UNIVERSITY OF EDINBURGH.

THESIS for the Degree of M.D.

written by

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Title: DISSEMINATED SCLEROSIS

(A clinical research).

FOREWORD.

The purpose of the author is to record his clinical research in a number of cases of disseminated sclerosis which have been examined in routine experience over a period of twenty years. The scope is limited to certain clinical aspects of the disease, so that the subject remain circumscribed within reasonable limits of space. No attempt will be made to describe all the various manifestations of a disease which may be so widely scattered throughout the central nervous system, because all these features are well-known nowadays, and wearisome repetition is the bugbear of what is euphemistically called medical literature.

A small series of twenty cases will be studied in detail under the following headings.

1. Aetiology and clinical manifestations.
2. Natural history and progress of the disease.
3. The effects of various modern therapeutic measures upon the course of the disease.

No résumé of the published works concerning this disease will be attempted;. nor will a detailed examination and criticism of current views be made.

It is the object of the author to make an individual contribution to Clinical Medicine from the exceptionally rich sources afforded him while he has been attached as Honorary Physician to the Public Dispensary at Leeds, the General Infirmary at Leeds, from The Ministry of Pensions Hospital, where he is Visiting Physician and Neurologist : and also from personal records compiled from private practice as a consulting physician.

The thesis is arranged as follows:-

1. Introduction, and general discussion.
2. Record of specially observed short series of twenty cases with analysis of symptoms and signs.
3. Conclusions upon (a) Aetiology
   (b) Natural history of the disease.
   (c) Effects of treatment.
4. Summary.

Introduction and General Discussion.

During the years 1913-1933, with a gap of two years, 1915-1917, when the writer was occupied by military duties abroad, approximately 311 cases of disseminated sclerosis were clinically examined by him.

The cases which form the basis of this thesis

number twenty and are chosen from a general mass because they have been studied in detail over long periods, so that full clinical facts are available, and personally recorded notes have been made in each case. In this disease, characterised as it is by periods of remission and exacerbation, a careful study of all the phases is essential if the natural history of the morbid process, and its clinical manifestations are to be fully understood. A series of cases enables research to be made into the comparative values of various therapeutic measures, and by comparison with cases subject to "natural" remission certain basic truths are exposed. In two years' time Disseminated Sclerosis will have been known to Clinical Medicine for 100 years. The pathological studies published in London by Carswell, and in Paris by Cruveilher, as separate observations on the sclerotic patches in the central nervous system appeared almost together in 1835. Time has not been lacking for the study of this disease and many publications dealing with all aspects of it have appeared, contributing something but not finality as to its aetiology and treatment.

The frequency with which the disease occurs in the Nordic stock of Europe offers ample opportunities

for study and research. Disseminated sclerosis is certainly the most common chronic organic disease of the nervous system in the young and early middle aged patients who are sent for advice to the Medical Out-Patient Department of a large voluntary hospital. This rough statistical statement relating to the Medical clinique would be emphasised the more by inclusion of all those early cases of the disease referred by family doctors to the special departments, particularly the Ophthalmic department on account of disorders of vision. In many cases such patients never reach the physician. The published statistical studies of disseminated sclerosis, almost without exception, are misleading. The earliest series published must now be corrected because of more accurate differential diagnosis from certain manifestations of, for example, Neuro-Syphilis, Encephalitis Periaxialis, Encephalitis Lethargica, Neromyelitis Optica, Sub acute Combined Degeneration, Acute Disseminated Encephalo-Myelitis, and even certain cases of Ataxic Peripheral Neuritis. Gone are the days when a clinical teacher or his undergraduates will be content with the final clinical diagnosis of "Spastic Paraplegia", yet so many such entries in the older statistical reports at our teaching hospitals

make it impossible to obtain accurate facts as to the incidence and other features of disseminated sclerosis from Hospital records.

When painstaking corrections are made in our Hospital statistics, these are still far from being an accurate estimate of the frequency of the disease, because so many cases of disseminated sclerosis in the early stages are not referred by the family doctor who, too often, ignores such symptoms as transient loss of clear vision in one of his patient's eyes; evanescent double vision, or some persistent area of numbness in a limb. A hospital physician has no accurate first-hand knowledge of the frequency of these early manifestations of disseminated sclerosis: and this is not surprising to one who finds that patients themselves forget these seemingly trivial incidents. The family doctor has supplied an entry of "influenza" or "feverish cold" from medical cards relating to patients who complain of "double vision" soon afterwards on several occasions in cases when the patient has forgotten that incident. These observations are stated at length to make good the claim of the writer that no complete or accurate statistics exist to cover the whole field of disseminated sclerosis. Certain general truths can

be accepted as bearing upon the complete story of the disease, and many accurate clinical and pathological details have been established during the last 98 years.

RECORD OF CLINICAL CASES.

Total number of cases examined and classified after clinical verifications, but not described in detail in the text.

Males	145
Females	166
Total	311

Cases selected for detailed description on account of completeness of clinical records over a period of years.

Males	8
Females	12
Total	20

Average age of first onset of first symptoms 28 years.

Possible Predisposing causes in 20 cases.

(a) Heredity. 3 cases.

Case No. 15, a sister suffers from disseminated sclerosis.

Case No. 17 epilepsy in the father.

Case No. 20, mother suffers from Parkinson's

(b) Previous illnesses. 8 cases.

Influenza, 5 cases (records 1,6,7,16,18).

Encephalitis (acute disseminated sclerosis) 2 cases. (records 2 and 11).

Herpes Zoster, 1 case (record No. 14).

(c) Trauma (2 cases) both doubtful. (Records 15 and 17).

(d) Occupational causes. Nil.

Individual Cases.

(1) A.H.B. male, 48, directing engineer.

History of illness.

In 1918 a severe attack of influenza, followed by severe neuralgic pain round the right eye, some loss of vision experienced temporarily.

1923, while golfing, the right eye "faded out". He could not see the ball. During this year gradually the left leg tended to "trail". Some lack of vision noticed in his left eye. The symptoms improved spontaneously.

February 1924, a short feverish attack, followed six days later by complete numbness in both feet. "I could not feel the ground."

The left leg "faded out", and the right leg followed in the same manner after a few days. From the chest downwards there was no musucular control,

he was unable to move his toes or any part of the legs. There was retention of urine. All sensation was abolished from about the level of the nipples downwards. Involuntary flexion movements of the left leg from the hip were troublesome.

May 1924. Cranial nerves normal except for pallor of the optic discs. The arms show no abnormality. There are abdominal reflexes. The knee and ankle jerks are increased, and extensor plantar responses were obtained on both sides. The cerebro-spinal fluid was under slightly increased pressure, clear, gave a negative Wassermann Reaction. Eleven lymphocytes per cubic m.m. were found in centrifuged deposit.
End of May 1924. One week after lumbar puncture the involuntary movement ceased. 14 days after puncture he was able to move the toes of both feet.

June 1924. Gradually recovering power in his legs but the sensory loss persists in an incomplete fashion.

October 1924. Walking well, went to business. Sensory disturbance nearly qualitative now.
Increased toe and reflexes in the legs and plantar reflexes extensor.

1924-1929. Slight numbness felt in the legs at times, and occasionally in the arms, and round the

body about the level of the nipples, where a feeling of constriction, without pain, was located. No return of the eye symptoms, headache, or other disabilities was experienced.

January 1929. The toes felt like parchment and were sensitive across the dorsal aspect. Some numbness of the pulp of the fingers was noticed. The right leg dragged while he was walking and some numbness across the left side of the chest and inner side of the left arm appeared.

February 1929. Drainage lumbar puncture was performed. A few days later the "trailing" of the right leg was less, and ten days after puncture he was able to walk "a good distance" . The numbness on chest was less noticeable.

2nd April 1929. He noticed a trailing of the left leg which became rapidly worse in a week, together with numbness of the left hand and tightness across the chest. One week later spontaneous improvement occurred and he was able to walk to business.

End of April 1929. He again deteriorated, the legs became weak and stiff, he was unable to walk unaided, and the left leg was definitely worse than the right.

10th May 1929. Involuntary flexion movements

of the left leg troubled him, and some difficulty in starting the act of micturition was experienced.

16th May 19291 Speech and mental function are normal. He is cheerful, though worried about his future. The cranial nerves are all normal to simple clinical tests, except for the pallor of both optic discs. The pupils are normal and there is no nystagmus found. The tone and co-ordination of the arm muscles were normal, and the tendon jerks reduced. No sensory loss detected by pinprick, touch, vibration (C.o. tuning fork), and tests for stereognosis. The abdominal reflexes were very sluggish and in testing them involuntary flexion movements were caused at the hips and knees. Both legs were weak, spastic, inco-ordinate, and the tendon jerks were exaggerated. The plantar responses were extensor. Reduced sensation to all forms of stimulation was found in the legs. There was complete loss of the vibration sensation in the legs, pelvic bones, and almost to the level of the fifth rib. Loss of joint and muscle sensation was complete in the legs.

The fractional test meal showed normal acidity. The cerebro-spinal fluid was clear, under very slightly increased pressure, and showed two lymphocytes per cubic m.m. in the centrifuged deposit.

The Lange test gave a paretic type of curve. The Wassermann reaction was a negative. Globulin was increased in amount. Cistern puncture and injection of Lipiodol was practised to determine the permeability of the spinal canal. The examination revealed no evidence of spinal block. The X-ray examination of the vertebrae gave normal findings.

June 1929. A full course of injections intravenously of Sulpharsènol was given, together with warm baths, massage and re-education movements.

27th July 1929. He was able to walk again, though he had some pain, a n i n the distribution of the left great sciatic nerve. Progress from helplessness to returning power was very striking.

30th September 1929. Re-examined after a holiday at Blackpool. He was looking pink and well. He was slightly unsteady in walking with his eyes closed, and some contracture in the hamstring muscles was apparent. The involuntary flexion movements were almost gone. Apart from the pallor of the optic discs the cranial nerves were normal. There was no nystagmus. Slight paraesthesia was noted on the inner side of both arms and over the whole of both legs. The left leg was spastic. Both knee and ankle jerks were increased and slight ankle clonus was elicited. The plantar

responses were both of extensor type. Vibration sense was still absent in the legs, but he had recovered joint sensibility.

6th December 1930. He walked with a normal gait except for a slightly stiff left leg. No change of any great moment in the reflexes. A little skin hypersensitiveness was noted in the neighbourhood of lumbar nerve root I on both sides. The long remission has continued and when the patient was last heard of in 1932 he was back at his business.

Case (2). Mrs. McM., age 26. Examined June 3rd 1926. History of illness.

At the age of 22, one year after marriage, suffered from a slight feverish illness in which she experienced double vision for six weeks. She was very sleepy, vomited repeatedly and was thought by a physician, who was specially skilled in neurology, to be suffering from Encephalitis Lethargica. She recovered slowly but walked with a high stepping gait afterwards.

1925. At the age of 25 she was definitely unsteady in walking, dizzy, and experienced transient numbness in the hands.

February 1926. Much difficulty in walking was apparent. There was numbness in the hands and some

loss of feeling. The symptoms continued to become worse up to June 1926 when she first came under observation. By this time there was great irritability of the bladder, an exaggerated emotional state, and unsteadiness in the hands. There had been no previous illnesses of any kind. The husband was alive and well; the parents alive and well. There was no history of any nervous disease amongst the blood relations. Patient was an only child. On examination she was mentally alert, cheerful, though lacking in control of her emotional expression. The pupils reacted equally well, and marked nystagmus was found. The left optic disc was very pale, the right normal in colour. The arms were slightly spastic and showed well marked intention tremor, together with inco-ordination. The reflexes were increased in the arms. No abdominal reflexes could be elicited. The legs were slightly spastic, the knee jerks increased, both ankle jerks markedly increased, clonus was found on both sides. The plantar reflexes were both extensor in type. There was greatly diminished vibration sensation in both legs but no other gross sensory change was noted. The bladder was extremely irritable without any local cause to account for it. The pelvic organs were

normal. The cerebro-spinal fluid was under slightly increased pressure, clear, and gave a negative Wassermann reaction. There were four lymphocytes per cubic m.m., the Lange test gave a luetic type of curve, and the total protein was 40 m.grms. per cent.

Treatment. Sulpharsènol was given intravenously in a full course, and afterwards the patient was given 15 c.c. of her own serum intrathecally. The reaction was severe, the temperature rising to 101 Fhr. for several hours. There was a severe dermatitis after the sulpharsènol injections. Within a few weeks a well marked remission started. The bladder irritation ceased and she was able to get about with very little discomfort. The left leg was rather stiff and both knee jerks increased, though no clonus was obtainable. Both plantar responses were extensor in type.

August 1929. The remission continued, she walked very well, the left leg was stiff, the tendon jerks were increased, particularly on the left side, the left plantar reflex was extensor, the right plantar reflex was doubtfully flexor. Further treatment was carried out by the injection of mixed typhoid vaccine, followed by drainage lumbar puncture.

1930. Information was communicated that the remission symptoms still continued.

Case (3). Mrs. M.B., age 32. Seen 28th November 1929.

History of Illness.

Gradual onset of weakness in the legs since 1927. Transient bladder weakness, transient loss of vision. Examination revealed well marked nystagmus, some loss of the full fields of vision, pupils normal, discs pale. The arms are normal in function though the tendon jerks are lively. There were no abdominal reflexes. The knee jerks and ankle jerks were exaggerated on both sides. The legs were spastic and weak. The plantar reflexes are extensor in type on both sides. There was loss of vibration sensation in both legs. Examination of the spine by X-rays was negative. The fractional test meal showed a complete achlorhydria. Blood examination showed the following features. R.B.C. 3,500,000. Haemoglobin 82 per cent. W.B.C. 5,700. The blood film showed no special features except some increase in the size of the red cells. Cerebro-spinal fluid was under normal pressure, one lymphocyte per cubic m.m. was found. The Lange test was quite negative and the globulin showed no increase. The Wasserman reaction was negative in both blood and spinal fluid.

Subsequent progress. This patient was treated by the intravenous injection of N.A.B. and after

a full course showed well marked remission which was continuous to 1931 when last heard of.

Case (4). Mrs.M.F., age 43. Seen October 1919. History of illness.

In 1909, for two weeks, she lost the sight in her right eye. This returned gradually, but since that time there have been periods of weakness in the legs and what she describes as "creeping sensations" in various parts of her body. It was noticed that she was excessively emotional within a few years of her first symptoms at the age of 23.

Subsequent history that of progressive weakness and stiffness in both legs. Family history quite negative for any neuropathic taint. One son died of meningitis in 1920. Examination. There was pallor of both optic discs, particularly of the right. The functions and reflexes of both arms were normal. There were no abdominal reflexes. The legs were spastic. The tendon jerks increased. The plantar reflexes gave doubtful responses, though there was no frank dorsi-flexion.

15th October 1929. Progress towards weakness and stiffness of both legs. Physical signs as before. The deep reflexes were exaggerated and extensor responses

doubtful on testing both plantar reflexes.
The cerebro-spinal fluid gave the following particulars: 3 lymphocytes per cubic m.m. Lange test paretic curve. Globulin increased. Wassermann reaction negative. Treated by full courses of N.A.B. without result.

Case (5). George P., age 51. Seen September 1919. History of illness.

Weakness and unsteadiness of the legs since he was 20 years of age. Family history negative; no previous illness. On examination a slight nystagmus, no abdominal reflexes, spastic weakness of both legs, extensor plantar responses and no sensory disturbance. No special treatment advised. Seen 9th September, 1929. The following physical signs were noted. Pallor of both optic discs, well marked nystagmus, slight intention tremor with exaggerated reflexes in both arms. There were no abdominal reflexes, both legs showed spastic ataxia. The tendon jerks were exaggerated and both plantar reflexes gave a classical Babinski's sign. Vibration sensation was almost lost in both legs. Cerebro-spinal fluid showed the following details: 1 lymphocyte per cubic m.m., Lange test negative, globulin not increased, Wassermann reaction negative in spinal fluid and blood.

The fractional test meal showed normal acidity and other features. This case was untreated by special methods receiving only simple medicines by the mouth. His progress has been steady deterioration.

Case (6). William F., age 40. Seen January, 1928.
History of illness.

Influenza in 1918, followed by persistent severe headaches for six months. During the acute period there was repeated vomiting in addition to headache. In 1920 pains in the back and round the sides. At this period he developed some weakness in his legs.

In January 1928 examined, when he complained of a tired feeling in the legs, with some difficulty in walking, and also of jerky movements in his hands. No emotional alteration noted. Both discs are pale; there is no nystagmus, but a well marked intention tremor was present. Tendon responses of both arms and legs are exalted. No abdominal reflexes were obtained; the plantar reflexes were extensor in type. There was diminished vibration sensation in both legs. Re-examined February 7th, 1929, after a full course of N.A.B. intravenously, followed by two doses of mixed typhoid vaccine intravenously. He is walking better, the arms are steadier, the plantar reflexes are both

extensor in type, the deep reflexes are less abnormal, the functional capacity for using his limbs is definitely increased. Cerebro-spinal fluid shows the following particulars: 4 lymphocytes per cubic m.m., Lange test gives a well marked Luetic type of curve, the globulin is slightly increased and the Wassermann reaction is negative. Fractional test meal showed high acidity.

1930. The remission continues.

Case (7). Miss M.T., age 44. Seen 1924.

History of illness.

Suffered from influenza in 1919 and states that she has never completely recovered since. Within a few months of her influenza she noticed a dragging of the right leg; gradually there appeared an unsteadiness in her gait and a dragging of the left leg. On examination she was definitely more emotional than normal, her speech was syllabic, the optic discs are pale, there was nystagmus. Functions of the arms were normal. There were no abdominal reflexes, the legs were slightly spastic, the knee jerks were increased, particularly on the right side, the right plantar reflex gave an extensor response. There was diminution in the vibration sensation on the left leg. The

cerebro-spinal fluid was under slightly increased pressure, the Lange test gave a luetic type of curve, the Wassermann reaction was negative, the total protein was 16 m.grms. per 100 c.c.

Treatment by the intravenous injection of sulpharsenol was practised and after a full course there was a well marked remission, so that the patient was able to return to her work as a lady's maid.
Re-examination was made on February 5th, 1928. The following signs were elicited: Pallor of the optic discs, slight nystagmus, no abdominal reflexes, and slightly increased tendon jerks in both legs. Right plantar reflex gave a doubtful extensor response. The patient walked well without fatigue. No further news of this patient is available.

Case (8). Mrs. E.E.W., age 28. Seen Oct. 31st 1930.
History of illness.

No previous illness has been noted, and in particular no influenza or other feverish ailment is remembered by the patient. For the last four years she had gradually become aware of a numb pain at the back of the right leg after walking. She first complained after a walking tour, and since that date, four years ago, she had become increasingly unsteady

on her legs. She made no other complaint. On examination she was found emotional and showed the following physical signs: Pale discs, nystagmus, intention tremor, exaggerated arm jerks, no abdominal reflexes, spastic legs with increased knee and ankle jerks, extensor plantar responses quite definite. There was diminished sensation qualitatively in the legs, but this was not marked. Cerebro-spinal fluid shows the following particulars: 7 lymphocytes per cubic m.m., Lange test paretic. Protein 30m.grms. per 100 c.c. Wassermann reaction negative.

Treatment by 8 doses of silver salvarsan, 0.1 grm. Result: no improvement. Subsequent treatment with liver extract and fresh liver, ½ lb. daily. Result: no change. The patient was re-examined in January, 1933, and was found to have deteriorated considerably. Her legs were more spastic and she walked with difficulty.

Case (9). Miss C.H., age 44. Seen 22nd Oct. 1930. History of illness.

Age 20, weakness of the right hand for 3 months.
Age 24, weakness in left-hand for a few weeks.
Age 28, dimness of vision in the right eye for 7 weeks.
Age 32, dimness of vision in the left eye for 2 months.
During the last eight years she has gradually become

stiff and weak in her legs. On examination there was pallor of both optic discs, nystagmus, no abdominal reflexes, intention tremor with exaggerated jerks in her arms. The legs are spastic, reflexes exaggerated, ankle clonus present, Babinski's sign positive on both sides. Loss of vibration sense in both legs, diminished sensation to pinprick. Cerebro-spinal fluid, 1 lymphocyte per cubic m.m., Lange test negative, Wassermann reaction negative in blood and spinal fluid. Total protein 40 m.grms. per 100 c.c.
Treatment by injection of N.A.B. followed by intra-thecal injection of serum. No reaction was obtained, and the patient remains without improvement.

Case (10). Mrs. N.C., age 33. Seen 23rd Nov. 1926.
History of illness.

Complained of numbness in the hands and weakness in the legs for the past six months. No history of any previous illness; family history negative.
She has four healthy children, and had no miscarriages.

On examination the left pupil was slightly larger than the right. Both react sluggishly to light, but well on convergence. Well marked nystagmus. The arms are normal, no abdominal reflexes, all the tendon jerks are increased in the legs, and extensor

plantar responses were observed. Both optic discs were pale. Slight diminution to the sensations of touch, pinprick, and vibration below the nipple line.

Treated as an out-patient by the intravenous injection of N.A.B. Re-examined at intervals up to December 1931, when she was very much better. The sensory changes were less noticeable but the reflex changes remained much the same. There was improvement in function rather than change in the physical signs.

Case (11). George L.B.S., age 47. Seen 31st Dec.1927. History of illness.

An acute onset with a feverish illness diagnosed as encephalitis lethargica in 1923. After the onset with headache, vomiting, lethargy, and double vision, the condition improved but was followed by chronic progressive paraplegia. On examination well marked staccato speech, pallor of the optic discs, nystagmus, intention tremor, with exaggerated arm jerks, no abdominal reflexes, weak and spastic legs, knee and ankle clonus, extensor plantar response on both sides, accompanied by involuntary flexion at the knee and hip. Family history negative. No previous illness of any kind. This patient was repeatedly re-examined during the period December 1927 to December 1931. During this

time he steadily deteriorated in spite of all treatment. The following treatments were employed in succession:

1. Intravenous N.A.B., followed by the intrathecal injection of his own serum.
2. The subcutaneous injection of Colley's fluid.
3. Mixed typhoid vaccine administered intravenously.
4. Therapeutic malaria.

No improvement of any kind resulted from these treatments.

Case (12). Miss M.H., age 20. Seen 10th July 1928. History of illness.

A two years' history of weakness in her legs and unsteadiness in walking, with slight disturbances in her speech and periods of remission. The onset was insidious, no preceding illness was noted. The family history is negative. On examination the following details were noted. Emotional state normal, optic discs normal, slight lateral nystagmus, the tendon jerks of the arms and legs exaggerated, some inco-ordination particularly in the legs, no abdominal reflexes. Plantar responses are both extensor in type. Cerebro-spinal fluid, 6 lymphocytes per cubic m.m., globulin increase. Lange test slightly luetic. Wassermann reaction negative. Treatment by intravenous

N.A.B. as an out-patient. Result, well marked remission. 31st December 1931, walking well, tone of legs more normal, plantar responses still extensor. Is able to do her work.

Case (13). H.J.D., age 21. Seen 14th April 1924. History of illness.

Twelve months ago he noticed the right foot "clumsy"; no other symptoms. No previous influenza, no visual disturbances. Gradual deterioration until March 1924, when the right hand became numb, after which more rapid deterioration. There has been unsteadiness of the right hand and arm. Family history negative, no previous illness of note. Examination, optic discs normal in colour, visual fields are normal, there is no nystagmus, slight unsteadiness of the arms, tendon jerks of right arm exaggerated, those of left arm the same but to a less extent. No abdominal reflexes, both legs spastic, knee and ankle jerks increased, extensor plantar responses. No alteration in sensation.

Treatment by simple medicines. No remission.

Case (14). James H.D., age 28. Seen 2nd Sep. 1924. History of illness.

1921, influenza, and pain round the abdomen.

November 1922, Herpes Zoster, pain in the left side of the face, and never well afterwards.

July 1923 weakness and pains in the legs and abdomen.

December 1923 tremors of the legs, knee jerks reported exaggerated. The spring of 1924 staggering gait; his own doctor reports exaggerated knee jerks and ankle clonus. Family history, tuberculous. No nervous disease. Examination, emotional, discs normal, slight nystagmus, arm reflexes increased, abdominal reflexes very sluggish , knee and ankle jerks exaggerated, ankle clonus on left side, plantar extensor responses. Admitted to hospital, treatment by N.A.B. Result, indeterminate.

Case (15). Miss E.D., age 37. Seen 7th March 1925. History of illness.

A four years' history, dating, she thinks, from an emotional shock and slight blow on the head, caused by an extensive fall of plaster from the ceiling. Onset with vomiting and a dull pain on the left side of the head, which persists. Some numbness in the legs, and in the sides of the hand. Some difficulty with micturition. No eye trouble. Family, one married sister, suffers from disseminated sclerosis.

On examination, the cranial nerves are normal.

The optic discs are healthy. No nystagmus, no intention tremor. Some exaggeration in the knee jerks and ankle jerks. The legs are weak and inco-ordinate. No abdominal reflexes, plantar responses are extensor in type. She lacks emotional control. This case was untreated except for simple remedies, and deterioration has been noted almost without remission, during 1928 and 1929.

Case (16). R.W.D., age 42. Seen 11th April 1930. History of illness.

1919 attacks of feverishness and vomiting, accompanied by severe headaches.

1927 whooping cough. At this time he had recurrent double vision.

March 1930. Sudden stammering in his speech, with loss of use in the right arm and leg. No complete paralysis.

On examination the right visual field showed a well marked contraction, especially to red colour. Discs are normal in colour, no nystagmus, right arm showed analgesia, the tone is increased and tendon jerks lively. Abdominal reflexes sluggish on both sides, right knee jerk more lively than the left. Right leg some spasticity, no clonus, right plantar

reflex extensor, left flexor. No sensory loss.

June 26th, 1930, transient diplopia. Speech and function of limbs better. Has been treated by intravenous N.A.B. at his local hospital.

14th November 1930, speech affected again, not so well. Physical signs almost unchanged.

Case (17). Charles C., age 38. Seen 12th Nov. 1926. History of illness.

No feverish illness. He dates his symptoms to a fall in the street in 1920, when he suffered from numbness in the right side of his face and neck a few days later.

1921, aching pain in the right shoulder. Spontaneous disappearance.

1923, double vision. From this date he has been ailing. Numbness in the face and transient pains have been his chief symptoms.

Examination. Pallor of both optic discs, concentric contraction of both visual fields. Fine nystagmus, pupils normal, abdominal reflexes very sluggish, knee and ankle jerks increased, flexor plantar responses. This patient also was suffering from mitral stenosis.

Treatment: Intravenous sulpharsènol, a full course, followed by the intra-thecal injection of serum.

Severe pyrexial reaction was obtained. Re-examined 6th January 1927, some remission, no nystagmus, sensation on the face much improved, slight diplopia on looking to the right. Abdominal reflexes still sluggish.

1930. This patient's remission still continues.

Case (18). Miss M.B., age 22. Seen 8th Jan. 1925. History of illness.

1923 had severe influenza. Was very nervous and under treatment for seven months.

December 1924, stiffness in the legs noticed to come on rather suddenly. There was also difficulty in starting the act of micturition. Family history negative; previous illnesses, nothing of note.

Examination, eyes normal, no nystagmus, well marked intention tremor, spastic legs with typical gait, no abdominal reflexes, knee and ankle jerks great exaggeration. Ankle clonus on both sides. Extensor plantar responses obtained. No gross sensory loss. Cerebro-spinal fluid, Lange test luetic curve, excess of lymphocytes, Wassermann negative reaction.

Treatment by intravenous N.A.B. Result, some remission.

Case (19). Mrs. L.B., age 34. Seen November 1925.

History of illness.

1920 numbness of the right arm and some loss of power. Double vision which persisted for 13 weeks and recovered slowly, but incompletely.

1924 gradual onset of difficulty in walking, bladder trouble, chiefly increased frequency and precipitate micturition. Family history negative, previous illnesses nil.

Examination, right pupil larger than the left, both react normally to light and accomodation. The optic discs are pale, no nystagmus, tendon jerks of the arms are increased, no abdominal reflexes, plantar responses are both extensor in type. Diminution in vibration sensation in both legs.

This case was untreated and gradually deteriorated while under observation, during 18 months.

Case (20). Miss M.H., age 43. Seen 30th Aug. 1930.

History of illness.

Onset in 1923 insidiously. She "threw her left leg" in walking, and one month after this was noticed the right leg was found to be weak. No other complaint.

Family history: her mother suffered from tremor of the hands and head, Parkinson's disease.

Previous illnesses, nil. Examination, pale optic discs, well marked nystagmus, some increase in tone of the arms with exalted tendon jerks. No abdominal reflexes, exaggerated knee jerks, plantar reflexes were both extensor in type, no sensory disturbance made out. Cerero-spinal fluid, 1 lymphocyte per cubic m.m., Lange test negative, Wassermann reaction negative in blood and spinal fluid.

Treatment by injection of N.A.B., intravenously, followed by the intrathecal injection of her own serum. Severe pyrexial reaction. Result, some remission .

1932, December. Knee jerks less exaggerated, co-ordination of leg better, extensor plantar responses persist. Patient expresses herself as "much better".

ANALYSIS OF CLINICAL CASES.

(Total number 20).

Modes of Onset, 1st symptoms.	Case No.	Symptoms observed during illness.
Emotional disturbance	7,8,11	2,4,7,8,9.
Lack of vision in one eye	1 & 4	1 & 9.
Double vision	2,16,19	2,16,17,19.
Alteration in speech	7	2,7,12,16.
Lethargy & vomiting	2,6,11,15,16	2, 6.
Headache	6,11,15,16	6.
Vertigo		2.
Pain or paraesthesia in face	1,14,17	1,17.
Weakness of arms or hands	9	1,2,6,9,13,14,16,18.
Paraaesthesia in arms or hands	9,10,19	1,2,6,9,10,13,15,16,17,19
do. in trunk	4,6,14	1,4,6,10,15.
do. in legs	4,7,8,14	1,2,4,5,7,8,10,15,19.
Weakness of legs	3,4,5,6,7,8,10, 12,13,14,18,20	1,2,5,6,7,8,9,10, 12,13,14,15,16, 18,19,20.
Ataxic gait	2,5,7,8,12,20	1,2,3,5,6,7,8,9, 12,13,14,15,18, 19,20.
Bladder trouble	3,18	1,2,3,15,19.

Physical signs. observed early.	Case No.	Observed during course of illness.
Emotional changes	2,7,8,14	1,2,7,8,14,15,16.
Reduced vision	1,4,9	1,4,9.
Reduced visual fields	1,16,17	1.
Pupillary changes	10,19	10,19.
Optic discs:		
(a) Swelling	Nil	Nil.
(b) Pallor	1,2,3,4, 6,7,8,9, 10,17,19,20.	1,2,3,4,6,7,8,9,10, 17,19,20.
Nystagmus	2,3,5,7,8,9,10, 12,14,17,20	2,3,7,8,9,10, 12,14,17,20.
Scanning speech	7, 12.	2,7,12.
Ataxia of arms	2,6,8,9,13,18	1,2,5,6,8,9,13,18.
Weakness of arms	2,6,9,13,18	1,2,5,6,9,13,18.
Increased tendon jerks in arms	2,6,7,9,10,12,13, 14,18,19,20	2,5,6,7,9,10,12, 13,14,18,19,20.
Absent abdominal reflexes	2,3,4,5,6,7,8,9, 10,12,13,15,18, 19,20	1,2,3,4,5,6,7,8,9, 10,12,13,15,18, 19,20.
Sluggish abdominal reflexes	1,14,16,17	1,14,16,17.
Ataxia of legs	1,2,3,5,6,7,8,9, 10,12,13,14,15, 16,18,20.	1,2,3,4,5,6,7,8,9, 10,12,13,14, 15, 16,18,20.
Weakness of legs	1,2,3,4,5,6,7,8, 9,10,12,13,14,15 16.	1,2,3,4,5,6,7,8,9, 10,12,13,14,15,16.
Knee jerks increased	1,2,3,4,5,6, 7,8,9,10,12,13,14, 15,16,17,18.	1,2,3,4,5,6,7,8,9, 10,12,13,14,15 16,17,18.
do. ankle jerks	1,2,4,5,6,7, 8,9,10,12,13,14,15 18.	1,2,4,5,6,7,8,9, 10,12,13,14,15, 18.
Extensor plantar responses.	1,2,3,4,5,6,7,8,9, 10,12,13,14,15,16 18,19,20.	1,2,3,4,5,6,7,8,9, 10,12,13,14,15,16, 18,19,20.

Alteration in sensation		
(1) Light touch	1,10,17	1,10,17.
(2) Pinprick	1,9,10,16,17	1,9,10,17.
(3) Vibration	1,2,3,6,7,9,10, 19.	1,3,6,7,9,10, 19.
(4) Joint and Muscle sense	1	1

Analysis of the findings in Cerebro-Spinal Fluid.

Pleocytosis	5 cases	2,8,10,12,18.
Lange Gold Sol Test.		
Paretic curve	3 "	1,4,8.
Luetic "	5 "	2,7,10,12,18.
Negative test	4 "	3,5,9,20.
Wassermann Reaction Negative	12 "	1,2,3,4,5,7,8,9,10, 12,18,20.
Albumin increase	2 "	8, 9.
Globulin "	4 "	1,2,4,12.
Globulin not increased	2 "	5, 7.

Fractional Test Meal.

Examined 3 cases 1,3,5,.

Normal in cases 1 and 5
Achlorhydria, case 3.

Treatment. (20 cases).

Intravenous arsphenamine with drainage lumbar puncture 5 cases 1,2,3,4,5.

Result: Remission 4 cases, 1,2,3,7.
No result, 1 case, 4.

Intravenous arsphenamine followed by typhoid vaccine intravenously 2 cases 5, 6.

Result: Remission, case 6.
No result, " 5.

Treatment (contd.

Intravenous arsphenamine followed by injection of patient's serum into subarachnoid space — 6 cases — 1, 9, 11, 17, 18, 20

Result: Remission, 4 cases, 1, 17, 18, 20.
No result, 2 " 9, 11.

(Note: Case No. 11 was treated also with Colley's fluid, malaria, and typhoid vaccine, with no result.).

Intravenous arsphenamine alone.
(Full courses of 8-10 injections Sulpharsenol .4 to .9 grm., or N.A.B. doses .4 to .75 grm.) — 3 cases. 10, 11, 12.

Result: Remission in all 3 cases.

Intravenous Silver Salvarsan.
(8 doses 0.1 grm.) — 1 case — 8

Result: No remission.

Liver Therapy. — 1 case — 8

Result: No remission.

Total number of cases treated 16
Remissions 11
No result 5

Cases untreated as a control 4
(13, 14, 15, 19)
No remissions while under observation.

Incidence and Frequency.

It is not proposed to give statistics of the locality incidence of the disease, because these would certainly be incomplete and misleading, as it is unlikely that there has been a complete "roundup" of all the cases in an area, and that these were referred from the various urban and rural districts concerned to the hospital. On the other hand, some areas send a great proportion of their cases because of special facilities existing between medical men of that district and the consulting staff of the hospital: this would give a misleading appearance of a high incidence of the disease in that particular area. In general terms it may be stated that there seems to be no greater incidence of disseminated sclerosis amongst the rural population than in that of the cities or smaller towns of the West Riding of Yorkshire. When corrections are made to ascertain the percentage of the population affected, and the average age of the people living in these districts is taken into consideration, the problem of incidence becomes more clear. The disease has affected women and men almost equally. Leeds affords an opportunity to examine the incidence of the disease amongst a large Jewish community, chiefly of Russian and Polish origin, who are largely employed in the

clothing trade and number approximately 30,000. The vast majority of these people would apply to the hospital for special advice in case of need. It is noted as a matter of interest that the percentage interest of disseminated sclerosis in this community is distinctly lower than in the surrounding native-bred Yorkshire stock.

There seems to be no occupational or trade factor which predisposes to disseminated sclerosis.

Family history and inheritance.

It has been stated frequently that a "neuropathic" inheritance is an aetiological factor. A careful search for neuropathic manifestations in the writer's series of cases has not produced any constantly recurring fact in the family history, e.g. consanguinity, nervous disease in the parents or blood relations, etc. A percentage of approximately 32 per cent. of patients have been classified upon enquiry as being "highly strung," "over anxious," or "nervy". Other similar expressions have been used which upon analysis seem to mean a personality brisk and alert rather than one sluggish or lazy.

The present series of cases provides one single instance where disseminated sclerosis affected more than one member of the same family (i.e. Case 15).

In approximately 10 per cent. has a neuropathic strain been found to exist in parents or blood relations. In the larger series of cases the writer has found two examples of disseminated sclerosis affecting a man who had suffered earlier in life from acute anterior poliomyelitis.

The co-existence of disseminated sclerosis and neuro-syphilis has not been noticed. It may be that an odd case has been overlooked because the cerebro-spinal fluid has given evidence of syphilis by positive Wassermann reaction, and in the absence of other typical signs all such cases would be excluded from the series classified as disseminated sclerosis. Other doubtful cases, monosymptomatic, and unverified by further investigation, have also been excluded as doubtful cases.

Aetiology. Predisposing Illness.

Among the predisposing illnesses and modes of onset "influenza-like", feverish attacks, must be given an important place. In no less than five of the short series of twenty cases given in detail does this incident appear as a starting point of the disease. Those cases only are included in which the feverish attack immediately precedes the unmistakable symptoms

of involvement of the central nervous system. Sometimes the pyrexial symptoms form part of an encephalitis; two cases in this small series of twenty were diagnosed as lethargic encaphalitis though subsequent events proved that the patients were in reality suffering from the acute type of disseminated sclerosis. (H.M. Turnbull has discussed this point, ref. I).

Having made the most searching enquiry into this mode of onset by a short feverish illness, the writer is convinced that it is much more common than most authorities have recorded. The medical record cards of Health Insurance scheme have shown "Influenza" or some such entry when the family doctor has been called in. A patient subsequently overlooks this trivial illness when his clinical history is being obtained, with the result that a negative finding is recorded. Eye symptoms and pains, or paraesthesiae in the limbs, have been dismissed as "just part of influenza", and it is only in those cases where the early manifestations persist, or are accompanied by the more dramatic double vision, that their close connection cannot be overlooked. On the other hand it is quite true that in a large number of cases no feverish attack immediately precedes the nervous symptoms.

In the small series of twenty observed cases 8 patients gave no history of any preceding feverish illness. The onset with Herpes Zoster is interesting when considered in the light of recent experience with neurotropic virus infection, vaccinal encephalitis, etc. (Perdrau, ref. 2). Head injury immediately followed by the disease is so rare that it may be regarded as an accident of no special aetiological importance. A bruise of the head caused by a fall in the street was followed by symptoms of disseminated sclerosis in one case of the short series. In another case where a ceiling fell, the resultant trauma was too trivial to be of any significance.

Occupational Causes.

No specially frequent incidence of the diseases found in any vocation or occupation. In particular there was no high percentage of incidence in joiners, woodworkers, or farm labourers. A larger proportion of textile workers were affected than other trades. The menders of faulty weavings were more often affected than spinners or weavers, but this fact seems to be explained by the local distribution of these occupations, and has no other significance.

Since published work has appeared suggesting

a "deficiency" factor in the causation of the disease (Goodall of Edinburgh), special enquiry has been made into diet and digestive processes. Fractional test meals have revealed that there is no higher percentage of achlorhydria in this disease than in the ordinary cases admitted to hospital for other reasons. No evidence of any deficiency factor has been brought to light.

Overstrain and Stress.

In the later phases of the war, and for a few years after its end, a slightly raised percentage of incidence was noted in returned soldiers, but it was not very striking. This would seem to be explained by the generally lowered vital resistance to all kinds of infection and disease in war-weary men. The increased incidence of other diseases, e.g. tuberculosis, has been more noticeable still amongst these men, and in this connection it will be recalled that they were originally chosen because of their physical fitness. The whole explanation seems to be that the hardships of the war lowered the natural resistance to all forms of disease, so that disseminated sclerosis took its toll as well as other forms of illness.

CONCLUSIONS.

AETIOLOGY.

Infection theory.

Owing to the large number of cases observed in which a very clear history of preceding febrile illness has lead on directly to disseminated sclerosis, the writer has acquired a strong bias in favour of infection theory in the causation of the disease. From the scattered distribution of the early patches in the central nervous system, it may be suspected strongly that the virus is a blood borne one, at any rate at first, though it may spread via the subarachnoid space and cerebro-spinal fluid later on. The writer is engaged upon a separate enquiry into the questions relating to direct infection from the nasal sinuses, and venous channels in the neighbourhood of the naso-pharynx. The large number of cases who complain of eye symptoms early in the disease is an arresting feature, and suggests that further detailed research may produce some new information of considerable value in attempting to solve the whole problem.

Deficiency Theory.

No evidence of any deficiency disease has been found, and the failure of vitamin and liver therapy

to benefit the patients has been a uniform experience of the writer.

Neuropathic Inheritance.

The theories which rely upon family susceptibility or individual neuropathic sensitiveness to this disease have not been sustained by a careful consideration of the evidence provided by the cases of the writer. In fact, the evidence is almost against the neuropathic inheritance susceptibility theories in the case of disseminated sclerosis.

Clinical Features.

Early symptoms. In common with most other observers, the writer has noticed the frequency of visual disturbances in the early stages of the disease. Disturbance of vision in one eye, or a lack of balance in the eye muscle which causes double vision, have been frequently found. Two cases out of twenty in the small series had retrobulbar neuritis, and three others had double vision as their first symptom, so that five cases out of twenty complained of eye symptoms very early in the disease. A total of seven cases out of twenty had developed visual symptoms at some period while under observation. These symptoms appear as transient

feature or a more permanent symptom.

Emotional Disturbance.

This symptom occurred early in the disease in 3 cases out of 20, and developed later in 3 others, a total of 6 out of 20. In the larger series of cases this symptom was noticed frequently in the later stages, so that the writer's experience coincides with that of S.A.K. Wilson and S.S. Cottrell (ref. 3).

Headache, Lethargy and Vomiting.

Two cases out of 20 were examples of the acute onset, with symptoms of encephalitis, a percentage too high to be sustained in the larger series of cases, but sufficiently arresting to draw attention to this mode of onset, which seems to have escaped the attention of many authors. Subsequent clinical studies prove that these acute cases eventually develop typical disseminated sclerosis of the relapsing type and were not examples of lethargic encephalitis. (H.M. Turnbull, ref. I.)

Weakness of the Legs.

This common symptom was noted in 12 cases out of 20, but as many cases come under observation late in

the disease, it is necessary to examine the records carefully if the symptom is to be placed in its true chronological order. As a rule it will be seen that involvement of the motor and sensory functions of the legs occurs later than the eye symptoms. In the majority of cases, when once established, it becomes more fixed and impressive to the patient. The paraplegic type of the disease is usually more progressive than the other types, and resists treatment. A large percentage of these intractable cases come to hospital and create a false impression in the minds of the staff as to the frequency of this clinical type of the disease.

Pain, Paraesthesia and Numbness.

Alteration of sensation in the skin of the face, arms, trunk, or legs, is a very common early symptom of disseminated sclerosis. Ten cases out of 20 complained of it. (Ref. Birley and Dudgeon, 4). The sensory disturbances, though very common, are not so striking as a complete loss of function, and tend to vary from time to time in intensity. They very often escape the attention of the private doctor and are so irregular and ill-defined, as a rule, that they lose their attraction from a diagnostic viewpoint.

Careful records of sensory changes are scarcely worth while, owing to the diffused character and changing intensity of these lesions. Occasionally irritation of one nerve root raises a doubt as to the presence of a spinal meningioma.

Later Symptoms.

Amongst the later symptoms most important are, weakness of the legs, and ataxic gait. In 16 out of 20 cases observed for some years, this feature of the disease appeared sooner or later. In 9 out of the 20 cases pain, discomfort, or altered sensation, was noted late in the disease. In 10 out of 20 cases sensory symptoms were noted in the hands or arms, though in only 3 cases was this found in the earlier stages of the disease. Scanning speech is usually a late symptom. It was noted in 4 cases of the 20, while under observation, whereas only one had it as an early symptom.

Bladder Symptoms.

Difficulty with the motor functions of the bladder may occur early in the disease and improve, but re-appear later. Two cases out of 20 had trouble with the bladder control as early symptoms, and a total of 5 out of 20 developed this symptom within a few years.

Precipitate micturition is the most common bladder symptom.

PHYSICAL SIGNS.

Signs which appear early in the disease.

The most constant and striking sign elicited in the early stages has been the disappearance or sluggish conservation of the skin reflexes on the abdominal wall. In 15 out of 20 cases the abdominal reflexes were abolished, and in 4 additional cases they were sluggish. So that out of 20 cases all except 1 gave evidence of abolition of the abdominal reflexes fairly early in the disease. This observation agrees fairly closely with those of Birley & Dudgeon (ref. 4) who note this sign in 77.1% of their cases. Marquézy (ref. 5), working in France, notes this sign as being found in 68 per cent. of his cases.

Optic Discs.

An exaggerated pallor was noted in 12 cases out of 20 (c.p. 57.6 per cent. and 54 per cent. of Birley & Dudgeon, and Marquézy respectively). Diminished visual acuity was found in 3 cases and reduced fields of vision were verified in 3 out of 20. Changes in the pupils were noted in two cases out of 20. The

Argyll-Robertson pupil was noted in 3 cases out of 311 in the large series.

Nystagmus.

Unsteadiness of the eyes was found in 11 cases out of 20 at a fairly early stage in the disease, and persisted into the later stages. This percentage is lower than that of the two writers quoted above, who record 74.3 per cent. (ref. 4), 70 per cent. (ref. 5) while Sachs B. & Friedmann (ref. 6) record nystagmus in 70 per cent. of cases in America.

Inco-ordination of the Legs.

Ataxia of the legs was found in 17 out of 20 cases, but some of the cases came under observation too late to be termed early examples of the disease. In 15 cases the legs were weak, and in 17 there was a spastic ataxia with exaggerated tendon jerks. In 18 cases out of 20 extensor plantar responses were observed at the first visit.

Notes on the signs in later stages of the disease.

The stage of progressive spastic paraplegia with exaggerated reflexes and plantar extensor responses usually marks the final stages of disseminated sclerosis.

The tendon jerks are exaggerated in the arms, some ataxia appears, nystagmus, and increasing pallor of the optic discs are usually found. When most of these symptoms and signs arrive to constitute a classical, text book, description of the disease, it has entered upon the final stages and is usually beyond the reach of therapeutics.

Natural History of the Disease.

The well-known tendency to natural remission or spontaneous partial cure, followed by periods of exacerbation, have been exemplified very often in the writer's cases. A study of the mechanism of the natural remission may prove a most fruitful field. If the natural remission could be deliberately provoked and afterwards prolonged by therapeutic means, then some control of this disabling disease would be in the physician's hands. There seems to be a theoretical possibility that when once the virus obtains access to the perivascular spaces, and the subarachnoid space, it is beyond reach of colloid antibodies, which would pass with difficulty from the blood through the reticulo-endothelial system of the brain and spinal cord. Much the same state of affairs has been fully demonstrated in the case of S. pallida. It is

significant that there are many clinical similarities between the natural or artificially induced remissions of General Paralysis, and the remission of disseminated sclerosis. It is the writer's experience that remissions have occurred naturally, or have been artificially provoked by treatment, most often when the cerebro-spinal fluid has contained some excess of globulin, or has reacted to the Lange Gold Sol Test by precipitation in the earlier series of tubes. These changes, called "the Paretic" or "Luetic" types of curve, are apparent when the colour changes have been charted in the usual routine fashion. The present series of cases, however, provides exceptions even to this general statement. In 33 cases published by Ayer & Foster (ref. 7), the cerebro-spinal fluid gave the paretic curve in 16 cases, the luetic in 7, and was negative in 10. In the writer's short series of 12 cases, 5 gave luetic curves, 3 paretic and 4 were negative. The control Wassermann reaction was negative in all cases.

Effects of treatment.

Under this heading it is of interest to note that/all of the various remedies used for the treatment of disseminated sclerosis, those which have survived

longest on the list of remedies have little in common save that they all cause some temporary upset of the patient, for a short time after the administration. As examples, it may be noticed that the most popular remedies are:- (1) Various arsphenamine compounds, e.g. sulpharsenol, (which is one of the best), tryparsamide, novarsenobillon, neosalvarsan, etc. This group do best when given in full doses and result in some reaction with pyrexia. They probably act in a mild toxic fashion on the liver, and it may be that antibody production results. We have no means of proof at present that such antibodies are produced, as they cannot be identified in the blood.

(2) Compounds of antimony, e.g. stibenyl, Heyden 661, etc.

(3) Pyrexia artificially induced by the injection intravenously of mixed typhoid vaccine, or by the subcutaneous injection of Sulfosin.

(4) The injection of foreign proteins, e.g. sterilised milk, or whole blood, or serum.

(5) Therapeutic malaria.

(6) Lumbar or cistern puncture, followed by the injection of serum collected after the use of N.A.B. compounds. In this case the patient's own serum is used, due interval being allowed so that most of the arsenic injected intravenously will be out of the blood

before the serum is collected.

(7) A combined treatment of arsphenamine injection, after which serum is collected and injected into the subarachnoid space, simultaneously hypertomic saline is injected intravenously. The object of this method is to increase the penetration of the serum into the nervous tissues by means of osmosis.

The writer has used all the above methods with the exception of the antimony compounds.

During his clinical experience the writer has been convinced that remissions in the course of disseminated sclerosis are provoked by treatment. Untreated cases present shorter remissions though they may appear spontaneously, probably by the passage of antibodies from the blood into the perivascular spaces of the central nervous system.

The objects of treatment are to endeavour to promote antibody formation in the blood and next attempt to force a passage from the blood to the perivascular spaces. As an illustration of a similar mechanism, one might recall the passage albumin through the glomerular apparatus of the kidney into the urine in cases of feverish illness. In this manner the capillaries of the kidney would be regarded as analagous to the capillary circulation in the brain and spinal cord.

SUMMARY.

A clinical study is made of disseminated sclerosis, and based upon the examination of 311 cases over a period of nearly 20 years. A short series of 20 cases is fully described, and an analysis made of the symptoms, signs and natural progress of the disease, together with the results of treatment by various methods. Conclusions are drawn from the facts stated, and a theory is advanced in an attempt to explain the spontaneous and artificially induced remissions which characterise the disease.

The short series of 20 cases described in full form a small part of the clinical experience upon which the conclusions are based, but serve as examples in order that the subject may be dealt with in reasonable space.

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