been observed that skin reactions are stronger when the barometer reading is low than when it is high. It is also known that weather changes have a profound effect on the autonomic nervous system, and further, that the vascular

system undergoes exaggerated reactions following sudden changes in weather.

Lastly, should brucellosis play an aetiological role, prophylaxis in working with susceptible animals, milk, and excreta is of obvious importance. Further, vaccination in the human against this infection should be within the bounds of possibility.

(b) Active Treatment. No treatment can be considered specific until the causative agent is definitely known. The measures which will be discussed are used empirically, and are considered to exert a beneficial action on the infective-allergic nature of the disease.

Arsenic. It is our custom, in suitable cases, to administer organic arsenic intravenously. It is given either as neoarsphenamine or as mapharside. An injection is given at weekly intervals on six occasions. A rest period of four weeks is followed by a further course of six injections. Subsequently several more courses of arsenic are given alternating with similar rest periods. It is my impression that an annual course of six injections, after the initial four or five courses, has been attended by the best results.

During the intervals between courses of organic arsenic, the oral administration of this substance is advised, either in the form of liquor arsenicalis, Donovan's solution, or the pill of Ferri carb. et arseni. One of these preparations is

prescribed thrice daily on alternate months, or for the first ten days in each month.

No toxic manifestations have been encountered with this form of treatment.

Adams (1921) reported that the colloidal gold tends to change towards normality in cases of disseminated sclerosis under treatment with salvarsan. We are satisfied that such changes in the gold sol do occur, and this is exemplified by the following case:-

> H.M. Male, aged 32.
> This was clinically a typical case of disseminated sclerosis. The Wassermann reaction of the cerebrospinal fluid was negative and the colloidal gold before the commencement of treatment furnished the following curve - 5543100000. He was treated with several courses of neoarsphenanine, and one year after the initial observation had been made, the gold curve was - 1100000000

It is, of course, recognised that spontaneous changes occur in the colloidal gold reaction of the cerebrospinal fluid in disseminated sclerosis and, further, that progressive cases may be associated with a negative colloidal gold. It is felt, however, that a change towards normality associated with clinical improvement and following rational treatment should be regarded as significant.

Penicillin. The rationale of penicillin therapy in disseminated sclerosis has already been discussed. We have employed this form of treatment in 15 cases. Six patients received penicillin only. The remaining nine were given penicillin in addition to some

other form of active therapy considered by us to be beneficial. Owing to restricted supplies, the original cases received a smaller total dosage of penicillin than that now employed. In no instance, however, was the total dosage less than three million units.

As with arsenic, we have found changes in the colloidal gold to follow penicillin therapy. The colloidal gold results in the six cases treated with penicillin alone are now reported:-

Case 4 (P); Colloidal Gold.	1	2	3	4	5	6	7	8	9	10
18/11/46	5	5	5	5	4	3	2	1	0	0
After Penicillin (3 mega units)										
26/12/47	5	5	5	5	5	4	3	2	1	0
10/2/47	5	5	5	5	3	2	1	0	0	0
29/3/47	5	4	3	2	1	0	0	0	0	0
27/4/47	1	2	4	4	4	3	0	0	0	0

Case 7 (P); Colloidal Gold	1	2	3	4	5	6	7	8	9	10
14/1/47	3	3	4	4	3	1	0	0	0	0
After Penicillin (3 mega units)										
10/2/47	2	2	2	3	2	1	0	0	0	0
16/4/47	3	2	1	1	0	0	0	0	0	0
4/9/47	0	0	1	2	2	1	0	0	0	0
2/10/48	1	1	2	2	1	0	0	0	0	0

Case 8 (P); Colloidal Gold	1	2	3	4	5	6	7	8	9	10
3/1/47	5	5	5	5	5	3	1	0	0	0
After Penicillin (3 mega units)										
21/1/47	5	5	5	5	5	4	3	2	1	0
27/2/47	5	5	5	5	4	2	1	0	0	0

Case 9 (P); Colloidal Gold	1	2	3	4	5	6	7	8	9	10
12/12/46	2	3	4	3	2	1	0	0	0	0
After Penicillin (3 mega units)										
29/12/46	2	3	4	3	2	1	0	0	0	0
26/1/47	1	2	3	4	3	2	1	0	0	0
10/4/47	3	3	3	2	1	0	0	0	0	0
29/11/47	2	3	3	3	2	0	0	0	0	0

Case 11 (P); Colloidal Gold	1	2	3	4	5	6	7	8	9	10
22/9/47	5	5	5	5	4	3	2	1	0	0
After Penicillin (5 mega units)										
9/11/47	4	3	2	2	1	0	0	0	0	0

Case 14(P); Colloidal Gold	1	2	3	4	5	6	7	8	9	10
23/1/47	4	4	4	4	3	2	1	0	0	0
After Penicillin (5 mega units)										
29/3/47	2	1	1	0	0	0	0	0	0	0

Protein Shock Therapy. Protein shock, by the administration of intravenous T.A.B. vaccine, is used routinely in early and in

active or progressive cases of disseminated sclerosis.

The initial dose of T.A.B. vaccine employed is twenty million organisms. Injections are given every fourth day, the dose being doubled on each occasion up to a maximum single dose of two hundred million organisms. A course of protein shock consists of six to twelve injections, the number depending on the general condition of the patient, the results of treatment and other limiting factors.

I have been impressed with the fact that a temperature response of at least 102° F. is essential. To attain this, it may be necessary in some cases to administer a "boosting" does. This second injection is given at the height of the pyrexia if this be below the requisite level, and consists of one quarter to one half the original dose of vaccine.

The possible mechanisms whereby protein shock exerts a beneficial influence have been discussed. Whatever theory or theories may ultimately be proved correct, I am satisfied that in an encouraging proportion of cases a remission can be initiated by this means. Four facts of interest have emerged from the study of cases so treated:-

(i) An exacerbation of symptoms and signs have been observed to accompany the rise of temperature in many instances. For example, legs may become extremely spastic or diplopia may be complained of. Such exacerbations are only temporary and, indeed, I have

found them to have a good prognostic significance. Thus, in instances where extreme spasticity of the lower limbs is observed during a protein shock, walking will ultimately be better than before treatment was commenced. These focal reactions indicate, however, that pyretotherapy should not be employed in a patient with signs or symptoms referable to a lesion in the brain stem. An over reaction of such symptoms may be attended by a fatal issue.

ii. Herpes febrilis is not infrequently observed during the course of treatment with protein shock. Of its prognostic significance, if any, I am in doubt, and certainly I have seen cases derive benefit from protein shock therapy in whom herpes febrilis was never manifest. The presence of herpes is no deterrent to the continuance of treatment. Of some interest is the fact that protein shock by means of T.A.B. vaccine appears to evoke this virus infection in individuals who had never previously suffered from such an eruption. In one case, in my experience, a typical herpes zoster appeared coincident with protein shock therapy.

iii. The effect of protein shock on the leucocyte count in the peripheral blood was studied in a number of cases. Our findings did not differ from those of Whitby and Britton (1944) who observe that the onset of a shock

is associated with intense leucopenia. This is accounted for by an almost total disappearance of the polymorphonuclear cells. When the temperature is falling the count returns to normal, this being followed by a polymorphonuclear leucocytosis.

iv. The effect on the colloidal gold has been studied in a number of cases treated with protein shock therapy. It has been found that this form of treatment tends to result in an alteration towards normality of the gold curve. Examples:-

M.W. Female aged 40

Colloidal gold before treatment..... 0 0 2 4 4 3 1 0 0 0

Immediately after treatment..... 0 0 1 2 3 2 1 0 0 0
(after six shocks)

J.McH. Male aged 44.

Colloidal gold before treatment.... 5 5 4 4 4 3 2 1 0 0

Nine months after treatment..... 0 0 0 0 0 0 0 0 0 0

One case is perhaps of particular interest in that on two occasions a slight exacerbation of symptoms was accompanied by increased precipitation of the gold sol. On each of these occasions two protein shocks were followed both by remission of symptoms and also a flattening of the gold curve.

Malaria Therapy. In view of the improvement obtained with malaria therapy in general paralysis, we have employed this form of treatment in disseminated sclerosis. With regard to general paralysis Rudolf (1927) reports improvement in:-

The general physical condition of the patient.

Tremor.

Gait.

Sphincter control.

Knee jerks.

Pupillary reflexes.

The cell count, globulin content, colloidal gold and Wassermann reaction of the cerebrospinal fluid.

A number of adult female anopheline mosquitoes infected with plasmodium vivax were obtained. These mosquitoes were used to infect two cases of disseminated sclerosis with malaria. Unfortunately, it was considered that the strain of malarial parasite was too virulent to justify the continuance of its use and this form of therapy was discontinued.

In addition to being infected with malaria, both the patients so treated were also given penicillin. The value of penicillin and malaria therapy in the treatment of neurosyphilis has been stressed by Nicol (1946) and Martin (1948).

Plasmodium vivax gives rise to quotidian and not tertian fever in approximately 80% of primary cases. The effects of this daily fever is one of the causes of a mortality rate of 10% which attends this form of treatment. To avoid this, Whelen and Shute (1943) have recommended the use of sodium bismuth thioglycollate. In the present series the preparation employed was

"thio-bismol" (P.D. & Co.). This substance was administered intramuscularly on one occasion only, once the pyrexial process had become established in a quotidian manner. The slective action of the drug on alternate malarial cycles was at once apparent, the daily paroxysms being replaced by a regular tertian fever.

The mosquitoes were contained in a glass jar covered with a fine mesh gauze. Inversion of the jar so that the gauze was firmly applied to the patient's thigh permitted the insects to feed. At the same time, the mosquitoes could be examined through the jar for evidence of ingested blood. Thereafter the number of "bites" were counted. These were painted with tincture of iodine to allay subsequent irritation. The mosquitoes were fed in this manner on several occasions, each patient receiving approximately twelve to fifteen "bites".

The two cases treated with malaria and penicillin will now be briefly reported:-

M. McG. Female aged 54.

Two years before admission to hospital, this patient developed weakness in both legs. The death of her son on war service appears to have been a precipitating factor in the illness. Subsequent to this onset she experienced paraesthesiae of the left forearm, blurring of vision in one eye and precipitancy with occasional incontinence of urine.

Clinical examination revealed the presence of a pathological degree of temporal pallor in one eye. There was a marked intention tremor, and over active knee jerks were associated with a bilateral extensor plantar response and absent abdominal reflexes.

The presence of free hydrochloric acid was disclosed by fractional test meal examination and

blood examination revealed no anaemia. The Wassermann reaction of the cerebrospinal fluid was negative and the colloidal gold on 24/4/47 was 5432100000.

She was infected with the malarial parasite on 24/4/47, and on 4/5/47, some ten days later, the first malarial paroxysm occurred. Penicillin therapy was commenced on 7/5/47, and on 8/5/47, 0.2 c.c. of thio-bismol was injected intramuscularly. Treatment was terminated on 16/5/47, after eight typical paroxysms by quinine and mepacrine.

Following this treatment lumbar puncture was again performed on 9/6/47. On this occasion the colloidal gold curve obtained was 1132100000. She was subjectively better. In addition, the tremor was lessened, vision was improved, and a more satisfactory control of micturition was re-established.

G.B. Male aged 43.

The initial symptom in this case occurred two years before admission to hospital, when the patient complained of weakness of his left leg. This became progressively worse and four months before admission a marked intention tremor developed in his left arm. He also complained of hesitancy of micturition of several weeks duration.

On examination he was euphoric and somewhat facile. The pupils were unequal and the temporal half of the right optic disc was abnormally pale. There was gross intention tremor of his left hand. The knee jerks were exaggerated and unequal, the abdominal reflexes were not elicited and Chaddocks Test furnished a bilateral extensor response.

The Wassermann reaction of the blood was negative, whilst in the cerebrospinal fluid it was reported as being very weakly positive. The colloidal gold test showed no precipitation of the gold sol.

Malaria therapy was instituted by allowing mosquitoes to feed on his leg on four occasions over seven days. Quotidian malaria developed after an incubation period of thirteen to twenty days. This was converted into tertian paroxysms by the administration of thio-bismol as previously described. Penicillin therapy was instituted once the pyrexial condition was established. The patient became extremely exhausted after the seventh paroxysm and treatment was therefore terminated by quinine and mepacrine.

Subsequent to treatment the patient's walking was greatly improved and tremor was noticeably diminished. Of particular interest, perhaps, was the personality change which occurred. The euphoric outlook

previously present passed through a stage of extreme facility to a more average and normal mentality. Since treatment this patient has maintained a full remission; no fresh symptoms or signs have appeared and he is subjectively and objectively better than before the institution of treatment with malaria and penicillin.

Mental changes, including a "sobering" of the general outlook of the patient have been reported following malaria therapy by Rudolf (1927).

Combinations of Active Methods of Treatment. The combined use of malaria therapy and penicillin has already been reported. Other combinations of treatment which we have employed are organic arsenic and protein shock, and penicillin and protein shock. Of these, the former has been used extensively and may be regarded as the routine form of treatment in the present series. The power of organic arsenic and protein shock to alter the colloidal gold reaction is well exemplified by the following cases. It should be noted that in each case the serological improvement coincided with clinical improvement:-

W.G. Male aged 36.

Colloidal gold	1	2	3	4	5	6	7	8	9	10
12/8/47	4	3	4	3	2	1	0	0	0	0
After Protein shock and N.A.B.										
25/9/47	1	1	2	2	2	1	0	0	0	0

H.M. Male aged 32.

Colloidal gold	1	2	3	4	5	6	7	8	9	10
1/7/43	5	5	5	4	3	2	1	0	0	0
After Protein shock and N.A.B.										
14/8/43	3	3	3	2	1	0	0	0	0	0
22/9/43	1	1	0	0	0	0	0	0	0	0

The above case (H.M.) is of particular interest. After a remission of some three and a half years he reported back complaining of transient dimness of vision in his left eye associated with paraesthesiae in both feet. These symptoms commenced shortly after an influenzal illness. On 9/1/47, the colloidal gold was 4444321000. He was again treated with protein shock this time, combined with large doses of penicillin, and one month later the colloidal gold was 1111000000. Once again this improvement in the cerebrospinal fluid was associated with clinical improvement, in that the vision of his left eye returned to normal and paraesthesiae disappeared.

A further example of serological and clinical improvement coinciding with protein shock and penicillin therapy is recorded in the following case:-

L. McG. Male aged 46.
This man, with evidence of scattered lesions in the central nervous system, had before treatment the following colloidal gold curve.... 1112210000. After protein shock and penicillin, walking was greatly improved and intention tremor markedly diminished. Four months after the termination of treatment the colloidal gold curve was found to be... 0001110000.

Penicillin, arsenic and protein shock have been used concurrently with good results, both clinically and serologically. It is too early as yet to assess the late results of this form of treatment. The results obtained, however, covering periods up to three years following treatment, have been encouraging; the majority of cases have not shown any fresh lesions in the central nervous system, whilst symptoms and signs present at the time of treatment have not progressed.

Forty cases of disseminated sclerosis, treated with protein shock alone, were followed up over a period varying from

one year to six years after discharge from hospital. The condition of these patients at the time of the follow-up examination, are embodied in Table 26. These results may be compared with those obtained in 5 cases of disseminated sclerosis which, for various reasons, received only symptomatic treatment. Whereas 23 (57.5%) of the treated cases were found to be either improved or unchanged, only 1 (20%) of the untreated cases was in like condition. Seventeen patients (42.5%) were either considered to be worse or had died since receiving active therapy. Of the untreated cases, 4 (80%) were worse or had died. It should be noted that the 5 untreated cases were not terminal or otherwise "hopeless" cases.

Copper Therapy. In view of the possible relationship existing between disseminated sclerosis and swayback in sheep, we have treated several cases with copper sulphate. We have been completely unimpressed with the efficacy of this form of therapy. In three out of four cases an exacerbation of symptoms occurred whilst the patient was receiving this treatment. In view of this, and because of the risk of toxic effects, copper therapy has been discontinued.

Anti-Allergic Treatment. Five cases received anti-allergic treatment with either histamine azoprotein "lertigon" or "benadryl"; both preparations were employed in two cases.

"Benadryl" appears to protect the "shock" organ or effector mechanism by competing with histamine for its site of action.

"Lertigon", on the other hand, in responsive cases stimulates the production of antibodies which have the power of neutralising histamine. The two actions are thus synergistic and it is rational to use the two drugs concurrently. I have not experienced any marked success with "benadryl" alone except in one case in which recent acute symptoms rapidly subsided subsequent to the administration of this drug. On the other hand, the concurrent use of "benadryl" and "lertigon" have been followed by good results. This is exemplified by the following case:-

> G.B. Male aged 18.
> This patient was admitted suffering from a recent exacerbation of disseminated sclerosis. The colloidal gold test performed on 14/4/48 furnished the following curve.... 5555421000. He was treated with large doses of "benadryl" and in addition "lertigon" was administered subcutaneously, in increasing amounts, every fourth day.

After thirteen injections of "lertigon" his clinical condition was greatly improved and the colloidal gold curve on 2/6/48 was.... 1543210000.

(c) Ancillary Treatment.

Iodides. The use of potassium iodide as previously mentioned is upheld by such authorities as Collier and Adie. By itself, it has possibly little effect on the course of the disease, but it is used by us as a routine adjuvant to other forms of therapy in the hope that, as expressed by Marie, it may influence the sclerotic element of the disease. It may be given either in a

mixture containing fifteen grains to the dose or along with arsenic in the form of Donovans solution.

Vitamins. For a considerable time Vitamin B.1 (Aneurin) was administered orally and by intramuscular injection, as a routine measure. The rationale underlying its use was twofold -

(i) Aneurin was thought to protect the peripheral neurones from the toxic effect of arsenic given orally or parenterally.

(ii) Subclinical avitaminosis B is probably common. The nervous system suffers readily and early from such a deficiency. It was felt that whereas in otherwise normal central nervous systems little harm would eventuate from such a condition, in disseminated sclerosis the accumulation of pyruvic acid resulting from a deficiency of Vitamin B might be sufficient adversely to influence the patient's condition and thus promote an exacerbation.

We have also employed nicotinic acid principally because of its vasodilating properties. More recently, partly because the administration of one member of the B complex might result in a relative deficiency of the other members, and because of the suggestion that some factor in the B complex either aids the metabolism of myelin or inactivates a hypothetical lipolytic enzyme, we now prescribe a Vitamin B complex preparation such as "benerva compound" which contains aneurin, riboflavine and

and nicotinic acid amide. Still more recently we have employed "becosym" which contains, in addition to the above members of the B complex, Vitamin B6 (pyridoxine) and calcium pantothenate.

Vitamin E (alpha-tocopherol) has been administered in large doses to 9 cases of disseminated sclerosis. The dosage employed varies between 300 mg. and 400 mg. daily, and was given orally. The rationale underlying its use was the ubiquitous anti-ischaemic properties ascribed to this vitamin. The cases chosen were those which exhibited a marked degree of peripheral vaso-spasm. It was felt that this peripheral vaso-motor abnormality might be duplicated in the vessels of the central nervous system. It is too early to assess the results of treatment with alpha-tocopherol but in some cases improvement in peripheral vaso-spasm was observed subsequent to administering the drug. Nicotinic acid has been seen to dilate the vessels of the central nervous system of the cat (Moore, 1940). It would be of considerable interest to ascertain if alpha-tocopherol has a similar action on the vessels of the brain and spinal cord.

I have been able to collect from the literature, from three series, 20 cases of disseminated sclerosis who received treatment with Vitamin E. Of these cases a complete remission appears to have ensued in 2; in 7 a remission with varying degrees of improvement occurred; in 9 the patient's condition was considered to be static, whilst in 2, deterioration followed this treatment.

It would therefore seem reasonable to continue further experimental work with this vitamin both in the treatment of disseminated sclerosis and in the field of experimental laboratory work.

Liver. Although not used routinely, in certain cases liver is administered. The rationale of liver therapy has already been discussed. We favour a "crude" preparation and one is available (heparglandol-B) which fortifies the naturally occurring Vitamin B complex in liver with five members of the group.

Although the basis for the use of liver is largely hypothetical, I have been impressed with the general tonic effect it exerts. This is of value not only in influencing the balance of the disease process in the patient's favour, but is also a factor of importance in permitting the patient to derive maximum benefit from intensive physiotherapy.

(d) Symptomatic Treatment.

Physiotherapy. We are convinced of the value of re-education exercises and massage in the treatment of disseminated sclerosis. On the assumption that the central nervous system is "over wired", it is believed that appropriate exercises train pathways not normally utilised to assume the function of those irreparably damaged.

Massage, by increasing the efficiency of the musculature, plays a complementary role.

Curare. Curare is employed by us in the form of an oil-wax suspension of d-tubocurarine chloride containing 30 mg. per c.c. This drug is indicated in cases in which spasticity masks considerable muscle power. We have not been impressed by its value in cases in which contractures are already present, but its use as an adjuvant to physiotherapy is recommended for preventing the occurrence of this painful and distressing complication.

The dosage employed depends both on the body weight of the patient and on the severity of the condition. Because of the occasional risk of idiosyncrasy, it is our custom to start with a very small dose. Should no untoward reaction occur, one mg. per stone of body weight is administered intramuscularly. This dose is increased by 3 mg. every fourth day until the optimal response is obtained. Such consists of diminution in spasticity without loss of muscle power. This reaction is generally obtained with doses between 15 mg. and 30 mg. In one case, however, 45 mg. was administered every fourth day for several weeks. On no occasion have side effects been marked, and no toxic reactions have occurred.

Although it is not claimed that results have been uniformly good, it is our impression that d-tubocurarine is of limited value in the treatment of disseminated sclerosis. Such value consists mainly in allowing certain cases to derive the maximum benefit from physiotherapy. In this respect it

should be stressed that the action of curare is not transient. Although the immediate effects of an injection pass off within a few days, over a period there is a marked lessening of spasticity, walking is improved and co-ordination of movement is better.

An investigation was planned to measure the effect of curare on muscle tone. The technique employed was that of Yandell Henderson and his colleagues (1936) (1) and (2), with the modifications of procedure advised by Kerr and Scott (1936).

This technique is based on the fact that there is always a degree of tonic longitudinal pull exerted by the bundles of fibres in a muscle. Internal pressure is thus dependent on the tonicity of the fibres, which varies with the state of contraction or relaxation present. This variation, however, can be avoided by ensuring that the muscle examined is at rest. If a hollow needle is introduced into a muscle the pressure required to induce a minute amount of saline can be measured. The fluid from the needle will exert a side-thrust on the muscle fibres. This displacing force will be resisted by the tonicity of the muscle fibres and the pressure of saline required to overcome this counter thrust will be an estimation of the degree of tonus present in that muscle.

It was found, however, in a trial experiment on twelve patients that the results obtained in any given individual were too inconsistent over a period for the technique to be of much

value in estimating the results of a therapeutic agent designed to influence muscle tone.

It was observed, however, that the readings obtained in cases of spastic paraplegia were considerably in excess of those previously reported by Henderson and his associates in a series of normal individuals. No conclusive results followed the intramuscular administration of curare as regards the manometer readings. Further, the variations which occurred from day to day in the same muscle appeared to render useless further investigation along the above lines.

Prostigmin is indicated in cases in which there is a marked loss of muscle power. It is our impression that prostigmin is of value as an adjuvant to physiotherapy. The best results have been obtained in patients who complained that they became readily exhausted when performing re-education exercises. In such instances the administration of prostigmin has been followed by improvement in performing the exercises and a substantial lessening of fatigue has been observed.

Prostigmin is generally prescribed orally in tablets containing 15 mg., but in severe cases oral administration is combined with daily subcutaneous injections of the drug. Muscarine-like side effects are minimised by the simultaneous administration of belladonna.

With regard to other symptomatic measures, the treatment of upsets of micturition and constipation require brief comment.

Frequency and precipitancy of micturition benefit from the administration of tincture of belladonna in 5 minim doses thrice daily, whilst Carbachol given orally in 2 mg. tablets is effective in cases showing hesitancy of micturition or retention of urine.

Constipation generally responds to the administration of liquid paraffin or one of the agar-liquid paraffin preparations. It was observed that many cases of disseminated sclerosis showing frequency of micturition also complained of constipation. This may be explained, at least in part, by the fact that such cases voluntarily limit their fluid intake to combat the urinary symptoms. It has been stressed by McKenney (1946) that a poor fluid intake predisposes to constipation.

(e) Supportive Treatment. The necessity for supportive treatment is evident to all who have had contact with cases suffering from disseminated sclerosis. This disease has the effect of rendering patients helpless whilst, to a considerable extent in the early stages at least, leaving unimpaired their mental faculties. Thus, the victim is left to combat how best he can an unknown and unseen enemy who, week by week, month by month, and year by year, leaves him less able to fend for himself and his dependents. The adverse effect of feeling that he is alone in such a fight is obvious. Supportive treatment consists of affording the patient a sympathetic understanding of the various problems which confront him.

A case suffering from this disease must be made to feel that active steps are being taken to combat the cause and effect of his illness. Cold, scientific, therapeutic nihilism has no place in the treatment of disseminated sclerosis, and the expression so often heard "nothing can be done for you" is both misguided and erroneous.

To accomplish such supportive treatment, all cases of disseminated sclerosis who have received treatment from us are brought back at intervals for examination and advice. The duration of the intervals between these interviews depends on the requirements of each case and their individual need for "morale building".

An integral part of this aspect of treatment is to secure, for male cases in particular, a suitable form of employment. Such patients must not be allowed to adopt the demoralising belief that they are no longer capable of being of service to the community. Every effort is therefore made through the Social Service Department of the Infirmary and through other agencies to secure suitable employment for them. No attempt is made in the first place to change the occupation of a patient provided that such entails no risk either to the patient or to others. Further, the employment should not be such as to leave the patient mentally or physically over fatigued. In some instances, however, a more sheltered occupation is considered advisable. No broad generalisation can

be made as to the advisability or otherwise of securing sheltered employment for these cases from the time the disease is first diagnosed. Each case must be considered on its individual merits. For example, many cases with a remission of long duration have achieved a position of importance in professions or in commerce which they could not have attained had their occupation been changed at the time of the original diagnosis. On the other hand, patients with established symptoms are unable to compete for employment in the open labour market; these cases must be helped to secure a suitable occupation.

VII

CONCLUSIONS.

The present study has embraced a consideration of the aetiology, symptomatology, serology, prognosis and treatment of disseminated sclerosis. The literature relative to each aspect has been briefly reviewed, and the work performed by the author is reported.

It is apparent that with regard to the aetiology of the disease, there is no uniformity of opinion. The infective theory is, however, gaining ground, particularly as many aspects of the disease process can now be explained on a secondary allergic basis. It follows, however, that should the progress of the disease depend on altered myelin acting as antibody, the aetiology of the clinical syndrome of disseminated sclerosis may be a diverse one. Thus, any process, whether infective, toxic, vascular or metabolic which has the property of altering myelin, may be followed by a clinical syndrome indistinguishable from that of infective disseminated sclerosis. It is suggested, therefore, that whereas disseminated sclerosis is a pathological entity, the clinical syndrome may result from multiple causes.

With regard to the experimental work on sheep which has been briefly reported, there is little to add. The inoculated animals did not develop a disease which could be identified on clinical or pathological grounds as one which occurs naturally in sheep. In particular, neither swayback, nor scrapie, nor louping ill was reproduced. Histological examination of the nervous system of one inoculated animal did, however, reveal the presence of a diffuse meningo-encephalitis of subacute type. There was no evidence of demyelination. It is not possible to say whether or not this inflammatory process was occasioned by the causative agent of disseminated sclerosis in the human subject. Although the histological picture bore little resemblance to the human disease, it is not, as already emphasised, reasonable to expect the tissues of a sheep to react to a noxious agent in the same way as do the tissues of the human subject. As previously indicated, two other inoculated sheep died. Careful post mortem examination failed to disclose any primary cause of death, and histological examination of the nervous system did not reveal any marked pathological changes. Three other inoculated animals and two control sheep are at present in good health.

It can be inferred from this investigation that at present there is no experimental evidence to support the suggested relationship between disseminated sclerosis and swayback. Further, the infective nature of disseminated sclerosis has neither been

proved nor disproved. Facilities, however, were not available to permit investigation into a possible virus aetiology.

At present there is but little evidence to support the view that disseminated sclerosis is related to brucellosis. Positive skin reactions to brucellin have been obtained in a number of cases of disseminated sclerosis. In no instance, thus far, have positive agglutination reactions in the blood or cerebrospinal fluid been obtained, and it can be concluded that, at present, evidence in favour of this relationship lacks experimental or statistical support. Although the brucellin group of microorganisms may not play an aetiological role in disseminated sclerosis, it is possible that the cow and other animals may harbour another microorganism which may thus frequently coexist with Br. abortus and which in man may occasion disseminated sclerosis.

The mode of transmission of disseminated sclerosis is still unknown. It is suggested, however, that insects may in some instances be responsible for transmitting the causative agent to man.

The importance of early diagnosis is indicated in a statistical analysis of the symptomatology of disseminated sclerosis. This standard of diagnosis depends on an appreciation of the initial symptomatology and of the disease process.

In discussing the abnormalities found in the cerebrospinal fluid, it was stressed that non-specific changes in the Wassermann

reaction were frequently encountered in cases of disseminated sclerosis. The assistance derived from the examination of the cerebrospinal fluid in the diagnosis of disseminated sclerosis outweighs the suggested adverse influence lumbar puncture may have on the course of the disease. It is felt that evidence in support of this view is lacking, and that lumbar puncture is a justifiable diagnostic procedure in disseminated sclerosis.

In connection with the prognosis of disseminated sclerosis, the suggestion is made that many cases of disseminated sclerosis never require treatment and that, after the initial manifestation, a life-long remission may ensue. In general, the prognosis would appear to be more favourable than was once supposed. This may be due to the disease assuming a less virulent form in recent years.

It is frequently stated that the enormous number of methods and drugs used in the treatment of disseminated sclerosis is an indication of our present inability to treat this disease efficiently. Exception should be taken to such statements and we are of the opinion that, although in the present state of our knowledge disseminated sclerosis can not be treated specifically, much can be done in many instances to retard the progress of the disease and to improve the lot of those who suffer from it.

It is not claimed that the methods of treatment used in the present investigation are completely satisfactory. It is believed, however, that they compare favourably with other forms

of therapy at present in vogue. If treatment with protein shock and arsenic and penicillin be instituted, the chances of a prolonged remission ensuing are reasonable. It is important to institute further treatment along these lines at the earliest sign of extension of the disease process or deterioration in the patient's condition.

It is not inconceivable that the lack of a specific remedy depends to a considerable extent on a varied and imperfectly understood aetiology. Thus in some cases anti-infective treatment is indicated, in others vascular abnormalities should be combated and in a further group deranged metabolism may require treatment.

It is suggested that the present position is capable of improvement along the following lines:-

(1) Continued research.

(2) Increased facilities for treatment.

(3) Organisation of suitable employment.

Controlled, continued, and expanding <u>research</u> is an obvious need. The problem is too vast to be attempted by other than a team consisting of clinicians, research workers, and statisticians. Instead of isolated and independent groups of workers, I am convinced that the best results will accrue from research organised on a national, or preferably an international basis.

Lack of bed space and nursing facilities are probably the

greatest handicaps to treatment. As this depends on far reaching economic ramifications, no improvement can be expected at the present time. Many cases, however, can and should be treated as out-patients. It is in this respect that the present position is capable of improvement. Whereas clinics exist for the specialised treatment of peptic ulcers, varicose veins, venereal diseases and other conditions, in this respect, disseminated sclerosis, one of the most common organic nervous diseases, has been completely ignored. It would indeed be worth while to establish clinics to which cases of disseminated sclerosis and other chronic nervous disorders, such as Parkinsonism, could be referred. Not only would the sufferers from these diseases benefit from such a scheme but research would also be advanced. In such an organisation, the general practitioner, the nursing profession, physiotherapists and the social service department would all play important and complementary parts.

As previously indicated, disseminated sclerosis is one of the most common organic nervous diseases. It is, however, unknown by name to the general public. It thus compares unfavourably with poliomyelitis, which in this country at least, is far less common. Propaganda designed to educate the lay public on this subject is important from the point of view of early diagnosis. Further, it is essential to awaken public interest in those problems of aetiology and treatment which demand solution as soon as possible.

With regard to the question of employment, patients suffering from disseminated sclerosis fall into one of four categories:-

(1) Patients capable of following their normal occupation.

(2) Those requiring "sheltered" occupations.

(3) Those who are unable to travel to a place of employment, but who could undertake work at home.

(4) Those unable to undertake work of any description.

With categories one and four we are not concerned. There is, however, a large disseminated sclerosis population which falls into either the second or third categories. In the case of the former, some advance has already been made and factories exist which, by affording a "sheltered" occupation for those who are disabled, to a certain extent cover this need. Extension of such a scheme is urgently desirable as at present the bulk of workers so employed are partially disabled ex-service personnel.

No organisation exists, however, to assist patients who, by reason of their disability, are only fit to undertake work in their home surroundings. An organisation could be established to cater for this category. In this direction we hope to improve the present position. Financial support to purchase materials which can either be made or assembled in the patient's home is necessary. A second essential is a system whereby the completed article can be placed on the market. In this connection it might be possible to obtain the goodwill of retail shops and stores.

Voluntary workers would be required to collect and distribute raw materials or parts and to deliver the product to the stores. This assistance, I feel, could be readily obtained.

The Science of Medicine is not inseparable from the Art. Both aspects are complementary and, in disseminated sclerosis particularly, it is important - and indeed essential - to reconcile the two. Science must play its part in definitely establishing aetiology of the disease and in devising specific treatment. With the Art lies the responsibility of lightening the burden of the sufferers and permitting them to realise that, even though afflicted, they are still able to play a useful part in maintaining the social structure.

THE DISEASE PROCESS IN DISSEMINATED SCLEROSIS

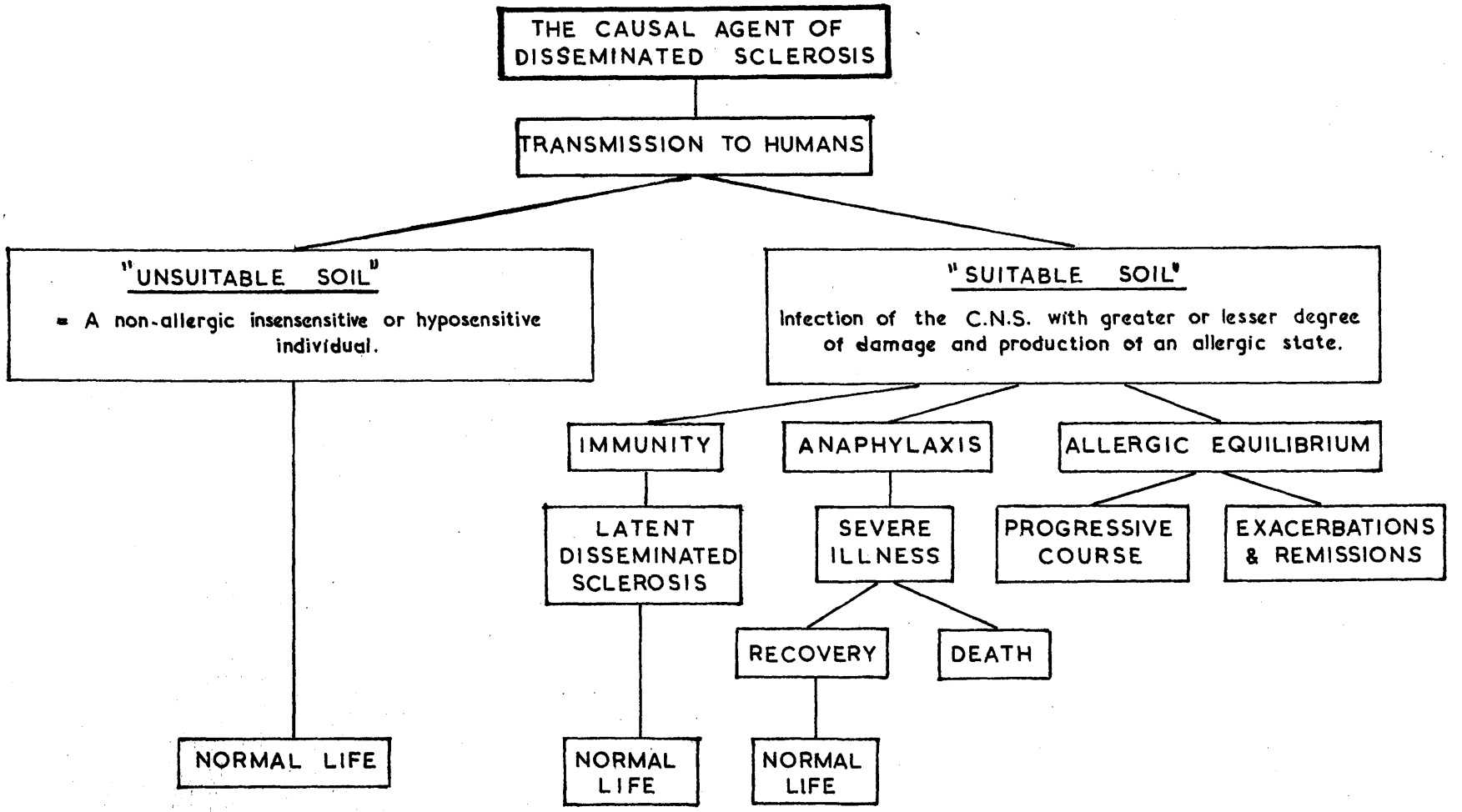
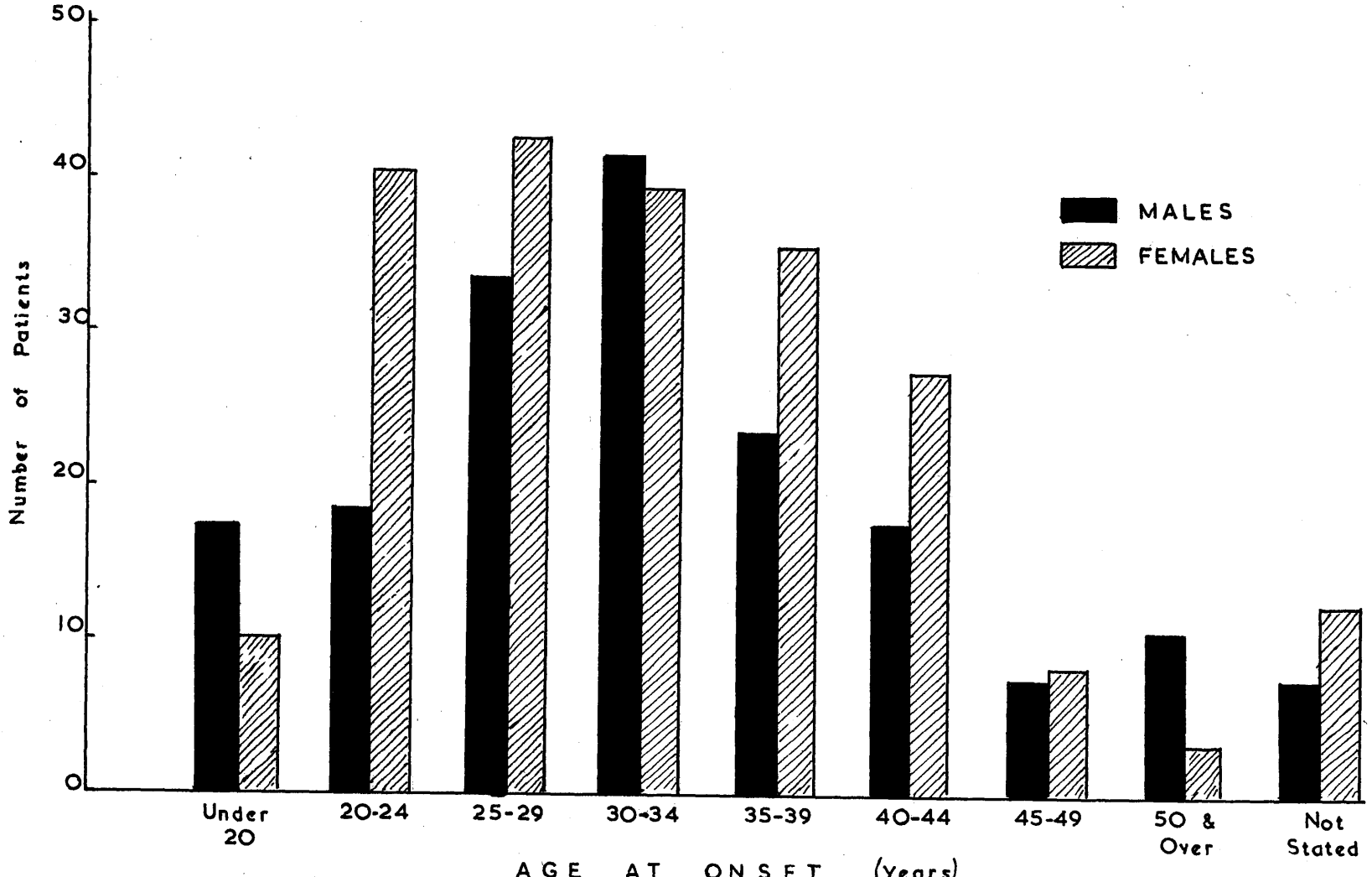


DIAGRAM 2.

DISSEMINATED SCLEROSIS

SEX AND AGE INCIDENCE AT ONSET (389 CASES).



(Diagram 2)

Table 1.

Disseminated Sclerosis.

Occupational incidence in 173 Male cases.

Occupation.	No. of cases.	%
Agricultural occupations.	18	10.4
Metal Workers	19	11.0
Textile Workers	3	1.7
Makers of Foods, Drinks & Tobacco	2	1.2
Workers in Wood & Furniture	8	4.6
Painters & Decorators	4	2.3
Shipwrights	2	1.2
Transport Workers	4	2.3
Commercial, Finance & Insurance occupations	18	10.4
Public Administration & Defence	6	3.4
Professional Occupations	15	18.7
Personal Service	2	1.2
Clerks & Draughtsmen: Typists	11	6.3
Other & Undefined Workers	12	6.9
Not Stated	49	28.4
Totals	173	100.0

Disseminated Sclerosis.

Country Association in 389 cases.

	Males	Females	Total No.	Total %
Lived in Country	55	63	118	30.3
Worked in Country	3	1	4	1.0
Been in Country	38	35	73	18.8
Not been in Country	6	6	12	3.1
Association with Country not stated	71	111	182	46.8
Totals	173	216	389	100.0

Disseminated Sclerosis.

Sex incidence in 310 cases over three decades.

Sex		1921 - 29 No.	1921 - 29 %	1930 - 39 No.	1930 - 39 %	1940 - 46 No.	1940 - 46 %
Males		44	38.6	60	48.0	30	42.3
Females		70	61.4	65	52.0	41	57.7
	Totals	114	100.0	125	100.0	71	100.0

Disseminated Sclerosis.

Age incidence at onset of disease in 389 cases.

Age at onset (years)	Private series No.	Private series %	Hospital series No.	Hospital series %	All patients. No.	All patients. %
Under 20	22	7.1	5	6.3	27	6.9
20 - 24	48	15.5	10	12.6	58	14.9
25 - 29	56	18.0	19	24.1	75	19.3
30 - 34	61	19.7	19	24.1	80	20.6
35 - 39	46	14.8	12	15.2	58	14.9
40 - 44	33	10.7	11	13.9	44	11.3
45 - 49	14	4.6	1	1.3	15	3.9
50 +	11	3.5	2	2.5	13	3.3
Not stated	19	6.1	-	-	19	4.9
Totals	310	100.0	79	100.0	389	100.0

Disseminated Sclerosis.

Comparison of sex and age incidence in 389 cases.

Age at onset (years)	Males		Females		All patients	
	No.	%	No.	%	No.	%
Under 20	17	62.9	10	37.1	27	100
20 - 24	18	31.1	40	68.9	58	100
25 - 29	33	44.0	42	56.0	75	100
30 - 34	41	51.3	39	48.7	80	100
35 - 39	23	39.7	35	60.3	58	100
40 - 44	17	38.6	27	61.4	44	100
45 - 49	7	46.7	8	53.3	15	100
50 +	10	76.9	3	23.1	13	100
Not stated	7	36.8	12	63.2	19	100

Table 6.

Disseminated Sclerosis.

Initial symptoms in 389 cases.

Symptoms	No. of patients.	%
Weakness - one lower limb	90	23.1
Weakness - both lower limbs	73	18.8
Temporary dimness or loss of vision in one eye	54	13.9
Diplopia	50	12.9
Paraesthesiae	34	8.7
Weakness - one upper limb	19	4.9
Weakness - one lower and one upper limb	16	4.1
Vertigo	15	3.8
Upset of micturition	11	2.8
General debility; exhaustion; weakness	4	1.0
Mental confusion; inability to concentrate	3	0.8
Pain in leg(s)	3	0.8
Pain in back	3	0.8
Weakness all four limbs	2	0.5
Epileptiform attacks	2	0.5
Dysarthria	2	0.5
Unilateral facial paralysis	2	0.5
Loss of sensation over side of face; weakness of mastication	2	0.5
Staggering gait	2	0.5
Vomiting	1	0.3
Nervousness	1	0.3
Total	389	100.0

Table 7.

Disseminated Sclerosis.

Initial symptom in relation to sex of patients.

Initial symptom	Female cases		Male cases		Total	
	No.	%	No.	%	No.	%
Paresis	110	50.9	90	52.0	200	51.4
Transient loss or dimness of vision	36	16.7	18	10.4	54	13.9
Diplopia	28	13.0	22	12.7	50	12.9
Upset of micturition	2	0.9	9	5.2	11	2.8
Paraesthesiae	24	11.1	10	5.8	34	8.7
Vertigo	6	2.8	9	5.2	15	3.8
Miscellaneous	10	4.6	15	8.7	25	6.5
Totals	216	100.0	173	100.0	389	100.0

Disseminated Sclerosis.

Initial symptom in relation to age of patient.

Initial symptom	Age (in years)											
	Under 20		20 - 29		30 - 39		40 - 49		50+		Not stated	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Paresis	10	37.0	61	45.9	72	52.2	37	62.7	8	61.5	12	63.1
Transient loss or dimness of vision	5	18.5	28	21.0	13	9.4	4	6.8	1	7.7	3	15.8
Diplopia	3	11.1	20	15.0	20	14.5	3	5.2	2	15.4	2	10.5
Upset of micturition	2	7.5	3	2.3	5	3.6	1	1.7	-	-	-	-
Paraesthesiae	3	11.1	9	6.8	16	11.6	5	8.4	-	-	1	5.3
Vertigo	1	3.7	6	4.5	4	2.9	4	6.8	-	-	-	-
Miscellaneous	3	11.1	6	4.5	8	5.8	5	8.4	2	15.4	1	5.3
Totals	27	100.0	133	100.0	138	100.0	59	100.0	13	100.0	19	100.0

Table 9.

Disseminated Sclerosis.

Main symptoms in 389 cases on presenting for treatment,

Symptoms	Patients affected.	
	No.	%
Paresis of limb(s)	368	94.6
Upsets of micturition	173	44.5
Paraesthesiae	135	34.7
Diplopia	84	21.6
Dimness or loss of vision	57	14.7
Vertigo	32	8.2
Facial paralysis	12	3.1
Pain in legs	11	2.8
Pain in back	10	2.6
General debility	10	2.6
Headache	8	2.1
Disorder of speech	6	1.5
Loss of sensation one side of face	4	1.0
Vomiting	3	0.8
Deafness	3	0.8
Epileptiform attacks	2	0.5
Difficulty in swallowing	2	0.5
Mental confusion	1	0.3

Table 10.

Disseminated Sclerosis.

Symptoms of urinary bladder dysfunction in 34 out of 79 hospital cases.

Symptom	No. of patients	% of all hospital patients
Frequency and precipitancy	11	13.9
Frequency	9	11.4
Hesitancy	4	5.1
Precipitancy	3	3.8
Precipitancy and incontinence	2	2.5
Retention	2	2.5
Frequency and incontinence	2	2.5
Incontinence	1	1.3
Totals	34	43.0

Disseminated Sclerosis.

Mental condition in relation to sex.

	Male		Female		Total	
	No.	%	No.	%	No.	%
Euphoria	24	13.9	8	3.7	32	8.2
Emotionally unstable	15	8.7	20	9.2	35	9.0
Depression	3	1.7	1	.5	4	1.0
Lack of emotional tone	3	1.7	-	-	3	.8
Impaired memory	4	2.3	2	.9	6	1.5
Normal	110	63.6	163	75.5	273	70.2
Not stated	14	8.1	22	10.2	36	9.3
Totals	173	100.0	216	100.0	389	100.0

Table 12.

Disseminated Sclerosis.

Frequency of occurrence of the components of Charcot's Triad in 61 out of 79 hospital cases.

Component(s)	No. of patients.	% of all hospital patients.
Nystagmus; scanning speech; intention tremor	12	15.2
Intention tremor alone	12	15.2
Nystagmus alone	11	13.9
Nystagmus; intention tremor	10	12.7
Scanning speech alone	7	8.9
Scanning speech; nystagmus	5	6.3
Scanning speech; intention tremor	4	5.0
Totals	61	77.2

Disseminated Sclerosis.

Average Blood Pressure levels of various age groups in 54 hospital cases.

Age Group (years)	No. of patients.	Blood Pressure (mm of Hg) Systolic	Diastolic
Under 20	2	107.5	62.5
20 - 29	7	128	81.5
30 - 39	19	119	78.8
40 - 49	23	130.7	83.6
50 +	3	128.6	80

Disseminated Sclerosis.

Frequency distribution of Systolic and Diastolic blood pressures in 54 hospital cases.

Systolic B.P. (mm of Hg)	No.	%
90-	2	3.7
95-	-	-
100-	-	-
105-	5	9.2
110-	6	11.1
115-	2	3.7
120-	12	22.2
125-	6	11.1
130-	8	14.8
135-	2	3.7
140-	6	11.1
145-	1	1.9
150-	1	1.9
155-	-	-
160-	1	1.9
165+	2	3.7
Totals	54	100.0

Diastolic B.P. (mm of Hg)	No.	%
60-	1	1.9
65-	4	7.4
70-	7	12.9
75-	6	11.1
80-	15	27.8
85-	7	12.9
90-	10	18.5
95-	-	-
100-	3	5.6
105-	-	-
110-	-	-
115-	-	-
120-	1	1.9
Totals	54	100.0

Disseminated Sclerosis.

The average Blood Pressure values in a normal series compared with the values in a series of 54 hospital cases.

Age Group (years)	Healthy Males McKinlay & Walker series (1935)			Disseminated Sclerosis Series.		
	No. of cases.	Blood Pressure (mm of Hg)		No. of cases.	Blood Pressures (mm of Hg)	
		Systolic	Dyastolic		Systolic	Diastolic
Under 20	123	126.2	77.4	2	107.5	62.5
20 - 29	398	129.9	80.5	7	128	81.5
30 - 40	45	132.7	85.7	19	119	78.8
40 +	-	-	-	23	130.7	83.6
50 +	-	-	-	3	128.6	80

Disseminated Sclerosis.

Fractional test meal in 64 out of 79 hospital cases.

	Age (years)										Totals	
	Under 20		20 - 29		30 - 39		40 - 49		50 & over			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Free HCl	3	100	20	86.9	25	96.2	7	70	2	100	57	89.1
Achlorhydria	-	-	3	13.1	1	3.8	3	30	-	-	7	10.9

Table 16.

Disseminated Sclerosis.

Wassermann Reaction of the Cerebrospinal Fluid in 79 Hospital cases.

	Negative		Positive - weak		Positive - very weak		Suspicious		No information		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Males	26	66.7	-	-	1	2.6	10	25.6	2	5.1	39	100.0
Females	20	50.0	2	5.0	6	15.0	9	22.5	3	7.5	40	100.0
Totals	46	58.2	2	2.5	7	8.9	19	24.1	5	6.3	79	100.0

Disseminated Sclerosis.

Colloidal Gold Reaction of the Cerebrospinal Fluid in 79 Hospital cases.

	Negative		Paretic		Luetic		No Information		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Males	12	30.8	15	38.5	8	20.5	4	10.2	39	100.0
Females	5	12.5	18	45.0	13	32.5	4	10.0	40	100.0
Totals	17	21.5	33	41.8	21	26.6	8	10.1	79	100.0

Disseminated Sclerosis.

Comparison of the Wassermann reaction and Colloidal Gold.

Test results in 79 Hospital cases.

	Wassermann Reaction											
	Negative.		Positive weak.		Positive very weak.		Suspicious.		No information.		Total.	
Colloidal Gold.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Negative	13	76.5	-	-	2	11.8	2	11.7	-	-	17	100
Paretic	20	60.6	1	3.0	2	6.1	10	30.3	-	-	33	100
Luetic	11	52.4	1	4.8	3	14.3	6	28.5	-	-	21	100
No information	2	25.0	-	-	-	-	1	12.5	5	62.5	8	100
Totals	46	58.2	2	2.5	7	8.9	19	24.1	5	6.3	79	100

Disseminated Sclerosis.

Relationship between age of patient and Serological picture in 79 hospital cases.

Serological picture.	Age group (years)										Totals.	
	Under 20		20 - 29		30 - 39		40 - 49		50 +			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
"Altered" W.R. & Paretic C.G.	1	20.0	2	6.9	8	25.8	2	16.7	-	-	13	16.5
" " & Luetic C.G.	-	-	5	17.2	4	12.9	1	8.3	-	-	10	12.7
" " & negative C.G.	-	-	-	-	3	9.7	1	8.3	-	-	4	5.0
" " & C.G. not stated	-	-	1	3.5	-	-	-	-	-	-	1	1.3
Negative W.R. & Paretic C.G.	-	-	8	27.6	9	29.0	2	16.7	1	50.0	20	25.3
" " & Luetic C.G.	1	20.0	5	17.2	3	9.7	1	8.3	1	50.0	11	13.9
" " & negative C.G.	3	60.0	6	20.7	2	6.5	2	16.7	-	-	13	16.5
" " & C.G. not stated	-	-	-	-	1	3.2	1	8.3	-	-	2	2.5
W.R. & C.G, not stated	-	-	2	6.9	1	3.2	2	16.7	-	-	5	6.3
Total	5	100.0	29	100.0	31	100.0	12	100.0	2	100.0	79	100.0

NOTE: "Altered" W.R. = "Suspicious", "Very weakly positive", or "Weakly positive" Wassermann Reaction.
C.G. = Coloidal Gold.

Disseminated Sclerosis.

Relationship between country association and the serological picture in the cerebrospinal fluid, in 79 hospital cases.

Serological picture.	Country association.								Totals.	
	Lived there		Worked there		Been in country		Not been in country		No reply			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
"Altered" W.R. & Paretic C.G.	5	18.5	-	-	5	21.7	2	25.0	1	5.0	13	16.5
" " & Luetic C.G.	4	14.8	-	-	2	8.7	-	-	4	20.0	10	12.7
" " & negative C.G.	2	7.4	-	-	1	4.4	-	-	1	5.0	4	5.0
" " & C.G. not stated	-	-	-	-	1	4.4	-	-	-	-	1	1.3
Negative W.R. & Paretic C.G.	8	29.6	1	100.0	4	17.4	5	62.5	2	10.0	20	25.3
" " & Luetic C.G.	3	11.2	-	-	3	13.0	1	12.5	4	20.0	11	13.9
" " & negative C.G.	4	14.8	-	-	6	26.0	-	-	3	15.0	13	16.5
" " & C.G. not stated	1	3.7	-	-	-	-	-	-	1	5.0	2	2.5
W.R. & C.G. not stated	-	-	-	-	1	4.4	-	-	4	20.0	5	6.3
Total	27	100.0	1	100.0	23	100.0	8	100.0	20	100.0	79	100.0

NOTE: "Altered" W.R. = "Suspicious", "Very weakly positive", or "Weakly positive" Wassermann Reaction.
C.G. = Coloidal Gold.

Disseminated Sclerosis.

Duration of period between initial symptom and time of presenting for treatment, in relation to the sex of the patient.

	Duration of "latent period" (years)									
	Under 1 year No. %	1 & over No. %	2 & over No. %	3 & over No. %	4 & over No. %	5 & over No. %	7 & over No. %	10 & over No. %	15 & over No. %	Totals No. %
Males	43 24.9	33 19.1	20 11.5	13 7.5	4 2.3	10 5.8	25 14.4	15 8.7	10 5.8	173 100
Females	33 15.3	31 14.4	20 9.3	19 8.8	12 5.5	41 18.9	20 9.3	19 8.8	21 9.7	216 100

Disseminated Sclerosis.

Age at onset in relation to period between initial symptom and time of presenting for treatment.

Age at onset (years)	Years between initial symptom and treatment.									Totals.	
	Under 1 year	1 & over	2 & over	3 & over	4 & over	5 & over	7 & over	10 & over	15 & over		
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No.	%
- 20	5 18.5	3 11.1	2 7.4	2 7.4	- -	1 3.7	3 11.1	5 18.5	6 22.3	27	100
20 - 24	9 15.5	7 12.1	4 6.9	2 3.5	1 1.7	8 13.8	5 8.6	10 17.2	12 20.7	58	100
25 - 29	17 22.7	7 9.4	6 8.0	17 9.3	4 5.3	18 24.0	6 8.0	6 8.0	4 5.3	75	100
30 - 34	15 18.7	15 18.7	9 11.3	6 7.5	2 2.5	10 12.5	16 20.0	4 5.0	3 3.8	80	100
35 - 39	11 19.0	12 20.7	5 8.6	4 6.9	3 5.2	5 8.6	9 15.5	5 8.6	4 6.9	58	100
40 - 44	5 11.4	11 25.0	9 20.5	6 13.6	2 4.5	4 9.1	4 9.1	3 6.8	- -	44	100
45 - 49	5 33.3	4 26.6	1 6.7	2 13.3	1 6.7	1 6.7	1 6.7	- -	- -	15	100
50 +	3 23.1	3 23.1	3 23.1	1 7.7	1 7.7	1 7.7	1 7.6	- -	- -	13	100
Not stated	6 31.6	2 10.5	1 5.3	2 10.5	2 10.5	3 15.8	- -	1 5.3	2 10.5	19	100
All ages	76 19.5	64 16.5	40 10.3	32 8.2	16 4.1	51 13.1	45 11.6	34 8.7	31 8.0	389	100

Disseminated Sclerosis.

Febrile onset compared with period prior to treatment.

	Number of years prior to treatment.										Totals.	
	Under 1 year No.	%	1 & over No.	%	2 & over No.	%	3 & over No.	%	4 & over No.	%	5 & over No.	%	7 & over No.	%	10 & over No.	%	15 & over No.	%	No.	%
Febrile onset	13	23.2	9	16.0	3	5.4	8	14.3	2	3.6	6	10.7	6	10.7	6	10.7	3	5.4	56	100.0
Not Febrile onset	56	19.1	49	16.7	33	11.3	22	7.5	13	4.5	40	13.7	32	10.9	25	8.5	23	7.8	293	100.0
No information	7	17.5	6	15.0	4	10.0	2	5.0	1	2.5	5	12.5	7	17.5	3	7.5	5	12.5	40	100.0

Disseminated Sclerosis.

Initial symptom in relation to period of time prior to treatment.

Initial symptom.	Number of years prior to treatment.										Totals	
	Under 1 year		1 & over		2 & over		3 & over		4 & over			
	No.	%	No.	%	No.	%	No.	%	No.	%		
Paresis	42	21.0	37	18.5	23	11.5	16	8.0	6	3.0	200	100.0
Diplopia	8	16.0	8	16.0	2	4.0	6	12.0	2	4.0	50	100.0
Dimness or loss of vision	7	12.9	6	11.2	5	9.3	3	5.7	4	7.4	54	100.0
Upset of micturition	1	9.1	1	9.1	1	9.1	1	9.1	-	-	11	100.0
Paraesthesiae	4	11.8	5	14.7	4	11.8	3	8.8	2	5.9	34	100.0
Vertigo	5	33.3	2	13.3	3	20.0	-	-	1	6.7	15	100.0
Miscellaneous	9	36.0	5	20.0	2	8.0	3	12.0	1	4.0	25	100.0
All symptoms	76	19.5	64	16.5	40	10.3	32	8.2	16	4.1	389	100.0

Initial symptom.	5 & over		8 & over		10 & over		15 & over	
	No.	%	No.	%	No.	%	No.	%
Paresis	19	9.5	22	11.0	16	8.0	19	9.5
Diplopia	12	24.0	6	12.0	5	10.0	1	2.0
Dimness or loss of vision	7	12.9	7	12.9	7	12.9	8	14.8
Upset of micturition	1	9.1	3	27.3	3	27.3	-	-
Paraesthesiae	10	29.4	1	2.9	2	5.9	3	8.8
Vertigo	1	6.7	2	13.3	1	6.7	-	-
Miscellaneous	1	4.0	4	16.0	-	-	-	-
All symptoms	51	13.1	45	11.6	34	8.8	31	7.9

Disseminated Sclerosis.

Treatment by Protein Shock: condition on follow-up of 40 cases showing treatment since discharge from hospital.

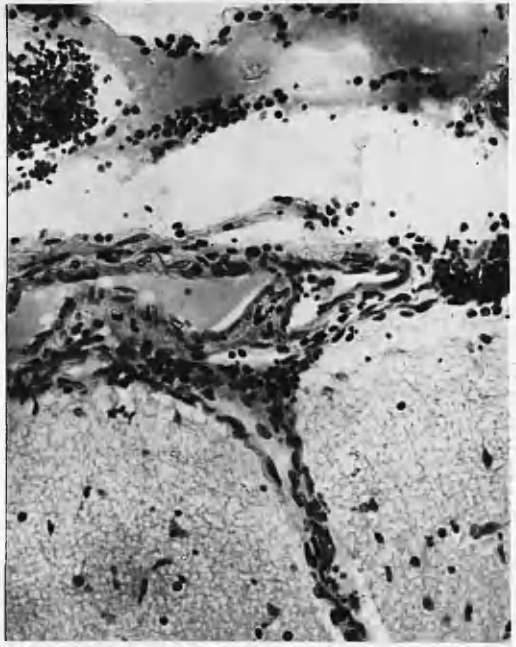
Treatment Since Discharge.	Condition on follow-up.																					
	Unchanged						Improved						Worse						Dead			
	Years after discharge						Years after discharge						Years after discharge						Years after discharge			
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Arsenic orally	1	1	1	4	-	-	1	1	3	1	-	-	-	-	1	-	1	-	-	-	-	-	-	-
Vitamin B	-	-	-	1	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Arsenic and Vitamin B	-	-	-	-	1	-	-	-	2	1	-	-	1	1	-	-	-	-	-	-	-	-	-	-
No treatment	-	1	-	2	-	-	-	-	-	-	-	1	2	-	2	2	2	1	2	-	-	2	-	-
Totals	1	2	1	7	1	-	1	1	6	2	-	1	3	1	3	2	3	1	2	-	-	2	-	-

Photographs

SECTION FROM CEREBRUM OF SHEEP (Stained H. & E.)

SHOWING CELLULAR INFILTRATION WITH PERIVASCULAR CUFFING.

X 100



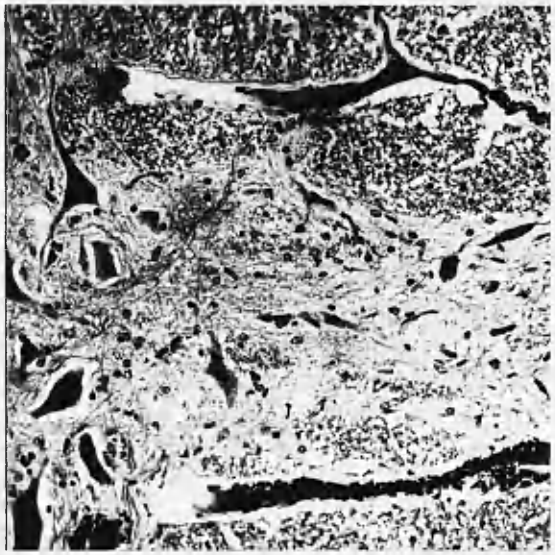
X 250

(P. I.)

SECTION FROM MEDULLA OF SHEEP (Stained H. & E.)

SHOWING INFILTRATION OF CELLS ALONG THE PERIVASCULAR SPACES

X 100

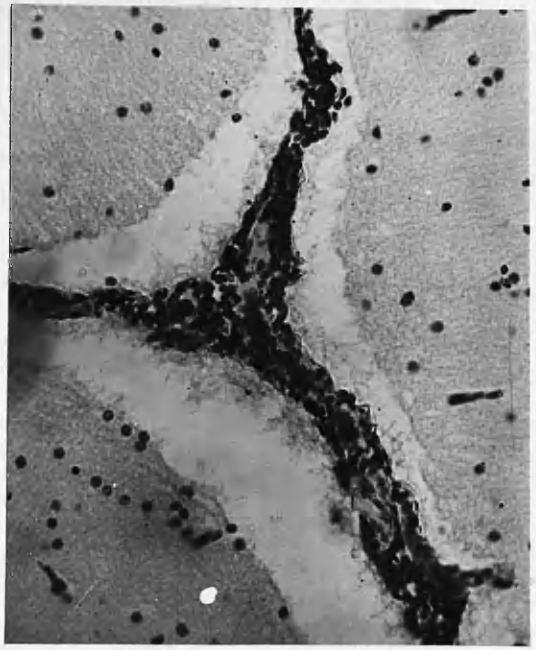


X 250

SECTION FROM CEREBELLUM OF SHEEP (Stained H. & E.)

SHOWING CHANGES SIMILAR TO THOSE ALREADY SEEN IN CEREBRUM AND MEDULLA.

X 100



X 250

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