A CLINICAL AND EXPERIMENTAL CONTRIBUTION TO THE PATHOGENESIS OF DISSEMINATED SCLEROSIS.

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THE investigations with which this paper deals were begun in the autumn of 1913, and resumed in 1920 after an interruption of five years caused by the War. At the time when our work was begun no evidence from the experimental side had been published which served to throw any light on the obscurity in which the pathogenesis of disseminated sclerosis has so long been shrouded. In October, 1913, a paper appeared by Bullock [2], who claimed to have transmitted the disease from man to rabbits, while in 1914 an exhaustive work was published by Siemerling and Raecke dealing with the morbid anatomy and histology of the disease. During and since the War other evidence was forthcoming in the direction of a solution of the problem confronting us, and it is mainly on this account that we have decided to publish the results of our investigations. It can at once be stated that our experimental results are almost entirely negative, and we are well aware that their publication may appear to some unnecessary. We feel, however, that negative evidence cannot be entirely disregarded, especially in view of the fact that much of the positive evidence which has recently appeared is to our mind unsatisfactory and unconvincing.

The clinical material on which this work was carried out was obtained from the wards either of the National Hospital, Queen Square, or of St. Thomas's Hospital. To the members of the staffs of both hospitals who gave us every facility for our investigations we wish to tender our grateful thanks.

Thirty-five cases have been investigated clinically and bacteriologically, while animal inoculations have been carried out in fifteen instances, in two cases with material obtained post mortem.

Clinical Study.

Although it is not our intention to enter into a detailed discussion regarding the differential diagnosis of disseminated sclerosis, nevertheless this aspect of the matter must not lightly be passed over. In more than one recent publication, for example, dealing with the transmissibility of the disease to animals, too little importance has been attached in our opinion to the clinical side. We are merely told that the case providing the material to be injected was one of "typical multiple sclerosis"; or else a brief clinical résumé is appended from which it is not always clear that the patient actually had this disease. In three cases investigated by us the provisional diagnosis of disseminated sclerosis was proved to be incorrect, and in two others (Cases IV and XIII) it remained doubtful. (*Vide* Appendix.) Of the three patients wrongly diagnosed, none of whom are included in our series, one proved to be a case of syringomyelia, while the other two were cases of cerebrospinal syphilis.

In no disease is accurate history-taking more important than in the one under consideration, and in a large majority of cases a diagnosis can be made from the history alone. The patient's description of the onset and character of the various symptoms is usually sufficient to make it clear that widely separated areas of the central nervous system have been affected at the same or at different times. This feature differentiates disseminated sclerosis from all other common diseases of the central nervous system with the *important exception of cerebrospinal syphilis*. Further, the history demonstrates that the course of the disease is not always slowly progressive and uneventful as was at one time supposed, but is more often interrupted by acute and unexpected disturbances. In more than half (54·3 per cent.) of our cases the onset was comparatively sudden, while in more than two-thirds (68·6 per cent.) some of the symptoms, but not necessarily the initial disturbance, came on acutely. In 85·7 per cent. of our cases the disease had run a discontinuous course, the symptoms pointing now to this and now to that locality of the brain or cord, appearing in an irregular and haphazard manner, and at greatly varying intervals of time. Remissions or quiescent periods, often of many years' duration, alternate with periods marked by the more or less rapid development of fresh disturbances in a manner which is bewildering in so far as it defies accurate anticipation.

We have taken care to select for the purposes of this investigation only those cases which presented evidences of *recent or progressive*

lesions. This selection excludes from the present review two types of case, first the non-progressive case, i.e, patients in whom the disease is in a state of arrest, the condition having remained completely stationary for several months or years, and secondly the so-called "cures," i.e., those in whom no trace remains of a previous pathological condition, as judged by an entire absence of both symptoms and physical signs. We wish to emphasize the fact that such cases occur not infrequently, and that patients, especially those in whom the initial disturbance was relatively sudden, may remain in perfect health for months or years at a time (*vide* Case XIX). How long this immunity can last we are not in a position to say, but in view of the fact that the existence of the non-progressive group is generally admitted, together with the circumstance that the initial stages of the disease are frequently overlooked or wrongly diagnosed, it seems possible at any rate that more cases than is commonly supposed recover from their early lesions and remain well permanently.

Although we desire to lay particular stress on the acute features of the disease, it must not be forgotten that a small number of cases begin insidiously and progress insidiously, while many cases also, which in the early stages were characterized by exacerbations and remissions, eventually assume a more chronic character and progress slowly downhill without new incidents. No hypothesis of the pathogenesis of disseminated sclerosis is satisfactory which fails to take into account the different clinical forms which the disease assumes in different individuals, or in the same individual at different stages of its development.

Clinically, therefore, disseminated sclerosis reveals itself in a haphazard series of relatively acute disturbances occasioned by focal lesions distributed at random both in the brain and cord, appearing at irregular intervals, and showing in their early stages a general tendency to improvement.

Sites of election have long been recognized in this disease, and it is well known that the white matter of the cord, as opposed to that of the brain-stem, is much more commonly affected than the grey. In consequence of this tendency to localize itself in certain areas, the disease presents clinical features which are said to be "typical." Nevertheless no single symptom or sign (e.g., "scanning speech") is of itself characteristic of the condition, but rather a combination of such symptoms and signs. We would further point out that a condition so kaleidoscopic in its symptomatology and clinical course as is

disseminated sclerosis seems peculiarly ill adapted for classification into types and sub-types so dear to the heart of many continental writers.

In the accompanying table is set forth the relative frequency with which certain symptoms and signs were found in our thirty-five cases. Besides indicating the multiplicity of the symptomatology of the disease, it shows that at any rate in the earlier stages the clinical picture departs widely from most text-book descriptions.

NUMBER OF CASES EXAMINED: THIRTY-FIVE.

	Number of cases	Percentage of total
Discontinuous course	30	85·7
Chronic progressive course	5	14·3
Paræsthesiæ	29	82·6
Loss or impairment of deep sensation	23	65·7
Loss or impairment of vibration in lower limbs (23 cases examined)	14	60·8
Disturbance of cutaneous sensibility	11	31·4
"Useless arm"	14	40·0
Extensor plantar response	32	91·4
,, bilateral	27	77·1
,, unilateral	5	14·3
Absent abdominal reflexes (bilateral)	27	77·1
,, ,, ,, (unilateral)	1	2·9
Spastic paraplegia	16	45·7
Sphincter disturbance	25	71·4
Nystagmus	26	74·3
Intention tremor of arms	15	42·6
Cerebellar inco-ordination of arms	15	42·6
Cerebellar gait	18	51·4
Tremor of unsupported head	13	37·1
Ataxic dysarthria	10	28·6
Pallor of optic disks (33 cases examined)	19	57·6
,, ,, ,, (bilateral)	15	45·5
,, ,, ,, (unilateral)	4	12·1
Sudden amaurosis	7	20·0
Severe bilateral visual failure	3	8·6
Diplopia	12	34·3
Rotatory vertigo	18	51·4
Defective emotional control	18	51·4

The most common symptom was paræsthesia, present in 32·6 per cent. of the cases. Although often transient, these subjective disturbances are absolutely definite and constitute one of the most characteristic features of the disease. They may be the first evidence of the pathological process, and although varying in their character and locality are rarely absent at one or other period of the illness. They are variously described as "tightness," fingling, numbness, boring pains (never lancinating pains as in tabes), aching, "rheumatism," "like water trickling down the skin," "like something tickling," coldness, "as if my legs were being scorched in front of a fire," pins and needles, "as if my body and legs were in plaster," &c. These

sensations were referred to the trunk and (or) limbs, and in two cases to the tongue, but were never associated with visceral disturbances such as occur in tabes. Except that they are far less frequently restricted to the peripheral segments of the limbs, they are comparable in every particular to the paræsthesiæ which form so notable a feature in the symptomatology of toxic degeneration of the posterior columns of the cord associated with pernicious anæmia (subacute combined degeneration), and they are to be regarded as evidence of morbid changes in the posterior columns.

Evidence of disturbance of deep sensibility in one or more limbs was obtained in two-thirds (65·7 per cent.) of our cases. Unfortunately vibration was not tested in every case, otherwise the proportion would probably have been greater. In the twenty-three cases in which vibration was tested, in fourteen (60·8 per cent.) loss or impairment of this quality of sensation was demonstrated in one or both of the lower extremities. We are, therefore, unable to agree with the statement current in most text-books that objective disturbances of sensation are rare in this disease. On the contrary we regard disturbance of deep sensation (i.e., compasses, tuning-fork, stereognosis, passive position and movement) as one of the most characteristic signs of the disease, and as evidence of involvement of the posterior columns of the spinal cord or of their upward continuations.

With regard to disturbance of cutaneous sensibility we agree with other authors that it is relatively uncommon; in our series it was present in less than one-third of the cases (31·4 per cent.).

Before leaving the subject of sensory disturbances we should like to draw attention to a symptom-complex, first described by Oppenheim, which may be called the "useless arm." The condition usually develops rapidly in the course of a few hours or days, with or without preliminary warnings in the shape of paræsthesiæ. As a rule it is unilateral, and the expression used by the patient to describe the condition is almost invariably the same, viz., "the arm is useless." Objectively there is profound loss of deep sensation in one of the upper extremities, e.g., no threshold to compasses, complete astereognosis, no response to vibration, and wild sensory ataxia with abolition of the sense of passive position and movement sometimes complete even at the shoulder-joint. Hence the patient says: "I lose my arm in bed," or "The arm has an existence apart from me." The limb is not paralysed, and provided the patient gazes fixedly at the arm when each muscle group is tested there is no loss of power, but

with closed eyes there is an apparent paresis, which is however entirely due to the falling out of afferent impulses from muscles and joints and a consequent inability properly to apply muscular power.

This curious condition may be the first and only evidence of disseminated sclerosis; in the present series it was not infrequently associated with nystagmus, more rarely with a transient impairment of tactile sensibility in the affected limb, and never with bulbar symptoms. The condition of the arm improved in every case, and cleared up entirely in Cases XIX and XXXIV. We regard the condition as the result of an acute but not necessarily destructive lesion in the external portion of the homolateral posterior column of the upper cervical cord. It occurred in 40 per cent. of our cases, i.e., in nearly the same proportion as two of the conditions which are commonly described as "typical" of the disease, namely, spastic paraplegia and intention tremor.

Evidence of interference with the pyramidal system of fibres was obtained in a large majority of our cases. Thus an extensor plantar response was present in 91·4 per cent., bilateral in 77·1 per cent., and unilateral in 14·3 per cent., while the abdominal reflexes were absent on both sides in 77·1 per cent. Spastic weakness of both legs sufficient to warrant the description of spastic paraplegia obtained in less than half the cases (45·7 per cent.). In only two cases was an atrophic paralysis present (Cases II and XIII).

Inco-ordination of movement, apart from that due to the falling out of afferent impulses from deep structures, was present in approximately half the cases. In a disease such as disseminated sclerosis where motor and sensory tracts are prone to be affected simultaneously at different levels of the cerebro-spinal axis, it is not always easy to identify precisely what elements of disordered co-ordination are due respectively to paresis, to loss of deep sensibility, or to interference with the cerebellar system. For example, the intentional tremor, which has so long held a prominent place in the symptomatology of the disease, is in many respects similar to, but is nevertheless not quite the same as, the rhythmical tremor associated with subthalamic lesions. The latter is a pure tremor initiated by the withdrawal of support from the affected limb, while the former is best demonstrated in the execution of some voluntary movement, and is a combination of tremor and inco-ordination. Hence we are inclined to regard the intention tremor of disseminated sclerosis as the result of

destruction of cerebello-rubral fibres and of certain other cerebellar connections in addition.

Definite evidence of cerebellar inco-ordination in one or more limbs, apart from intention tremor, was obtained in eighteen cases (51·4 per cent.). True intention tremor of one or both arms was present in 42·6 per cent., and a nodding to-and-fro tremor of the unsupported head in 37·1 per cent. Ataxic dysarthria on the other hand occurred in only one-fourth of the cases (28·6 per cent.).

Attacks of rotatory vertigo, usually sudden in onset and offset, but sometimes persisting for days or weeks at a time, were common at some period of the disease (51·4 per cent.). It is interesting to note that although tinnitus was associated with these attacks in a few cases, in no instance was any diminution of auditory acuity demonstrable at the time of examination, a fact which points to the vertigo being central, and not peripheral, in origin.

Sustained nystagmus in one direction or another, usually horizontal, was present in 74·3 per cent.

Regarding ataxic dysarthria, nystagmus, vertigo, nodding tremor of the head, intention tremor of the arms, and inco-ordination of the limbs (apart from sensory defects) as evidence of disturbance of the cerebellar system, we believe that there are good grounds for assuming that the lesions underlying these phenomena are situated in a vast majority of the cases in the brain-stem and mid-brain. The assumption is supported by the circumstance that some or all of these disturbances tend to be combined in the same individual.

For example, in eight of the ten dysarthric patients there were also present tremor of the head, intention tremor, and reeling gait, while all the cases with head tremor, except one, presented evidence of cerebellar inco-ordination in arms or legs, or in both.

Diplopia, usually transient, occurred in a third of the cases (34·3 per cent.), but evidence of involvement of cranial nerves other than the optic and oculo-motor group was rare. In no case did the pupillary reactions show any departure from the normal.

Disturbances of the visual mechanism have long been recognized as being one of the most frequent and characteristic features of disseminated sclerosis. Pallor of the optic discs was observed in nineteen cases out of thirty-three in which they were examined (57·6 per cent), bilateral in 45·5 per cent., unilateral in 12·1 per cent. The pallor sometimes involved the whole disc, but more commonly the temporal half only, and in a great many cases it was associated

with normal visual acuity. A history of sudden amaurosis in one eye with subsequent improvement in vision (retro-bulbar neuritis) was obtained in 20 per cent., while severe bilateral visual failure of sufficient degree to be termed disabling was present in only three patients (8·6 per cent.). Scotomata were present in several cases, but the details in this connection were not fully investigated.

Partial or complete loss of control over the bladder was noted in 71·4 per cent. of cases, and when not associated with a paraplegic condition was regarded as evidence of disease in the lumbo-sacral region of the cord.

As regards the mental condition, a majority of the patients were above rather than below the average intelligence. Definite loss or impairment of emotional control, with which was frequently associated an unduly sanguine temperament, was present in half the cases (51·4 per cent.), a defect which permitted the patient to regard his or her condition with indifference or even with amusement.

Loss of consciousness occurred in one patient only.

In no case were any indications observed pointing to disease of the thoracic or abdominal viscera, or to the hæmopoietic system.

The family and past histories failed to throw any light on the ætiology of the disease.

Sex.—There were twice as many females as males (65·7 to 34·3 per cent.).

Age.—The average age of onset was 24·6 years, the youngest case being 16, and the oldest 39 years old. The average age at the time of observation was 28·6 years.

Duration.—The disease had lasted four years on an average, the shortest case being three weeks, the longest fourteen years. Of the two fatal cases one lasted four years and the other thirteen months.

Summary of clinical study.—Disseminated sclerosis is a disease of young adult life, occurring in healthy individuals, characterized in a large majority of cases by an intermittent course, punctuated at irregular intervals by relatively acute exacerbations with subsequent periods of improvement and quiescence. The exacerbations consist either in the appearance of new symptoms due to lesions in fresh localities, or else in an accentuation of symptoms previously experienced, but at the time quiescent. In a small proportion of cases the disease pursues a chronic progressive course from the outset, with a gradual increase in the intensity of existing symptoms and a relative infrequency of new ones.

There is abundant clinical evidence of the random dissemination of the lesions throughout the brain, brain-stem, and cord, and of the involvement in the cord of the white matter rather than the grey. The general clinical course, especially in the case of single acute lesions, is highly suggestive of a localized acute, or subacute, inflammation. There is no evidence of thrombosis or embolism of large vessels, nor is there anything in the clinical study of our cases suggestive of meningeal inflammation or increased intracranial pressure.

Investigation of Two Fatal Cases.

Case I.—Girl, aged 19. Admitted August 12, 1913. Died November 24, 1913 (National Hospital, Queen Square). Good family and past history.

Aged 15: She suddenly lost power and feeling in the left upper extremity; the power soon returned but the hand was "useless" for nearly three months, after which it got perfectly well.

Aged 16: Sudden attack of pain in the right eye which rapidly became blind; examination revealed a retro-bulbar neuritis with profound but not complete loss of vision. Two months later the right optic disc was passing into atrophy and she could count fingers at 3 ft.

Aged 17: Numbness of the right thigh followed by weakness of the right leg and inability to walk. She was admitted to the West London Hospital where she rapidly developed incontinence of urine and fæces, with occasional retention requiring catheterization. She also had diplopia and attacks of rotatory vertigo. On discharge from hospital four moths later she walked "all over the place," and her head and her hands shook so much that she could hardly feed herself. In this condition she remained for eighteen months troubled with fleeting paræsthesiæ, diplopia, vertigo and headache.

Aged 19: One month ago the left arm became suddenly "useless," so that she could not feel what she had in her hand; this was followed a few days later by a similar condition of the right arm.

One week later a further series of symptoms developed: (i) persistent vomiting and constant vertigo, an ever present feeling of herself and her surroundings rotating, worse on movement of head and eyes, "nothing keeps still"; (ii) diplopia; (iii) inability to walk or sit up in bed; (iv) loss of emotional control; (v) retention of urine.

A week later (i) she lost all sphincter control, unconscious of "call" and of the passage of excreta; (ii) the legs became completely paralysed and numb: "I do not know that I have legs except for the pains in them;" (iii) speech became slow and stammering, and (iv) she had attacks of dyspnœa, and (v) difficulty in swallowing.

On admission (August 12, 1913).—Good physique and nutrition. Temperature 99·2° F., pulse 96. Sleepy expression (ptosis), with head turned to right.

Visceral examination negative; severe cystitis present.

Mental.—Distracted, inattentive and irrational. Wishes to die and the next moment evinces confident hopes of recovery. Lacking in reserve and emotional control.

Wassermann reaction (*blood*) negative.

Speech.—No aphasia. Cannot raise voice above a whisper, articulation jerky, slow and tremulous.

Vision.—Acuity, counts fingers at 3 ft. on right, $\frac{6}{6}$ on left. Fields: gross constriction with central scotoma in right eye, and no colour vision; moderate constriction in left. Both discs very white, edges clear, pigment disturbed; changes right more than left.

Hearing.—Normal. Constant vertigo; turning head to left causes a movement of objects from left to right.

Cranial nerves.—iii, iv, vi. Wide pupils, right more than left; the right is sluggish to direct light but reacts well consensually, left normal. Both react well to accommodation. Diplopia, paralysis of right superior rectus and left internal rectus. Ptosis, right more than left, with frontalis overaction. Constant jelly-like nystagmus with eyes at rest. On conjugate deviation both to right and left there is a slow horizontal nystagmus of large amplitude, and a rotatory nystagmus on looking up and down. v, vii, xii normal, except for slight paresis of left lower face. ix, x, xi: palate immobile, reflex absent. Dysphagia. Dysarthria.

Motor.—Head and neck: No paralysis; tremor when unsupported.

Upper limbs: (*a*) Right: General weakness, especially of extensors; normal tone, well-marked intention tremor and dysmetria. (*b*) Left: Hemiplegic attitude, spastic, movements at all joints minimal, extensors weaker than flexors, no wasting.

Trunk: Cannot move in bed. Intercostal movement below sixth rib is poor and abdominal muscles are paralysed.

Lower limbs: Right and left: Complete spastic paraplegia in extension with occasional involuntary flexor spasms.

Sensory.—(i) Subjective: Severe boring paroxysmal pains in abdomen and legs. Feels slight discomfort with distended bladder. (ii) On examination: Questionable impairment of tactile sensibility in both hands. Pain and temperature normal in upper limbs. Complete astereognosis in both hands. Profound loss of passive position and movement whole of left upper limb, considerable loss in right hand. Below the seventh rib there is an almost complete anæsthesia to all forms, both superficial and deep; a sharp prick or deep pressure sometimes gives rise to indefinite pain which cannot be localized.

Spinal column.—Healthy.

Sphincters.—Rectum: Complete incontinence; feels neither "call" nor passage. Bladder: Feels neither "call" nor passage, retention alternates with incontinence.

Reflexes.—All tendon-jerks brisk. Abdominals all absent. Extensor plantar response, right and left.

Treatment.—Bladder—wash twice daily.

Progress (September 9, 1913).—Patient has had frequent attacks of respiratory embarrassment, with very shallow movement of chest, cyanosis, restlessness, but no stridor. There is a curious irregularity of the respiratory rhythm. Increasing dysphagia, vomiting and mental deterioration.

September 15, 1913: The upper limit of complete anæsthesia and paralysis now reaches the fourth rib; the paraplegia is now in flexion rather than in extension. Urine is now free of pus.

September 25, 1913.—Irregular pyrexia the last few days; trace of pus in urine. Regurgitation of fluids through nose.

October 10, 1913: Pyrexia persists. Commencing sacral bed-sores with emaciation and cachexia. Less dysphagia, dyspnœa and vertigo.

November 18, 1913: General condition much worse: profound wasting and cachexia with rapid extension of bed-sores.

November 24, 1913: Died.

Pathological investigation.—The patient was lumbar punctured on September 30, 1913, and again on October 27, 1913, and the cerebrospinal fluid examined by the same methods and with the same results in each case, as follows:—

Cerebrospinal fluid quite clear; no cells and no excess of protein; Wassermann reaction negative. The fresh fluid was precipitated with absolute alcohol and the centrifugalized deposit stained with Giemsa and examined microscopically with negative results.

The fresh fluid was centrifugalized and the deposit added to four tubes of Noguchi's medium. Of these, two tubes remained sterile, while in the other two a long-chained streptococcus was grown which was Gram-positive and grew well in ordinary media with diffuse turbidity. The deposit from all four tubes after incubation was stained with Giemsa and examined microscopically; in each case small granular bodies were observed, but precisely similar bodies were found in the deposit of uninoculated tubes.

No animal inoculations were carried out with the fresh cerebrospinal fluid.

A post-mortem examination of the patient's body was carried out twenty hours after death by Dr. S. A. Kinnier Wilson, who kindly gave us every facility for our investigations. Before removal of the organs cultures were made from the frontal regions of the brain on both sides and from the cord. A long-chained streptococcus was grown from each site, which acidified litmus milk and lactose, but did not affect raffinose, inulin or mannite.

Portions of the patient's brain and cord were removed with all reasonable precautions and ground in a mortar. Films of the suspension

thus obtained showed diplococci and streptococci, but no spirochætes were found by the dark-ground illumination method. The suspension was then filtered through a Doulton candle and on November 26, 1913, injected under general anæsthesia into rabbits as follows :—

Rabbit 1.—Trephined: 0·25 c.c. of suspension injected intracerebrally and 5 c.c. intraperitoneally. The animal remained in perfect health and was killed nine weeks later. Post-mortem examination revealed no disease of the internal organs. Smears were made from the cerebral and spinal membranes and stained with Giemsa with negative results. The pons and mid-brain were examined histologically and found to be healthy.

Rabbit 2.—Trephined: 0·25 c.c. of suspension injected intracerebrally. The animal remained in perfect health and was killed five months later. Histological examination revealed no disease in brain or cord.

Rabbit 3.—Injected intraperitoneally with 8 c.c. of suspension. No immediate or remote results, and the animal was well five months later.

The histological examination of the patient's brain and cord were unfortunately very incomplete, and the notes concerning it have been lost. Both brain and cord were riddled with sclerotic areas, one large one involving the whole transverse area of the cord in the upper thoracic region. In the lower half of the pons very little normal tissue remained. A perivascular round-cell infiltration was a prominent feature of the diseased areas.

Case II.—Male, aged 26. Admitted November 19, 1913. Died February 20, 1914. Family and past history unimportant. Ten months ago (January 6, 1913) he "suddenly came over sick and giddy" but was well in three days. Three weeks later the same thing happened, and his legs became so weak that he could not walk and his hands were unsteady. He was admitted to the London Hospital where he improved, and after seven weeks he could write a letter and walk without support. On discharge he began to notice transient numbness and tightness in his left leg and arm, "as if my leg would burst." These paræsthesiæ persisted, but no further symptoms developed until August, when his sight began to fail and his left eye became rapidly blind. In September his walking got much worse and he had frequent falls; he also had difficulty in voiding his urine, and towards the end of the month he developed incontinence of both bladder and rectum.

Four weeks ago his left arm became much weaker and more unsteady, his left leg almost paralysed, his speech almost unintelligable, and his memory began to fail.

On admission (November 19, 1913): Poor physique. Temperature 100·4° F., pulse 80.

Visceral examination.—Negative. Urine normal.

Wassermann reaction (blood).—Negative.

Mental.—Intelligent but apathetic. Normal emotional tone.

Speech.—No aphasia. Articulation slow, scanning, tremulous and ataxic.

Vision.—Acuity: Left $\frac{6}{60}$, right $\frac{6}{18}$. Left optic disc very pale, edges fluffy, some disturbance of retinal pigment; consecutive atrophy. Right optic disc pale, especially on temporal side; primary atrophy.

Hearing.—Normal. No vertigo now, or tinnitus.

Cranial nerves.—Normal except for weakness of right lower face, and horizontal nystagmus of wide range on looking to right and left.

Motor.—Head and neck: Nodding tremor of unsupported head.

Upper limbs: (*a*) Right, power everywhere subnormal, tone a little increased, well-marked intention tremor and slight sensory ataxia. (*b*) Left, muscles of forearm and hand weak and wasted, with diminution of faradic irritability, extreme intention tremor and sensory ataxia.

Trunk: Cannot sit up without use of hands.

Lower limbs: Both weak and spastic, left more than right; all flexors weaker than extensors. Legs in extension with occasional flexor spasms in left leg. Musculature poor. Legs tremulous.

Sensory.—Profound loss to pin-prick and temperature to right of mid-line below umbilicus. Tactile sensibility greatly impaired whole of left lower limb. Vibration completely abolished in lower limbs and pelvis and much impaired in hands (left more than right).

Compasses: No threshold obtainable in palms or soles.

Complete astereognosis in both hands.

Passive posture and movement: Profound loss distally in upper limbs (left more than right), considerable loss in lower limbs (left more than right).

Spinal column.—No evidence of disease.

Sphincters.—Complete incontinence of urine and fæces; feels neither call nor passage.

Gait.—Cannot stand alone; very tremulous; no control over legs.

Reflexes.—Left supinator jerk absent, all other jerks very brisk. All abdominals absent. Extensor plantar response, right and left.

Progress (December 18, 1913).—Condition deteriorating. Dysarthria is now so profound that he is barely intelligible. Mild irregular pyrexia; bed-sore developing over sacrum; urine normal.

January 15, 1914: Legs are now completely paralysed; paraplegia in flexion.

February 13, 1914: Whole of left face and left side of palate paralysed. Dysphagia has developed with regurgitation of fluids through nose. Complete loss of upward movement of both eyes.

Still slight irregular pyrexia. Bed-sore has increased, but is not deep and is fairly clean. No cystitis.

February 20, 1914: Died.

Pathological investigation.—The patient was lumbar punctured on December 1, 1913, and on December 18, 1913. The cerebrospinal fluid was quite clear, there was no excess of globulin, and the Wassermann reaction was negative. In the fluid from the first puncture no cells were found, while in the second there was a very slight excess of small lymphocytes.

On December 1, 1913, two rabbits were injected intraperitoneally, one with 15 c.c. and the other with 10 c.c. of the patient's unheated blood-serum without immediate effect. Two days later fresh cerebrospinal fluid was obtained from Case III (from which a streptococcus had been previously grown; *vide infra*), and 0·25 c.c. of the centrifugalized deposit was injected intracerebrally into both rabbits. Both animals remained well; one was killed six weeks later and no histological or naked-eye changes were found in the brain or cord, the other was alive and well three months afterwards.

Cultures of the fresh cerebrospinal fluid of Case II, both aerobic and anaerobic, remained sterile, and examination of the stained centrifugalized deposit was negative. On December 18, 1913, two rabbits were injected intracerebrally with 0·5 c.c. of the centrifugalized deposit of fresh cerebrospinal fluid. Both remained well; they were killed three and four months later respectively and no lesions, naked-eye or microscopic, were found in the brain or cord.

Post-mortem examination of Case II (six hours after death).—No naked-eye evidence of disease in internal viscera. Numerous sclerotic foci were present in the cerebral cortex, basal ganglia, periventricular tissue, pons, medulla, and spinal cord (especially in cervical region); none were visible in the mid-brain. No naked-eye evidence of meningitis. Portions of the brain and cord were ground up in a mortar with physiological saline, filtered through a Berkefeld V-candle, and three hours after removal of the tissue from the body 0·5 c.c. of this filtrate was injected intracerebrally into a rabbit and 4 c.c. intraperitoneally. Three days later another 7 c.c. of filtrate was injected intraperitoneally. The animal remained well and was killed four and a half months later; nothing abnormal, naked-eye or histologically, was found in the brain or cord.

Histological.—Both kidneys showed chronic tubal change.

Sections of brain and cord stained by the Weigert-Pal method gave the following results:—

Numerous small foci of myelin sheath destruction were found scattered throughout the cerebral hemispheres both in the cortex and

adjacent white matter, especially in the anterior half of the brain. Extensive sclerotic patches were present in the basal ganglia and in the periventricular regions.

Subthalamic region: The red nucleus on either side was involved in a patch of sclerosis.

Pons: numerous sclerotic foci were scattered throughout the pons, especially round the fourth ventricle, in the region of the right middle cerebellar peduncle, and both facial nuclei.

Medulla: numerous foci were present, right more than left; the region of the right restiform body was occupied by an area of particularly dense sclerosis.

Spinal cord: (i) Upper cervical: sclerotic areas occupied the central and external portions of both posterior columns, and a large focus involved the left antero-lateral region and anterior horn.

(ii) Lower cervical: sclerotic foci present in both anterior columns, in the crossed pyramidal tract on the right side, and in the posterior columns on both sides.

(iii) Mid-thoracic cord: both posterior columns involved throughout in an area of sclerosis. On the right side the lateral column, and on the left the antero-lateral column were occupied by areas of dense sclerosis, which invaded the anterior horn on the left side.

(iv) Lumbar: whole transverse area, except the anterior columns, occupied by dense sclerosis.

Cerebellum, spinal roots, and ganglia—not examined.

Sections stained with Giemsa showed that the patches of sclerosis were not all sharply defined from the normal tissue. This lack of definition was greatest in the areas which appeared to be fresh; in these, especially in the cortex and brain-stem and to a very much smaller extent in the cord, the nerve cells showed chromatolysis and indistinctness of outline, and glia-cell proliferation was a prominent feature. In the older areas the gliosis was more intense and characterized by proliferation of glia fibrils.

In the leptomeninges and throughout the brain and cord a perivascular infiltration with round cells and endothelial cells was present. This change was particularly noticeable in the fresh areas of sclerosis, but was not entirely absent in areas which were of long standing.

Investigations carried out in Thirty-three Non-Fatal Cases.[1]

(1) *Examination of Cerebrospinal Fluid.*

The examination comprised the following points:—

(*a*) Cytology (all cases).

(*b*) Globulin reaction (all cases).

(*c*) Wassermann reaction (all cases).

(*d*) Microscopical examination of deposit obtained by precipitating the fresh cerebrospinal fluid with absolute alcohol, stained with Giemsa (all cases).

(*e*) Anaerobic cultivation (27 cases).

(*f*) Microscopical examination of deposit in Noguchi tubes after inoculation with cerebrospinal fluid and incubation (25 cases).

(*g*) Aerobic cultivation (19 cases).

The colloidal-gold reaction was not tested in any case.

The results obtained were as follows:—

(*a*) No excess of cells was obtained in any of the 33 cases. Occasionally one lymphocyte was found in the centrifugalized deposit but in the vast majority of cases no cells of any kind were present. It will be remembered that in one specimen of cerebrospinal fluid from Case II a slight lymphocytosis was present.

(*b*) Globulin reaction (tested by half saturation with ammonium sulphate); a positive reaction was present in Case XXXIV, a very slight reaction in Cases XXVII, XXXI and XXXV, and a negative reaction in the remaining 29 cases.

(*c*) The Wassermann reaction was negative in every case, both in the blood and the cerebrospinal fluid.

(*d*) Deposit obtained by precipitation with absolute alcohol: in Case VIII examination of the deposit stained with Giemsa revealed numerous small bodies resembling cocci. [In two cases (XXXIV and XXXV) small granules resembling fat were observed by the dark-ground illumination method; similar bodies have been observed in the cerebrospinal fluid and brain emulsions of cases of encephalitis lethargica and uræmia and are probably fragments of altered myelin. With these exceptions this method yielded negative results.]

(*e*) Anaerobic cultivation. The following media were used:—

(i) Noguchi's fluid medium (ascitic fluid + fresh rabbit's kidney, in 23 cases (III to XXI, XXX and XXXI, XXXIV and XXXV).

[1] For clinical details of cases *vide* Appendix.

(ii) Ascitic fluid + human. red cells in three cases (XXIII to XXV).

(iii) Noguchi solid medium (agar + rabbit's kidney) in two cases (XXX and XXXI).

(iv) Ascitic fluid only in Case XXII.

In twenty-one cases all the inoculated tubes remained sterile. In three Cases (IV, XIX, XX) a diphtheroid bacillus was grown; in Cases IV and XIX the same bacillus also grew in aerobic cultures. The bacillus grown anaerobically in Case XX was non-pathogenic to guinea-pigs.

Case III, from which a streptococcus was grown, merits a more detailed description. The patient was a girl, aged 18, and the illness dated back to just over a year previously when she was suddenly seized with pain behind the eyes and failure of vision. The vision improved somewhat, but in the course of the next four months she developed successively weakness of the trunk muscles, tremor of the left arm, loss of sphincter control, weakness of the right leg and then of the left. At the time of our investigations she was rather rapidly getting worse and becoming more paralysed below the waist; there were however no acute exacerbations, no bed-sores, cystitis, or pyrexia.

Lumbar puncture was performed on three occasions as follows:—

(i) September 30, 1913. The centrifugalized deposit of cerebrospinal fluid was added to four Noguchi tubes, of which two remained sterile, while in the other two a pure growth of a Gram-positive. long-chained streptococcus appeared, which grew well in ordinary media with diffuse turbidity. Three rabbits were then inoculated intracerebrally with 0·5 c.c. of a twenty-four hours' growth of the streptococcus. Two days later two animals were dead, and examination revealed frontal abscesses, the pus from which contained long-chained streptococci in large numbers. The third animal was ill two days after inoculation, but recovered rapidly. It was killed eight weeks later, and post-mortem examination revealed nothing abnormal in brain, cord, or meninges, and cultures from the meninges remained sterile.

Intraspinal injection into a rabbit of 1·5 c.c. of fresh cerebrospinal fluid was followed by no immediate or remote effects, and histological examination of the animal's cord ten weeks later revealed nothing abnormal.

(ii) October 27, 1913. Patient was again lumbar punctured, but on this occasion all anaerobic and aerobic media remained sterile.

(iii) December 3, 1913. Lumbar punctured. Two rabbits, both of which had two days previously received an intraperitoneal injection of the unheated blood serum of Case II (fatal case), were injected intracerebrally with 0·25 c.c. of the centrifugalized deposit of cerebrospinal fluid. In neither animal was any effect produced.

The streptococcus grown from the first sample of cerebrospinal fluid in this case resembled that grown post mortem from the brain of Case I in both its morphological and cultural characteristics.

(*f*) Examination of Noguchi deposit. Films were stained with Giemsa and searched for parasites with negative results. In several cases small granular amorphous bodies were found, which were particularly numerous in Case XXI. In this case 10 c.c. of the Noguchi fluid were injected intraperitoneally into a rabbit which two weeks previously had received 2·5 c.c. of the patient's cerebrospinal fluid along the course of one sciatic nerve plus 5 c.c. of the patient's blood serum intraperitoneally. The animal however remained well.

Similar granular bodies were frequently found in the deposit from Noguchi tubes which had not been inoculated with cerebrospinal fluid.

(*g*) Aerobic cultivations : various media were used, litmus milk, inulin, inulin plus serum, Besredka with and without human red cells, &c.

In Cases IV and XIX a diphtheroid bacillus was grown, and from Case XIII a pure culture of *Staphylococcus albus* was obtained, which we regard as a contamination.

With these exceptions the cultures all remained sterile.

(2) *Animal Experiments* (*Thirteen Cases*).

Rabbits were employed in every case, and in a few instances guinea-pigs in addition. All animal experiments were conducted under general anæsthesia and with strict aseptic precautions. We consider the use of a general anæsthetic important in order to obviate the traumatic palsies, especially of the hind limbs, to which rabbits are particularly susceptible ; these palsies which occur in animals improperly treated have been a fruitful source of error in the past.

To the experiments in connection with the two fatal cases in which intracerebral injections of suspensions of cerebral and cord tissue were effected, reference has already been made. The intracerebral route was also used in Cases III, XXVII and XXVIII, the material injected in each case being 0·25 c.c. of the centrifugalized deposit of fresh cerebrospinal fluid.

Injections were made of from 2·5 to 5 c.c. of fresh cerebrospinal fluid along the course of the sciatic nerve in Cases XIX, XX, XXI, XXVI and XXVIII. In the first three of these cases intraperitoneal injections of from 5 to 10 c.c. of the patient's unheated blood serum were given simultaneously, and in Case XXVIII an intracerebral injection (0·25 c.c.) of centrifugalized cerebrospinal fluid.

In Case III an intrathecal injection of 1·5 c.c. cerebrospinal fluid was given, in Case XXV an intravenous injection of 2 c.c., and in Case XXIX an intratesticular injection of 3 c.c.

In none of the above cases were the injections followed by any immediate or remote effects; all the animals remained in good health, and in those that were killed at some subsequent period no lesions, naked-eye or histological, were found in the internal viscera, meninges, brain or spinal cord.

In Cases XXXIV and XXXV the intra-ocular route was adopted. In each case a rabbit was inoculated with 0·25 c.c. of centrifugalized deposit of cerebrospinal fluid withdrawn from the patient two hours previously. Six days later the rabbit inoculated with cerebrospinal fluid from Case XXXIV was disinclined to move and its hind limbs were stiff. The following day the weakness and stiffness of the hind limbs were more obvious, the animal responded slowly when pricked, its gait was laboured and there was some "shivering" of the muscles in the lumbar region. Two days later the animal had completely recovered and is alive and well at the time of writing. Six days after injection the animal from Case XXXV showed an exactly similar condition, but the weakness of the hind limbs was rather more pronounced, and the limbs were actually dragged along without being definitely paralysed. After persisting for two or three days the disability completely disappeared and the animal has remained well ever since.

Two guinea-pigs injected intraperitoneally with fresh cerebrospinal fluid from Cases XXXIV and XXXV remained well.

Summary of animal experiments and bacteriological investigations.—It will be seen from the above experiments that in spite of a variety of routes employed for our injections we failed to produce in rabbits any condition of ill-health, with the exception of a transient stiffness of the hind legs in two animals, by inoculating them with the fresh cerebrospinal fluid and blood-serum of patients suffering from disseminated sclerosis, or by inoculating them with fresh, filtered suspensions of the brain and cord of patients recently dead of the isease.

In other words we have entirely failed in our attempts to transmit disseminated sclerosis to animals.

As regards our bacteriological findings a long-chained streptococcus was grown in two cases, from the cerebrospinal fluid of Case III, and from the cerebrospinal fluid during life and from the cerebral hemispheres after death in Case I. In the latter case (Case I) owing to cystitis and bed sores the patient had been in a profoundly septic and cachectic condition for six weeks prior to her death, and the bacteriological result may reasonably be thus explained. Case III however had neither cystitis, bed-sores, nor pyrexia, and the presence in the cerebrospinal fluid of a streptococcus, cultures of which on intracerebral injection into rabbits caused death with the formation of frontal abscesses, was not traced to a septic focus. At the same time, while unable to advance any adequate explanation of the bacteriological finding in this case, we are by no means inclined to regard it as of any significance with reference to the pathogenesis of disseminated sclerosis.

Review of Recent Work on the Pathogenesis of Disseminated Sclerosis.

(1) *Histological. Morbid Anatomy.*

Two exhaustive investigations of the morbid anatomy of the disease have appeared within the past few years.

(*a*) Siemerling and Raecke in 1914 published the results of detailed histological examination of eight cases together with a clinical review of sixty others. They consider that the primary and essential feature of the pathological process is a localized destruction of nervous tissue, the process being closely related to changes in the vessels, which show definite inflammatory phenomena, viz., congestion, perivascular infiltration with small lymphocytes, polymorphs and plasma cells, and in many cases capillary hæmorrhages.

They describe the early changes, best studied in the small, circumscribed patches ("Herde") in the brain, as being characterized by a focal destruction of axis cylinder fibres, with which is associated a considerable destruction of the medullary sheaths. The foci tend to coalesce and the medullary sheath destruction becomes more and more complete. In the cerebral cortex and periventricular region the lesions are grouped according to the distribution of terminal arteries and resemble infarcts, the cortical foci usually having a pial vessel in their centre. Immediately consequent on the destruction of nervous tissue

a marked proliferation of the glia occurs, which acts as scar tissue and helps to protect the tissues from further damage. The early stages of the glia reaction are characterized by a richness of glia nuclei, which later on are reduced in number to be replaced by a thick network of glia fibrils. Associated with the myelin sheath destruction numerous scavenger cells make their appearance, arising mainly from the neuroglia and to a less extent from the blood elements. These cells, which effect the transportation of the products of destruction, are chiefly compound granular cells, and are most numerous in fresh lesions and in the lymphatic spaces outside the vessels. They are never as numerous as in cases of softening due to arterio-sclerosis, and are much scarcer in the cortex than in the white matter, since myelin destruction is negligible in extent in the former as compared with the latter. These cells contain a large, deeply-staining, round nucleus and their protoplasm is frequently packed with fatty granules staining orange-red with scharlach.

Owing to the excessive glia reaction neighbouring foci tend to be bound together in a common sclerotic plaque. Moreover, the individual foci do not pass directly over into normal tissue, but are surrounded by a broad intermediate zone characterized by a pronounced increase of glia nuclei. In these zones the authors observed a tendency to recurrence of capillary hæmorrhages, while the presence in them of plasma cells was regarded as indicating a lighting up of the active process.

Secondary degenerations, as a result of axis cylinder destruction, were found in distant parts of the nervous system, and mingling with the essential focal lesions produce a complicated and confusing histological picture. While, however, axis cylinder destruction is the first stage in the morbid process and is demonstrable before the medullary sheath is affected, the authors admit that the latter change eventually exceeds the former, and they do not entirely oppose the long-accepted view that the axis cylinders remain relatively intact.

The ganglion cells, although more resistant than the nerve-fibres, also show changes when involved in the primary lesions, but the changes were limited to the focal lesions and were never systemic as in general paralysis.

Occasionally the glia over wide areas, and altogether outside the essential focal lesions, undergoes definite proliferation with an abnormal richness of both nuclei and fibrils and a few pathological spider cells. A section of such an area would certainly give the impression of a

primary glia proliferation, but the authors are of opinion that there are in reality no grounds for postulating a primary gliosis, and they explain the appearances by a leakage from the diseased areas into the periphery of a virus or toxin in a concentration too weak to evoke a focal inflammatory lesion, but sufficiently strong to give rise to a diffuse glia reaction.

The peripheral nerves showed inconstant, non-specific, neuritic changes, and the typical sclerotic plaques were strictly limited to the central nervous system and to the glial portions of the cranial nerves and nerve-roots. In correspondence with the inflammatory nature of the whole process meningitic changes were constantly present, e.g., patchy peri-vascular round-celled infiltrations of the pia-arachnoid; plasma cells were also observed in a few cases.

The cerebrospinal fluid was examined in both fatal and non-fatal cases, and is described as showing "usually a slight lymphocytosis and slight increase of globulin." Bacteriological investigation was negative.

The authors consider that the whole anatomical picture is in complete harmony with the clinical one, viz., acute lesions giving rise to acute symptoms which tend to clear up. They conclude that disseminated sclerosis is infective or toxic in origin, that the virus or toxin reaches the central nervous system through the blood-vessels, and they regard the presence of plasma cells as strong evidence in favour of an infective process and most probably a parasitic one.

(*b*) Dawson examined nine cases histologically and came to much the same conclusions as Siemerling and Raecke, although differing somewhat in his interpretation of the histological details. He describes six stages in the development of the essential lesion, viz.: (1) A commencing reaction of all the tissue components and degeneration of the myelin sheath. (2) Glia cell proliferation and commencing fat granule cell formation. (3) "Fat granule cell myelitis." (4) Commencing glia fibril formation. (5) Advancing sclerosis, and (6) Complete sclerosis.

He regards the primary degeneration of the myelin sheath as the most constant and uniform feature of the histological picture, and considers that the relative persistence of axis cylinders and ganglion cells is abundantly confirmed. Secondary degeneration occurs, but affects scattered fibres and not tracts in their entirety.

He traces the development of the essential lesions from their

earliest stages to the final development of the dense sclerotic areas visible to the naked eye and scattered throughout both brain and cord, and he finds areas of recent and of old disease in the same patient. Almost every diseased area shows evidence of an advancing process; they are either wholly "early" or show a peripheral advancing zone round a condensed centre, giving the impression that the primary process has never quite died down but is gradually extending peripherally.

According to Dawson vascular phenomena are not prominent in the earliest stages; "in its diffusion through the vessel wall the noxa causes no recognizable primary alteration, but there is probably an abnormal permeability and increased transudation of toxic lymph." The first vascular changes are found at, or just after, the stage of "fat granule cell myelitis," and are secondary to the resorption of the fatty products of destruction; this in time is followed by a proliferation of all the cell elements of the adventitia, and later by a modified infiltration of small round cells and a few plasma cells. Finally as the tissue condenses the vessel walls become thickened and undergo hyaline degeneration.

The cranial nerves and spinal roots are frequently involved in the glial portion of their extra-medullary course, but the meninges show no constant or specific changes.

While not attempting to explain the irregular distribution of the lesions, Dawson considers that the sites of predilection are "probably related (*a*) to the vessels; to the terminal ramifications of end-arteries, e.g., on the ventricular surfaces, and to the points where vessels break up, e.g., in the transition zone between white and grey matter both in the central and cortical grey matter, and (*b*) to areas where much glia is normally present, e.g., the peri-ventricular and peri-central tissue, the optic chiasma, the postero-median and para-median septa, the marginal glia zone, and the perivascular glia layer."

After discussing the somewhat different views as to what should be accepted as the histological criteria of "inflammation" when it affects the central nervous system, he concludes by regarding disseminated sclerosis as a subacute inflammatory disease, i.e., a localized, disseminated, subacute encephalo-myelitis which terminates in areas of actual and complete sclerosis, the causal agent being probably a soluble toxin which is conveyed to the nervous system by the blood-stream. He further points out that the remissions and relapses so characteristic of the disease "necessitate the assumption of the latent

presence of the morbid agent in the body, or, if this is an autogenous toxin, either of its intermittent evolution or of its accumulation from deficient elimination."

Reviewing the views propounded respectively by Siemerling and Raecke and by Dawson, while both sets of investigators regard the histological changes as inflammatory in character, the former look upon the process as acute, while Dawson calls them subacute.

Our own histological investigations are admittedly quite incomplete; but as far as they go they strongly support the view which regards the process underlying disseminated sclerosis as inflammatory in nature; in fact the most conspicuous feature of the sections in Case II was the well-marked perivascular infiltration with round cells and endothelial cells, similar to that met with in cases of encephalitis lethargica, although perhaps not quite so intense. On general grounds we have some difficulty in accepting Dawson's statement that the perivascular changes are absent in the earliest stages of the process, and only appear subsequent to, and as a consequence of, the absorption of the products of myelin destruction and the gradual condensation of the tissues. In Case II these changes were a prominent feature of areas where sclerosis was not yet apparent, and we favour as being more in conformity with the principles of general pathology the interpretation of Siemerling and Raecke, who regard the perivascular reaction as important evidence of the frankly inflammatory nature of the early stages of the morbid process.

(2) *Experimental.*

(*a*) Bullock in 1913 claimed to have transmitted the disease to rabbits by subcutaneous injection of the cerebrospinal fluid of a patient suffering from disseminated sclerosis. Ten rabbits in all were injected; of these four died without paralysis, two remained well, and two became paralysed in the hind limbs three weeks later and then recovered. One animal, twelve days after receiving 2 c.c. of unfiltered cerebrospinal fluid along the course of one sciatic nerve, became paralysed in the hind limbs; killed four days later, an intense cystitis was found, together with some fragmentation of the myelin sheaths in the white matter of the spinal cord, but no Marchi changes. The other animal three weeks after an injection of 1·5 c.c. filtered cerebrospinal fluid became weak in the hind limbs, but afterwards improved and was left with a slight spastic paresis. Six weeks later it was killed, and large areas of degeneration were found throughout the cord in Weigert-Pal

and in Marchi preparations. The verbal description of, and the figures which claim to illustrate, these changes are in our opinion unconvincing, and we are quite unable to accept the author's statement that the changes represent "a complete reproduction of the appearances found in the human subject"

(*b*) Siemerling and Raecke injected rabbits and two apes (*Macacus rhesus*) with cerebrospinal fluid of patients suffering from disseminated sclerosis, with negative results.

(*c*) Kuhn and Steiner injected blood and (or) cerebrospinal fluid of four disseminated sclerosis patients into guinea-pigs and rabbits. From their brief description the diagnosis in Cases III and IV is, in our opinion, open to question. Six guinea-pigs were inoculated intraperitoneally with 1 c.c. of a mixture of blood and cerebrospinal fluid from Case III, of which four developed paralysis and two remained well. Of three guinea-pigs injected with 1 c.c. of blood diluted 1 in 5 from Case IV, one remained well, one was ill four weeks later and recovered, and one became ill five weeks later and died after nine days. Blood-stained cerebrospinal fluid (0·2 to 0·4 c.c.) from Case I, diluted 1 in 4, was injected intraperitoneally into ten guinea-pigs and five rabbits. Three of the guinea-pigs showed paralytic phenomena a few days later, one became affected seven weeks later, two died of epidemic disease, and four remained well. The rabbits showed transient phenomena, not definitely paralytic, but otherwise the results in them were negative. A little later blood-free cerebrospinal fluid from Case I was injected intraperitoneally into five guinea-pigs with negative results, and 1 c.c. of defibrinated blood into another set of five guinea-pigs, of which one died with paralytic phenomena eighteen days later, and the other four of epidemic disease. Intraperitoneal injections of cerebrospinal fluid from Case II into ten guinea-pigs were without result, while similar injections of 1 c.c. of blood diluted 1 in 3 were followed six or seven weeks later by paralytic phenomena in two out of three animals. Intra-ocular injections of cerebrospinal fluid (0·2 to 0·5 c.c.) from Case II were followed by paralytic phenomena in two out of five rabbits.

These authors also claim to have transmitted the disease through a series of four guinea-pigs and later of two rabbits, using for the first injection material obtained from previously inoculated animals who had developed paralytic phenomena. The exact nature of the material used and the route employed for the injections are not stated.

Control experiments (fifteen rabbits and thirty guinea pigs) were negative.

All the affected animals showed symptoms in from three days to three months after injection (average six to seven weeks); they moved about less, sat hunched up, the hind legs became stiff and weak, and total paralysis preceded death.

Post-mortem examination of the paralysed animals revealed no naked-eye lesions in the internal viscera or nervous system, and at the time of publication the histological examination had not been completed.

Delicate, slender spirochætes, resembling those found in epidemic jaundice, were demonstrated during life and after death in the heart's blood of several of the affected animals, and also in the blood-vessels of the liver.

If we analyse these experiments it will be evident that in the absence of any histological examination of the brain and cord of the affected animals there can be no justification for assuming that the animals had developed disseminated sclerosis. This being so we are justified still less in assuming that the finding of spirochætes in the heart's blood and liver is in any way related to the origin of disseminated sclerosis, whatever may have been its relation to the morbid condition from which the experimental animals were suffering.

(*d*) Simons, using sterile cerebrospinal fluid of a patient with disseminated sclerosis, kept at 0° C. for ten days, inoculated nine rabbits, of which seven remained well. One animal, which had received 3 c.c. in one sciatic region, nine days later developed paralysis of the hind legs and died totally paralysed on the nineteenth day; no naked-eye lesions were found in meninges, brain, or cord. The other animal developed paresis of the hind limbs on the fifth day, which persisted; the animal was killed on the fourteenth day but nothing abnormal was found post mortem.

(*e*) Marinesco inoculated the cerebrospinal fluid of two patients with disseminated sclerosis into six guinea-pigs, of which four were unaffected. The other two, who had received 1 c.c. intracerebrally, presented three or four days later difficulty in moving about. In the fluid obtained by puncture of the fourth ventricle of these animals spirochætes were found similar to those described by Kuhn and Steiner. This fluid injected into guinea-pigs, and a repetition of the experiments *de novo*, all gave negative results.

(*f*) Steiner, in March, 1917, injected 1 c.c. of cerebrospinal fluid from Case I of Kuhn and Steiner's series into an ape (*Macacus rhesus*). The animal remained well until February, 1918, when some awkwardness and weakness of the hind limbs was noticed by the attendant.

This passed off to reappear in June when the limbs were observed to be weak and spastic. The condition persisted and a month later the animal was killed. At the post-mortem examination nothing abnormal was found in the viscera, but focal lesions were visible to the naked-eye scattered irregularly throughout both cerebral hemispheres. Histologically these foci were found to consist of fairly sharply outlined areas characterized by a patchy destruction of medullary sheaths; compound granular cells were present in large numbers, both these and the glia cells containing granules which stained red with scharlach. Proliferation of the glia cells was a prominent feature, and in the periphery of the lesions numerous multi-nucleated glia cells with abundant protoplasm were present, the cells showing a definite tendency to form fibrils. The axis cylinders were relatively intact and there were no vascular changes. The spinal cord apparently was not examined.

Steiner considers that the lesions found are indistinguishable from those of human disseminated sclerosis, but utters a note of warning against drawing hasty conclusions.

(*g*) Rothfeld, Freund, and Hornowski inoculated by a variety of routes guinea-pigs and rabbits with blood and cerebrospinal fluid from four undoubted cases of disseminated sclerosis. The blood of the experimental animals was examined for spirochætes almost daily, minute histological examination was made of the brain and cord, and emulsions of brain and cord from inoculated animals was injected into a further series. In no case were spirochætes found, and the authors express the opinion that the spirochæte found by Kuhn and Steiner was an accidental infection transmitted from animal to animal. Many of the inoculated animals died, but the cause of death in the vast majority of cases was either coccidiosis or tuberculosis. In one animal slight neuroglia changes were found, but precisely similar changes were observed in animals with coccidiosis who had received no injections. In all other respects histological examination of the nervous system was negative. Some of the animals appeared to be ill for a day or two after inoculation with cerebrospinal fluid, the fluid being probably toxic in some way. In no case, however, did the authors succeed in transmitting to guinea-pigs or rabbits any condition resembling human disseminated sclerosis.

(3) *The Finding of Spirochætes in the Brains of Patients dead of Disseminated Sclerosis.*

(*a*) Siemerling was the first to publish a positive result. In the brain of a patient with disseminated sclerosis who died of erysipelas, examined two hours after death, numerous focal lesions were present; minute pieces from the diseased areas were removed and examined by the dark-ground illumination method. In two preparations living spirochætes were found, similar to those discovered by Kuhn and Steiner, but attempts to stain them in sections did not succeed.

(*b*) Büscher reported the finding of spirochætes by the dark-ground illumination method in the brain of a chronic case of disseminated sclerosis; the parasites exhibited undulatory movements from fifteen to thirty-nine hours after death. They could not however be detected in hardened sections of the brain in ordinary silver preparations.

(*c*) Schuster describes the case of a boy which he regards as a combination of juvenile general paralysis and disseminated sclerosis. Mental symptoms were a prominent feature of the illness and in the later stages the pupillary reactions to light became sluggish. At the autopsy the brain was found to be atrophic, the leptomeninges thickened, and the lateral ventricles dilated. The peri-vascular spaces were packed with small lymphocytes and plasma cells, and there were numerous areas of myelin sheath destruction, especially in the cerebral white matter. Spirochætes, hardly distinguishable from the *Spirochæta pallida*, were found in the brain in silver preparations of hardened material. The Wassermann reaction was positive during life in both blood and cerebrospinal fluid and the case appears to us, but not apparently to the author, to be of no decisive importance in relation to the pathogenesis of disseminated sclerosis.

General Discussion and Summary.

In attempting to elucidate the pathology of any obscure disease there is a natural temptation to make comparisons between the disease in question and certain other apparently similar conditions the cause and nature of which are understood. In the case of disseminated sclerosis, however, it is difficult if not impossible to conjure up any analogous condition, nor, even if we could, would such analogy be decisive. In view of the suggested spirochætal origin of the disease one naturally compares it with syphilis of the nervous system, to which it bears certain resemblances in its clinical course and manifestations;

it differs however from syphilis in two important particulars, first by being rigidly confined to the nervous system, and secondly by the irregular, patchy distribution of the essential lesions in marked contrast to such systemic processes as tabes dorsalis and general paralysis.

The past and family histories of our patients, so valuable in the etiological studies of other diseases, tell us nothing as to the origin of disseminated sclerosis. It is neither familial nor epidemic, although its rarity in certain countries (it is said to be unknown in Japan) points rather to some extraneous factor.

The pathogenesis of any disease can be considered from two points of view, first the nature of the morbid process, and secondly its origin. As to the nature of the morbid process underlying disseminated sclerosis two views are held. According to the first or exogenous theory, supported by a majority of observers, the process is set up by some irritant distributed through the nervous system by the blood-stream, and is inflammatory or toxi-infective in character. The second or endogenous theory, advocated particularly by Strümpell and Müller, regards the disease as the result of some developmental or congenital defect of the neuroglia, which is thus rendered more liable to be affected by irritation than is normally the case; in other words the disease is a primary gliosis.

There would appear to be an insuperable obstacle to the acceptance of the second or endogenous theory, namely, the clinical character of the disease, since it is hardly conceivable that a condition so frequently characterized by an acute or subacute onset and a clinical course punctuated at irregular intervals with exacerbations and remissions can be ascribed to a congenital or developmental defect. Müller has attempted to overcome this difficulty first by postulating certain external factors as "agents provocateurs" acting on a neuroglia which is congenitally vulnerable and susceptible, but exactly what these factors are he is unable to say. Secondly, and more important, he attempts to draw a distinction between true disseminated sclerosis and secondary disseminated sclerosis. According to Müller the only true disseminated sclerosis is the chronic progressive case originally described by Charcot, which one can perhaps accept as being clinically intelligible as a primary progressive gliosis, whereas the cases with acute symptoms and a discontinuous clinical course, with which this paper mainly deals, he excludes altogether from the category of true disseminated sclerosis, and regards them as something else which he calls " disseminated encephalo-myelitis."

We have now to inquire whether this differentiation advocated by Müller is warranted by the clinical and histological facts at our disposal. Clinically while it is useful to recognize the chronic progressive and the subacute remittent type of case, the distinction must not be pushed too far, since cases not infrequently occur which are intermediate between the two and serve to link the one type with the other. Secondly there is a definite tendency for the remittent type in its later stages to lose its subacute characters and to take on a chronic progressive course. Thirdly, just as the chronic type of case progresses downhill by an increase in intensity of the same symptoms which initiated the disease, so too one frequently observes in the exacerbations of the remitting type a tendency to the reappearance of symptoms which have already been experienced, so that for example the same arm again becomes astereognostic, the same paræsthesiæ are again complained of in the same part of the body, the same leg again begins to drag, and so on. Fourthly, the localization of the lesions as judged by the symptoms and physical signs is roughly similar in the two types; in both, for example, there is the same curious liability to affection of the optic nerve and tract. Consequently in spite of differences in the chronological order of individual symptoms, the symptomatology of the later stages is very similar in both types, and although the individuality of no disease can be established by its symptomatology alone, this factor nevertheless must be given due weight in an attempt to determine the entity of any morbid condition. Finally, in both types there is the same absence of any obvious etiological factor and the same age incidence.

Histologically no essential differences have been shown to exist between the chronic progressive and the remittent type of case. In the former it is true that a progressive gliosis is perhaps the most prominent feature, and that areas of diffuse gliosis occur apparently unrelated to areas of tissue-destruction. Nevertheless it has been abundantly demonstrated that even in these long-standing cases areas of tissue destruction are present in which the changes are of recent date and associated with an inflammatory reaction. While therefore gliosis may be the predominating feature of the chronic case, it must be recognized that the differences in the histological picture in the two types of cases are differences of degree only; in both types the essential lesions are of the same kind, although variations in the age and intensity of the morbid process undoubtedly occur.

Neither from the clinical nor histological standpoint therefore can we find adequate grounds for distinguishing between *true* and *secondary* disseminated sclerosis as advocated by Müller, and we believe that the two clinical types, namely, the chronic progressive and the subacute remittent, represent variations of the same pathological process. If this conclusion is correct, the endogenous theory automatically becomes untenable, since it is impossible to explain the remittent type with its sudden exacerbations and long remissions on an endogenous basis.

The question therefore arises: Can a disease so variable in its clinical manifestations, and running sometimes a chronic progressive and at others a subacute remittent course, be satisfactorily explained on a single pathogenetic basis? We believe that this is possible provided one assumes the presence of a morbid agent acting with varying degrees of intensity over a considerable period, and since variations in intensity are characteristic of all inflammatory and infective processes, such an assumption is practically equivalent to postulating an inflammatory lesion as the essential morbid process underlying disseminated sclerosis. Arguing on these lines the acute clinical disturbances are to be regarded as the result of an acute inflammatory process, and their partial or complete disappearance represents a dying down of the process with absorption of exudate and consequent functional recovery of the tissues; where however sufficient structural damage has occurred permanent effects will remain. The chronic progressive condition on the other hand, whether it supervenes on a previously more acute phase or whether it has characterized the illness *ab initio*, is evidence of the same morbid process, less intense in its action, but one nevertheless which never becomes entirely inactive. In such cases one expects to meet not so much new focal areas of disease in parts of the brain and cord some distance removed from those already affected, but rather a gradual extension of already existing areas and a consequent spread and intensification of already existing symptoms; in other words, the legs become more paraplegic, an eye more blind.

Again one cannot altogether ignore the existence of cases which after a variable time become definitely non-progressive, and we have already hinted at the possibility of the existence of spontaneous "cures." In the former cases, a small minority of the total, the disease has entirely ceased to be active, while the latter correspond to the "formes frustres" of many other infective processes.

The absence of cytological and chemical changes in the cerebrospinal fluid, as determined by ourselves in common with many other investigators, in no way militates against the hypothesis that the process is an inflammatory one. In the first place it seems probable that the increase in protein and morphological elements when occurring in other conditions should be ascribed to a diffuse or local reaction on the part of the meninges rather than to changes in the nervous parenchyma itself, and meningitic changes although present in some cases cannot be regarded as an invariable feature of the morbid histology of disseminated sclerosis. Secondly, pathological changes in the cerebrospinal fluid may be conspicuous by their absence in such frankly inflammatory conditions as acute poliomyelitis and encephalitis lethargica.

Histological investigations confirm the arguments based on clinical studies. Our own histological examinations have unfortunately been far from complete, but as far as they go they are in agreement with the more recent work which insists on an inflammatory reaction, acute or subacute, in the affected areas. Both Siemerling and Raecke, and Dawson describe a general tissue reaction in the early, and an essentially glia reaction in the later stages, the general architecture of the tissues being to a great extent preserved owing to the relative escape of axis cylinders and ganglion cells. Although the inflammatory phenomena of the earlier stages occupy a more prominent position in the description published by the German writers than in that given by Dawson, the latter nevertheless expresses the opinion that "there is overwhelming evidence that the great majority of the areas have arisen on an inflammatory basis." Both sets of observers lay stress on the fact that in the same individual different stages of the morbid process can be identified in different areas, some of recent origin and others of long standing, a state of affairs entirely in keeping with the clinical histories so characteristic of the remittent type of disseminated sclerosis. Moreover at the edges of areas even where sclerosis is complete there is histological evidence that the morbid process has never become entirely inactive, but is capable either of lighting up acutely, or, and perhaps more frequently, of advancing slowly by peripheral extension. In this connection we hesitate to accept the suggestion put forward by Siemerling and Raecke that the scar tissue formed by the glia proliferation protects the tissues from further damage. On the contrary we consider it much more probable that the virus lies latent in the scar tissue, but capable of initiating further infection when the local or

general conditions permit: in other words we regard the scar tissue as the starting-point from which reinfection originates. Finally both sets of observers agree that the histological changes can only be explained by a variation in the intensity of the morbid process in different areas; thus while rapid destruction of tissue is a feature in some, in others there is little more than a spreading gliosis, which they attribute to the leakage of a diluted virus from the essential primary lesions, and it is on this latter basis that the chronic progressive case finds its readiest explanation.

As regards the origin of the morbid process underlying disseminated sclerosis our own investigations have failed to throw any light on the subject; in no case have we succeeded in transmitting the disease to animals, while our bacteriological and parasitological investigations have been without result. Neither can we admit the claim of those writers, whose work we have reviewed, that they have transmitted the disease to rabbits and guinea-pigs. Even if we admit that in certain instances they have transmitted *a* disease, there is an entire absence of histological proof that the disease so transmitted was disseminated sclerosis. In view however of Steiner's monkey experiment it would seem advisable to continue experimental investigations with *Macacus rhesus*. Neither can we regard the finding of spirochætes in the hepatic vessels and ventricular fluid of inoculated guinea-pigs and rabbits as being of any decisive significance, in the absence of adequate evidence that the animals which harboured the parasite were suffering from disseminated sclerosis. Moreover it is not fully known to what extent spirochætes occur in animals under different conditions of health and disease; they have been found, for example, by one of us (L.S.D.) in the livers of apparently healthy guinea-pigs, while according to Fiessinger they are present in human urine in over 2 per cent. of normal individuals.

Adams in a recent contribution is inclined to support the spirochætal origin of the disease partly on clinical grounds, but mainly owing, first, to the presence in the cerebrospinal fluid of 95 per cent. of his cases of a luetic or paretic reaction to colloidal gold, secondly to the modifications which this reaction undergoes under neo-salvarsan treatment, and thirdly to the beneficial clinical effects of anti-syphilitic treatment in early cases of the disease. We feel however that until the rationale of the colloidal gold reaction is more completely understood, arguments based on the presence and behaviour of the reaction are unsubstantial, while in view of the remissions so characteristic of the disease the

beneficial effects claimed for any therapeutic measures must be treated with the greatest reserve.

Finally the finding of spirochætes in the cerebral hemispheres of two patients dead of disseminated sclerosis needs confirmation and amplification before we should be justified in accepting unreservedly the spirochætal origin of the disease.

While therefore we are of opinion that in spite of recent investigations the origin and nature of the morbid agent has yet to be discovered, we believe that there are sound reasons, both clinical and histological, for the view which regards the morbid process underlying disseminated sclerosis as inflammatory in character.

Conclusions.

(1) It is useful to recognize two clinical types of disseminated sclerosis: (*a*) the remittent type characterized by acute exacerbations at widely varying intervals alternating with quiescent periods, and (*b*) the chronic progressive type.

(2) In the present series (thirty-five patients) the proportion of remittent to chronic progressive cases is as six is to one.

(3) In early cases of the remittent type, once the acute disturbance has subsided, the patient may present no clinical evidence of organic disease over prolonged periods. The possibility of spontaneous cure cannot therefore be entirely denied.

(4) The remittent type in its later stages tends to assume the characteristics of the chronic progressive type.

(5) The great bulk of clinical and histological evidence is opposed to the view that these two types correspond to two different pathological processes. On the contrary, they are to be regarded as manifestations of one and the same disease, namely, disseminated sclerosis.

(6) Cultural and microscopic examination of the cerebrospinal fluid has in our hands thrown no light on the pathogenesis of the disease, and no specific organism has been isolated.

(7) Our attempts to transmit disseminated sclerosis from man to animals (rabbits) have been unsuccessful.

(8) We regard the transmissibility of the disease from man to animals as unproved.

(9) We are of opinion that the evidence in favour of the assumption that the pathogenic agent is a spirochæte is incomplete and in many

respects unsatisfactory, and we consider that the origin and nature of the morbid agent must for the present remain *sub judice*.

(10) We consider that the clinical and histological evidence is overwhelmingly in favour of the view that the morbid process underlying the disease is inflammatory in character.

APPENDIX.

Clinical Notes of Non-Fatal Cases.

Case III.—E. B., girl, aged 18, domestic servant. Admitted to National Hospital, Queen Square, on April 28, 1913.

Family and past history: Only child. Two sisters stillborn. Always delicate.

History of present illness: September, 1912: Retro-ocular pain with rapid failure of vision, so that she could not see her hand held in front of her eyes. October, 1912: Pain disappeared; vision improved so that she could see to get about; noticed difficulty in sitting up in bed unsupported. January, 1913: Tremor of left hand when she used it; could not hold a cup without spilling it; the condition cleared up within three weeks. February, 1913: Sudden weakness of right leg, unable to walk without support since this date; difficulty in holding her water, numerous "accidents"; this lasted for three weeks, and was then replaced by hesitancy of micturition which persists. March, 1913: Paræsthesiæ in right leg; never diplopia, dysarthria, or loss of emotional control.

On examination, April 28, 1913: Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, normal. Vision: acuity, $\frac{1}{60}$, right and left. Both discs are pale all over, somewhat opaque, retinal pigment disturbed, edges clear (primary atrophy with probably a little antecedent œdema). Hearing, normal. Cranial nerves: pupils normal; congenital concomitant strabismus; no diplopia; nystagmus to right > left; weakness right lower face, otherwise negative. Motor.—Head and neck, natural. Upper extremities: no paresis; both arms a little unsteady, left > right: slight sensory ataxia on right; trunk muscles weak: no wasting; umbilical excursion upwards. Lower extremities: considerable weakness and spasticity, right much weaker than left; no wasting or obvious ataxy. Gait: spastic, reeling and very feeble; cannot walk unsupported. Sensory.—Subjective: numbness right leg; girdle sensation. Objective: slight astereognosis and raised threshold to compasses in right hand; diminution of tactile and painful sensibility on right from fifth rib to middle of thigh; some loss of sense of passive position and movement in ankles and toes, right > left; vibration much impaired in lower limbs. Sphincters: hesitancy of micturition. Reflexes: all jerks very brisk, lower > upper limbs; all abdominals absent; both plantars extensor.

Progress: The patient got gradually worse the whole time that she was under observation. July 21, 1913: Numerous paræsthesiæ in all limbs and trunk; both legs very spastic and almost completely paralysed; lower abdominal muscles are also spastic and paralysed; numerous flexor spasms in legs; sensory loss below fourth rib to touch and prick is increasing right > left; intention tremor has developed in both arms, left > right; profound asynergia and dysmetria; well sustained horizontal nystagmus; complete incontinence of urine and fæces; no bed-sores or pyrexia; vision *in statu quo*. December 8, 1913: Complete paraplegia in flexion; sensory loss to all forms below fourth rib is now profound, complete on right, almost so on left; general condition remains fairly good in spite of incontinence.

Summary: Sudden onset, remissions, partial recoveries, then steady and rather rapid progression downhill with few fresh symptoms.

Case IV.—N. C., woman, aged 32, widow. Admitted to National Hospital, Queen Square, on October 31, 1913.

Family history: Father dropped down dead, aged 43, from a ruptured aortic valve. Mother died of pulmonary tuberculosis. Several brothers and sisters alive and well.

Past history: Good. Husband died, aged 29, of rheumatic heart disease. One daughter died of diphtheria; one boy, aged four, alive and well. No miscarriages.

History of present illness: Four years ago sudden attacks of severe rotatory vertigo without deafness or tinnitus; these persisted for two years. Three years ago noticed curious fleeting sensations of numbness in legs and tightness round waist, which have never quite disappeared. Four months ago woke up one morning and found that her left hand was completely paralysed and she had lost all feeling below the left elbow. The right hand was numb and peculiar. She could not tell what she held in her hand unless she looked to see, and her writing became a scribble. She also had a tight band across the stomach and both legs were weak and quite numb; she could not feel hot or cold water in her legs, her walking was very unsteady "as if I was walking on air." The legs have improved, feeling has returned and she can walk better, but cannot even stand unsupported in the dark. The right hand has not altered, but the loss of sensation in the left upper limb gradually extended up to the shoulder, so that the whole arm "has an existence apart from me"; it is not paralysed. No affection of vision, speech, or sphincters.

October 31, 1913: Visceral examination negative; no developmental defects. Vertebral column healthy. Wassermann reaction (blood) negative. Mental condition: normal emotional tone; good type. Vision: acuity, $\frac{6}{12}$ left, $\frac{6}{9}$ right; fields normal; temporal pallor of both discs, left > right. Hearing normal. Cranial nerves: well sustained slow horizontal nystagmus, otherwise normal. Motor: head and neck natural, no rigidity. Upper extremities.—Right: hypotonia distally, no paresis with eyes open; no wasting or trophic changes; all finer movements of fingers characterized by overaction;

fingers wander with eyes shut; sensory ataxy. Left: profound hypotonia and complete inability to apply muscular power with eyes shut; no wasting. Trunk: slight diaphragmatic weakness; nothing else to note. Lower extremities: considerable weakness, left > right; no spasticity; no wasting or obvious ataxy. Gait: weak and ataxic; Rombergism present. Sensory: subjective—paræsthesiæ, limbs and trunk. On examination: complete loss to all forms below shoulder in left upper limb except algometer pressure which is recognized but not localized; loss of sense of passive position and movement is almost complete even at shoulder-joint; slight impairment of cutaneous sensibility in right hand below wrist; partial astereognosis right hand, compass threshold raised, and sense of passive position and movement impaired in wrist and fingers; to the left of the mid-line from the second cervical segment down to the foot there is profound loss to touch, pin-prick and temperature, and a similar condition prevails on the right below the umbilicus; there is profound loss to vibration in left pelvis and lower limb, and a slight impairment in right pelvis and lower limb; the sense of passive posture and movement is normal in the right lower limb, but slightly defective in the left. Sphincters natural. Reflexes: all tendon jerks brisk; all abdominals absent; both plantars indefinite, but probably extensor.

Progress: Two months later the sensory loss over the left arm was not quite so deep, and the patient had some idea of the position of the limb, but the ataxia with eyes shut was still very wild. The loss of deep sensation in both legs had increased and the gait was more ataxic. The right plantar response was definitely extensor, the left indefinite. Otherwise no change.

Summary: This case is regarded as doubtful, seeing that the condition can be explained by an extensive lesion in the upper cervical cord, such as one sees in syringomyelia. On the other hand the previous history of vertiginous attacks, paræsthesiæ, and the presence of temporal pallor points to a dissemination of lesions, and renders the diagnosis of disseminated sclerosis probable, although by no means certain. Attempts to trace this patient have not been successful.

Case V.—N. R., male, aged 32, farmer. Admitted to National Hospital, Queen Square, on November 3, 1913.

Family history: Nothing of importance.

Past history: When aged about 15 he injured the left shoulder (? fracture dislocation); his arm wasted above the elbow and never recovered. In 1904 he contracted a wart-like, venereal sore which was said to be not syphilitic; no evidence of syphilis ever developed.

History of present illness: In 1899 he lost the sense of taste on the left side and his tongue and face felt dead and numb. This disappeared entirely in a few weeks. In 1906 he had a severe attack of furunculosis, and during convalescence he rather suddenly became aware of weakness of the left leg, his gait became unsteady, and he often vomited. His legs then became so weak that he could hardly get about, and he later developed diplopia and urgent micturition with frequent "accidents." After some months he began

to improve, the diplopia disappeared, and his legs recovered sufficiently to allow him to get back to his ranch and do his ordinary work. In 1909 he relapsed and could hardly walk unsupported; he was admitted to Queen Square and was found to have a typical spastic paraplegia, but no other physical signs beyond wasting of the muscles round the left shoulder. During the past four years his condition has varied considerably, there have been no new symptoms beyond weakness of the legs and loss of control over the bladder.

November 3, 1913: Good type and physique. Visceral examination negative: no evidence of syphilis. Wassermann reaction (blood) negative. Mental condition normal. Vision: acuity, $\frac{6}{24}$ right, $\frac{6}{12}$ left; temporal pallor of both discs. Cranial nerves: horizontal nystagmus to right and left, otherwise negative. Motor.—Head and neck normal; upper limbs normal, except for atrophic palsy of muscles round left shoulder and of upper arm, due to old injury; no tremor or ataxia. Lower limbs: severe spastic paraplegia; very little power at any joint, numerous flexor spasms. Sensory.—Subjective: *nil*. Objective: blunting of tactile sensibility in right leg; some loss of sense of passive position and movement in ankles and toes; vibration not tested. Sphincters: retention of urine; requires catheter. Gait: impossible. Reflexes: all jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Condition unchanged two months later.

Summary: Remittent type in early stages; in later stages assuming a chronic progressive course with absence of new symptoms.

Case VI.—P. E., male, aged 27. Admitted to National Hospital, Queen Square, on August 15, 1913.

Family and past history: Nothing of importance.

History of present illness: Seven years ago he developed diplopia, which persisted for six months. Soon after he had begun to see double he experienced difficulty in holding his water, and walked as if drunk. His walking gradually deteriorated, and he lost all control over his bladder, but after several months both these symptoms improved. The improvement, however, was not maintained, his walking became more unsteady than ever, and his hands began to shake so that he had difficulty in feeding himself. Later his head shook when he talked and his speech became affected. During the past five years he has got gradually worse, but no fresh symptoms have developed. Never paræsthesiæ or vertigo.

On examination, August 15, 1913: Fair type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: Unduly sanguine; defective emotional control. Vision: acuity, $\frac{6}{36}$ right and left (uncorrected); well-marked temporal pallor of both discs. Hearing normal. Cranial nerves: jelly-like nystagmus with eyes at rest; coarse horizontal nystagmus on looking to right and left; weakness of left external rectus and diplopia on looking to left; typical scanning, staccato

speech, very tremulous, with explosive element well marked. Motor: head and neck, nodding tremor when unsupported, greatly accentuated when he talks; upper extremities no paresis, typical intention tremor right and left, dysmetria and asynergia readily demonstrable; trunk normal, can sit up without use of hands; lower extremities, tone increased, slight weakness of dorsi-flexors at ankles, tremulous. Sensory: subjective and objective, nothing to note; vibration not tested. Sphincters: urgent micturition: frequent "accidents." Gait: reeling and drunken, characteristic of cerebellar inco-ordination; steps unequal in size and direction; no Rombergism. Reflexes: all jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Four months later *in statu quo.*

Note: Chronic progressive type; prominence of cerebellar signs and symptoms.

Case VII.—W. S., male, aged 21. Admitted to National Hospital, Queen Square, on October 31, 1913.

Family and past history: Nothing to note.

History of present illness: Three years ago his arms began to shake when he used them and his speech altered; a little later he walked as if drunk. The general unsteadiness of all four limbs and the affection of speech have since got progressively worse, and he laughs for hours together for no apparent reason. He has been absolutely helpless for twelve months, and more recently has lost control over his bladder. Never ocular disturbance or paræsthesiæ.

On examination, October 31, 1913: Poor type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: intelligence below the average; silly and giggling; laughs when spoken to and at his own tremor. Vision: acuity, $\frac{6}{9}$ right and left; temporal pallor of both discs. Cranial nerves: coarse nystagmus in all directions, no ophthalmoplegia; speech typical of advanced disseminated sclerosis, slow, staccato, explosive, and barely intelligible; some difficulty in swallowing, but never nasal regurgitation. Motor: no obvious paresis or tone changes; even when lying he is a mass of oscillations; tremor of head and limbs of extreme degree greatly accentuated by effort; unable to do anything for himself; dysmetria of upper limbs is well shown. Sensory: subjective and objective negative; vibration not tested. Sphincters: incontinence of urine, feels "call" and passage. Gait: impossible without support, attempts show wild cerebellar inco-ordination. Reflexes: all tendon jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: One month later, *in statu quo.*

Note: Chronic progressive type; profound cerebellar inco-ordination of speech and limbs.

Case VIII.—V. B., male, aged 34, shop-fitter. Admitted to National Hospital, Queen Square, on October 3, 1913.

Family and past history good.

History of present illness: Ten years ago the right arm suddenly became useless: it was not paralysed but he could not control it properly nor distinguish what he held in his hand without looking. In three months the arm was perfectly well again. A little later he became unduly emotional, laughing and crying for no reason; this has got much more obvious lately. A year and a half ago his walking rather rapidly became affected and his friends thought he was drunk (patient is a teetotaller); this symptom has varied considerably. Latterly his left foot has dragged and he tires easily. At the same time he noticed curious sensations of "tightness" and numbness in his face and legs, followed by itching of the thighs; these lasted for six months. Recently he has had aching pain in both legs. Six months ago he experienced difficulty in holding his water; recently he has had difficulty in passing it, and has become impotent. He also noticed an alteration in his speech which became slow and awkward; this defect amuses him and he can always keep up his spirits by talking to himself. Four months ago his hands began to shake; his writing became bad and it took him half an hour to do his collar up. Two months ago his vision got rather poor, but has since improved. Never diplopia or vertigo. During the past eighteen months his condition has varied considerably and at times he seems almost well.

On examination, October 3, 1913: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: very intelligent; grossly defective emotional control; he laughs till he cries. Vision: acuity, $\frac{6}{9}$ partly, right and left; temporal pallor with fluffiness of inner edges of both discs, suggestive of preceding œdema. Cranial nerves: horizontal nystagmus on looking to right and left; no ophthalmoplegia; coarse tremor of tongue; typical dysarthria, staccato, jerky, explosive. Motor.—Head and neck: coarse nodding tremor when sitting and standing; no loss of power in limbs or trunk, no spasticity; well-marked intention tremor especially of arms, right > left: dysmetria and asynergia of both arms. Sensory.—Subjective: pains in legs. Objective: superficial sensation good; some impairment of sense of passive posture and movement in toes and ankles; vibration greatly impaired in pelvis and femora, lost below knees. Sphincters: hesitancy of micturition. Gait: slight dragging of feet; reeling and staggering, well marked disturbance of equilibration; no Rombergism. Reflexes: all tendon jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Two months later *in statu quo*.

Note: Remittent type of ten years' duration; early symptoms separated from later ones by a long interval (eight years). Cerebellar manifestations a prominent feature.

Case IX.—L. K., woman, aged 39, widow. Admitted to National Hospital, Queen Square, on November 25, 1913.

Family and past history negative. Two children, no miscarriages.

History of present illness: Two years ago began to have attacks of severe rotatory vertigo with headache and tinnitus in both ears; these gradually

disappeared and she has had none for over a year. Eighteen months ago she had severe retro-ocular pain and her vision rather rapidly failed, so that three months later she was only able to get about in familiar places. The condition has since remained stationary. One year ago she began to have trouble with the bladder, hesitancy of micturition alternating with precipitancy; occasional "accidents." For the past six months she has noticed curious sensations in arms and legs, "tightness," numbness, "tickling," &c. Never dysarthria, tremor, or disturbance of gait."

On examination, November 25, 1913: Normal appearance. X-ray of sella turcica normal. Sugar tolerance normal. Wassermann reaction (blood) negative. Visceral examination negative. Mental condition normal. Vision: counts fingers correctly at 3 ft., right and left; large scotoma right and left eye, extending into temporal more than into nasal field; both discs very pale—primary optic atrophy. Hearing normal. Cranial nerves: negative; no nystagmus. Motor: normal in every particular. Sensory.—Subjective: numerous paræsthesiæ. Objective: normal; vibration not tested. Sphincters: urgent micturition. Gait: natural. Reflexes: all jerks rather exaggerated; left abdominals normal, right much diminished; both plantar responses flexor.

Progress: One month later *in statu quo.*

Note: Atypical case, but clear evidence of dissemination of lesions. Severe bilateral visual failure.

Case X.—T. R., woman, aged 27, single. Admitted to National Hospital, Queen Square, on November 2, 1913.

Family history: Negative; one of a large family.

Past history: Trivial accident to right knee eighteen months ago, followed by painful swelling of joint.

History of present illness: One year ago the right leg became weak and dragged, and she has not walked about for six months. Weakness of the left leg noticed quite recently. (N.B.—Patient is a very unreliable witness and can give no accurate account of her illness.)

On examination, November 2, 1913: Poor type and physique. Visceral examination and vertebral column normal. Wassermann reaction (blood) negative. Mental condition: poor intelligence; facile, fatuous and inattentive; gross loss of emotional control; laughs at her own disabilities. Vision and hearing normal. Cranial nerves normal; no nystagmus or dysarthria. Motor.—Head and neck: natural. Upper limbs: no loss of power; both hands rather unsteady and tremulous; no very definite ataxia. Trunk: all abdominal muscles spastic and weak. Lower limbs: tone increased; considerable weakness, especially of flexors; numerous flexor involuntary spasms; spastic paraplegia. Sensory.—Subjective: normal. Objective: difficult to test, as examination amuses patient, rendering her an impossible witness; some impairment of both deep and superficial sensation below knees. Sphincters: urgent micturition. Gait: spastic, right leg > left. Reflexes:

all jerks very brisk, especially in lower limbs; all abdominals absent; both plantar responses extensor.

Progress: Two months later unchanged.

Note: Chronic progressive type; lesions not numerous.

Case XI.—F. R., male, aged 28. Admitted to National Hospital, Queen Square, on September 22, 1913.

Family and past history: Negative.

History of present illness: Two years ago his gait became unsteady and his right foot dragged. The condition has varied, but recently has become worse, so that he is unable to walk without support. One year ago he began to have difficulty in voiding his urine, but this has now disappeared. His arms became shaky and weak, especially his right, and he had difficulty in writing. Six months ago the vision in his left eye rather rapidly failed, but has improved recently. During the past three weeks he has been subject to attacks of severe giddiness accompanied by vomiting. Never dysarthria or diplopia; no paræsthesiæ.

On examination, September 22, 1913: Good type, fair physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition natural. Vision: acuity, $\frac{6}{6}$ right, $\frac{6}{24}$ left; no note of ophthalmoscopic examination. Hearing normal. Cranial nerves normal; no nystagmus or dysarthria. Motor.—Head and neck normal. Upper limbs: no spasticity; power below normal, right > left; moderate intention tremor with dysarthria and asynergia, right > left. Trunk normal. Lower limbs: spastic paraplegia in extension; right leg weaker than left; power in both greatly diminished. Sensory: subjective and objective normal; vibration not tested. Sphincters natural. Gait: impossible without support; very spastic. Reflexes: all jerks greatly increased, especially in legs; absent abdominals; both plantar responses extensor.

Progress: Three months later the condition had vastly improved; the intention tremor of the arms had largely disappeared and he could walk unaided. There was less spasticity, and the gait was more reeling and like that seen in cerebellar disease.

Note: Remittent type; onset of different symptoms never very acute.

Case XII.—E. T., woman, aged 35, married. Admitted to National Hospital, Queen Square, on December 11, 1913.

Family history: Nothing to note.

Past history: Has always been "nervous"; two children alive and well; no miscarriages.

History of present illness: Four years ago she complained of pains in the legs, her walking became unsteady, and her hands shook at times. She also became unduly emotional, crying and laughing for no reason, and suffered from urgent micturition with occasional "accidents." She remained in much the same condition for three years, varying round a more or less constant mean. Following a mental shock a year ago her walking became progressively

worse and her hands shook when excited. She now complains of aching pains in hips and arms, and her feet feel stone cold. The emotionalism has almost disappeared. Never ocular symptoms or dysarthria.

On examination, December 11, 1913: Good type, fair physique. Visceral examination, negative. Wassermann reaction (blood), negative. Mental condition, normal; reserved, and good emotional tone. Vision and hearing: normal in every particular. Cranial nerves: nothing to note except ill-sustained nystagmus. Motor.—Head and neck normal. Upper limbs: no loss of power; both hands are rather unsteady and awkward, but there is no true intention tremor or dysmetria. Trunk: very weak; cannot sit up without use of hands; abdominal muscles spastic. Lower limbs: spastic in extension; gross loss of power, left > right; no wasting. Sensory.—Subjective: paræsthesiæ in limbs, especially legs. Objective: slight loss to light touch and pin prick below knees, left > right; definite impairment of sense of position and movement at and below knees, right > left; vibration impaired slightly below eighth thoracic spine, and barely recognized in pelvis and lower extremities, especially on right. Sphincters: urgency of both: feels "call" and passage. Gait: very spastic; can walk a few steps without support; Rombergism present. Reflexes: all jerks exaggerated, lower > upper limbs; all abdominals absent; both plantar responses extensor.

Progress: Condition unchanged two months later.

Note: Chronic progressive type without exacerbations.

Case XIII.—J. B., male, aged 45, shop assistant. Admitted to National Hospital, Queen Square, on December 16, 1913.

Family history negative.

Past history: Always had good health; gonorrhœa twenty years ago; denies syphilis.

History of present illness: Six years ago his right foot began to drag; this got worse for a year and has remained stationary since. Four years ago he rather suddenly lost the use of his left hand; he could move his fingers, but they seemed clumsy, and he could not identify objects in his left trousers pocket. About the same time he had some difficulty in passing his water, which entirely disappeared after a few months. For the past three years he has been unnaturally nervous and apt to burst into tears, "a matter beyond my comprehension." One year ago his left leg began to get weak; his left arm also became rapidly much worse, and he now loses it in bed and it gets "out of control." Also, "When I move my right hand up to my mouth, the left arm goes across and catches hold of it." His left arm often feels numb and his feet cold. He has never noticed any loss of sensation in arms or legs. No defect of speech or vision, and no tremor.

On examination, December 16, 1913: Good type and physique, rather stout. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition normal; no loss of emotional control detected. Cranial nerves normal; no ophthalmoplegia or nystagmus. Vision and hearing

perfect. Motor.—Head and neck: no tremor, rigidity or wasting. Upper limbs: power at shoulder and elbow is impaired on left, but there is no sign of wasting and the electrical reactions are normal; power in hand is normal, there is a profound degree of sensory ataxia in the left arm and tabetic athetosis; in the right arm power is normal, except for flexors of wrists and fingers, which are definitely weak and wasted with lowered faradic excitability; no ataxia or tremor. Trunk good. Lower limbs: both spastic and weak, right much more so than left; flexors weaker than extensors; no wasting. Vertebral column normal. Sensory.—Subjective: occasional tingling in both hands. Objective: complete loss to light touch over left cervical segments 2 to 5 and slight impairment over left C. 6 and 7, and right C. 2 to 5; pin-prick and temperature lost or impaired over C. 2 to 7 on left, and C. 2 to 6 on right; profound loss of sense of passive position movement whole of left arm, complete in hand; no threshold for compasses in left hand, which is completely astereognostic; threshold to compasses in right hand = 2·5 cm.; no astereognosis; vibration lost in left upper limb, good in right; completely lost in spinal column below sixth spine, and impaired in left pelvis and lower limb. Sphincters natural. Gait: spastic, right leg > left; no ataxy or Rombergism. Reflexes: triceps jerks brisk, right and left; biceps and supinator present and normal on right, absent on left; all abdominals absent; both plantar responses extensor; associated movements are present in the upper limbs—e.g., grasping with right hand is associated with a similar movement in left.

Progress: No change three months later.

Note: This must be regarded as a very doubtful case. The patient insisted on his loss of emotional control, but it was not demonstrable during the time that he was under observation. The rest of the condition can be explained by a central lesion of the upper cervical cord such as occurs in syringomyelia; at the same time neither the clinical course nor physical signs can be regarded as typical of syringomyelia.

Case XIV.—M. B., woman, aged 31, married. Admitted to St. Thomas's Hospital on January 3, 1914.

Family history negative.

Past history: Chlorosis at age of 15. Three children alive and well; one twin stillborn (difficult labour); no miscarriages.

History of present illness: Eleven years ago she noticed pains and various odd sensations in her limbs, especially the left arm and leg, and simultaneously her walking became unsteady. A year later she became subject to sudden attacks of rotatory vertigo, in which she invariably fell to the left, accompanied by headache and noises in the ears; she has had none of these attacks during the past two years. Ten years ago she began to have difficulty in holding her water; this has gradually increased, and she now has frequent "accidents." Eight years ago the paræsthesiæ and difficulty in walking almost entirely disappeared, but after nine or ten months her walking rapidly got bad again, so that her friends thought she was drunk. At the same time she

became unduly emotional and "laughed at everything." These various symptoms have persisted, but vary enormously in their intensity from time to time, the improvements sometimes lasting for several months. On the whole, however, her legs have got weaker, and for six months she has been unable to walk at all. Six months ago her left hand began to shake, and she had difficulty in using a fork. Two months ago she was told that her speech was "funny," but she never noticed any alteration herself. Three weeks ago she woke up with a squint, and has seen double ever since.

On examination, January 3, 1914: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: very intelligent; defective emotional control. Vision: acuity, $\frac{6}{12}$ right, $\frac{6}{9}$ left; both discs pale all over and clear cut. Hearing normal. Cranial nerves: weakness right external rectus with internal strabismus; fine nystagmus of moderate speed with both lateral and vertical movements; no dysarthria. Motor.—Head and neck normal. Upper limbs: right normal; slight weakness of hemiplegic type on left, with intention tremor and dysmetria. Trunk normal. Lower limbs: spastic paraplegia in extension; flexors much weaker than extensors and left much weaker than right. Sensory.—Subjective: numerous paræsthesiæ. Objective: only loss discovered is to vibration, which is lost or impaired in pelvis and lower limbs; left > right. Sphincters: urgent micturition; feels "call" and passage. Gait: spastic and ataxic; well marked disequilibration and asynergia; no Rombergism. Reflexes: all tendon jerks much exaggerated: abdominals absent; both plantar responses extensor.

Progress: Six weeks later the gait was much improved and she could walk a few steps unaided.

Note: Remittent type with exacerbations and wide dissemination of lesions.

Case XV.—H. S., woman, aged 25. Admitted to St. Thomas's Hospital on January 1, 1914.

Family history negative.

Past history: Asthma up to the age of 16.

History of present illness: Eighteen months ago woke up to find that she saw double, and that she could not shut the right eye, which was turned outwards. In six months time she was quite well again. Six months ago her walking rather rapidly became unsteady, and she reeled about as if drunk. One month ago her walking became much worse, the diplopia recurred, and the left arm suddenly became useless, so that she could not control it or feel what she held in her hand. She also noticed numbness of the right leg and aching pain in the right arm and left leg. Never dysarthria or sphincter disturbance.

On examination, January 1, 1914: Good type, poor physique. Visceral examination: congenital pulmonary stenosis; no cyanosis; otherwise negative. Wassermann reaction (blood) negative. Mental condition: intelligent;

poor emotional tone; unduly sanguine. Vision: acuity, $\frac{6}{24}$ (corrected), right and left; central scotoma for colour in both eyes; discs distinctly pale, especially in temporal halves. Hearing: normal. Cranial nerves: weakness of right internal rectus; rapid nystagmus on looking to the right, otherwise negative; no dysarthria. Motor.—Head and neck: nodding tremor when unsupported. Upper limbs: good power; no intention tremor; profound sensory ataxia on left with tabetic athetosis. Trunk normal. Lower limbs: slight spasticity with some weakness of flexors. Sensory.—Subjective: paræsthesiæ in limbs. Objective: superficial sensation perfect: profound loss of sense of passive position and movement in left arm, complete in fingers; complete astereognosis, no threshold obtainable to compasses; vibration not tested. Sphincters natural. Gait: no obvious spasticity, but profound cerebellar inco-ordination; no Rombergism; cannot walk without support. Reflexes: all jerks increased; all abdominals absent; both plantar responses extensor.

Progress: Ten weeks later the walking had improved, but was still very inco-ordinated. Otherwise *in statu quo*.

Note: Typical remittent type with wide dissemination of lesions.

Case XVI.—E. M., woman, aged 25, married. Admitted to National Hospital, Queen Square, on October 23, 1913.

Family history: Mother died of "creeping paralysis," aged 47.

Past history: Good. Three healthy children, no miscarriages.

History of present illness: Six years ago, three months after a normal confinement, her walking became unsteady, her left hand weak, and she had difficulty in passing her water. Nine months later all these symptoms became greatly aggravated, micturition became urgent, she developed diplopia, her sight began to fail, she lost control over her emotions, and had frequent boring pains in the legs. At this time she was admitted to the National Hospital, when the note was as follows: Visual acuity, $\frac{6}{24}$ right and left, temporal pallor, nystagmus, intention tremor of arms, spastic paraplegia, with increased tendon reflexes, absent abdominals, and double extensor plantar responses. She rapidly improved, the diplopia disappeared, and except for some slight unsteadiness on her legs she remained quite well for four years. Two years ago, three months after her third confinement, her walking rapidly deteriorated again, and she can now only get about the house by holding on to things. Six months ago micturition again became urgent, but there have been no "accidents." Two months ago she suddenly experienced difficulty in getting her words out and her head began to shake when she talked. Her right hand had also become shaky; and her legs go quite numb from the knees downwards.

On examination, October 23, 1913: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: rather sanguine; no loss of emotional control. Vision: acuity, $\frac{6}{12}$ right, $\frac{6}{24}$ left: right disc generally greyish but whiter in temporal half, edges

clear; left disc very white and atrophic looking. Hearing normal. Cranial nerves: no ophthalmoplegia; jelly-like nystagmus with eyes at rest: quick nystagmus of wide amplitude on looking in all directions. Articulation slow, scanning, syllabic, and explosive; slight tremor of tongue. Motor.—Head and neck: nodding tremor when unsupported. Upper limbs: no weakness; intention tremor of moderate degree in both arms; well-marked dysmetria, right and left. Trunk: rather weak; no local palsy. Lower limbs: both a little spastic, considerable weakness, right > left, especially of flexors, and well marked intention tremor. Sensory.—Subjective: paræsthesiæ in legs. Objective: no disturbance except slight impairment of sense of position in ankles and toes; vibration not tested. Sphincters: urgent micturition. Gait: only possible with support; generalized tremor, reeling and drunken, slight spasticity; no Rombergism. Reflexes: all jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Unchanged two months later.

Note: Typical remittent case; onset and exacerbation related to confinement. Generalized cerebellar ataxia.

Case XVII.—L. E., woman, aged 34. Admitted to St. Thomas's Hospital on February 12, 1914.

Family history negative.

Past history: Rheumatic fever, aged 15. Always been "hysterical."

History of present illness: Two years ago her left arm and leg suddenly became weak; recovery within a week. Two months later she noticed that she was blind in the left eye, and began to experience tightness and tingling in the right arm and hand, which has persisted. Six months ago her walking became unsteady, especially in the dark. No dysarthria, diplopia, or sphincter trouble.

On examination, February 12, 1914: Poor type, good physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: highly suggestible; good emotional tone. Vision: acuity, $\frac{6}{24}$ left, $\frac{6}{6}$ partly right; concentric limitation of visual fields; left disc pale all over, edges clear; right disc slight temporal pallor. Hearing normal. Cranial nerves negative, no nystagmus. Motor: No paresis or intention tremor; definite sensory ataxia of right arm with well-marked tabetic athetosis. Sensory: various disturbances of cutaneous sensation can be manufactured or dispersed by suggestion; compasses threshold 1·0 cm. left palm, 3·0 to 3·5 cm. right palm: astereognosis right hand and disturbance of sense of passive posture and movement; questionable impairment of deep sensation in right leg; vibration not tested. Sphincters natural. Gait: slight tabetic ataxia of right leg; Rombergism present. Reflexes: all tendon jerks increased, right > left; all abdominals absent: right plantar response extensor, left flexor.

Progress: The patient was readmitted three months later with an hysterical gait, which disappeared under treatment.

Note: Remittent type with superadded hysterical manifestations.

Case XVIII.—E. C., woman, aged 33. Admitted to National Hospital, Queen Square, on February 19, 1914.

Family and past history: Good. Mild influenza two months ago.

History of present illness: Three weeks ago the left hand suddenly "went funny and useless" so that she could not feel things properly, followed two days later by weakness of the left leg and urgent micturition. She had a severe headache which persisted for four days, and then gradually disappeared. No vomiting, vertigo, or diplopia. The left hand now feels numb and cold.

On examination, February 19, 1914: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, vision and hearing normal. Cranial nerves: no nystagmus; definite weakness of right lower face with emotional movements only; otherwise negative. Motor.—Head and neck normal. Upper limbs: right normal; no paresis of left arm except when eyes are closed or limb is screened from view during testing; tabetic athetosis of left hand with pronounced sensory ataxy of whole limb. Trunk normal. Lower limbs: extended and adducted with some extensor rigidity, left much > right; some weakness especially of flexors on left, power good on right. Sensory: slight impairment to touch and pinprick below left elbow; partial astereognosis of left hand, compass threshold 4·5 cm. left palm; impaired sense of passive posture and movement whole of left upper limb, more marked distally; vibration not tested. Sphincters: urgent micturition. Gait: spastic, left much greater than right; no gross inco-ordination; Rombergism negative. Reflexes: all tendon jerks exaggerated, left > right; abdominals diminished on left, normal on right; both plantar responses extensor.

Progress: The patient rapidly improved. One month later the right plantar response was flexor, sphincter control was normal, and the loss of deep sensibility in the left arm was much less.

Note: Early case; acute onset with lesions in spinal cord and subthalamic region, and rapid improvement.

Case XIX.—F. G., woman, aged 23. Admitted to St. Thomas's Hospital on June 8, 1914.

Family history good.

Past history: Always high spirited. Six years ago had "St. Vitus's dance," and "could not control right arm"; well in six weeks. Otherwise good.

History of present illness: One month ago she experienced pains in both hands and forearms, especially the left, with numbness and loss of feeling. This got worse for four days until the hands were "useless"; they were not paralysed, but she could not feel what she held in her hands and dropped objects without being aware of it. The numbness has now spread up beyond the left elbow. At the same time her legs felt numb, and she felt as if a belt were tied round her chest; both these symptoms rapidly disappeared. One week ago she had a sensation as if someone were pouring water down her

neck and it was trickling down her left side, and she began to have difficulty in holding her water, but has had no "accidents." No other symptoms; walking entirely unaffected.

On examination, June 8, 1914: Good type; physique much above average. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, vision and hearing normal; first-rate witness. Cranial nerves: *no ophthalmoplegia; slow nystagmus of moderate amplitude on* conjugate deviation to the right; otherwise negative. Motor: Head and neck normal. Upper limbs: there is no gross paresis, but on the left there is a slight but appreciable weakness of the biceps and flexors of wrist and fingers; tested with the eyes shut there is an apparent weakness of all muscles; no wasting or tremor; the movements of both hands, the left more than the right, are *extremely awkward and suggestive of spasm, yet on manipulation* no spasm is present; there is well-marked sensory ataxia (left > right) with loss of direction, and with the arms outstretched and eyes closed the fingers and hands wander into all kinds of grotesque positions of which the patient is unconscious; writing is only possible with the eyes open. Trunk and lower limbs: normal in every particular. Sensory.—Subjective: numbness of both hands. Objective: *slight impairment of tactile sensibility in left* arm and hand, corresponding roughly to C. 5 and 6 segments; prick, temperature and localization perfect; profound loss to compasses both hands, threshold 5 cm. right, 7·5 cm. left; vibration slightly diminished left hand and carpus, normal elsewhere; passive position and movement—profound loss distally in both upper limbs (left > right), good at shoulders; complete loss to size, shape, weight and consistence in left hand, and almost complete loss in right. No disturbance in trunk or lower extremities. Sphincters: precipitate micturition. Gait normal. Reflexes: all tendon reflexes active except left biceps jerk which is absent; abdominals present and equal, both plantar responses flexor.

Progress: Three weeks later the left biceps jerk had returned, sphincter control was normal, there was no appreciable disturbance of deep sensation in the right hand, and that in the left was much less intense. Nystagmus was still present. Six months later (January, 1915) the patient felt perfectly well, and the only physical sign was nystagmus on looking to the right. In January, 1920, the patient was seen again; she had remained in perfect health, was married with two healthy children, and there was no physical sign of organic disease.

Note: Sudden onset with symptoms pointing to lesion of posterior columns in upper cervical region. Rapid recovery and disappearance of all physical signs; in perfect health six years later.

Case XX.—R. I., girl, aged 19. Admitted to St. Thomas's Hospital on June 2, 1914.

Family history; Twin sister excitable and emotional.

Past history: Excellent.

History of present illness: One year ago she was noticed to be unduly irritable and peevish, and complained of her legs feeling tired; shortly afterwards her walking become unsteady and she fell down if she attempted to run. Ever since she has staggered as if drunk and now can barely walk without support. At the same time she began to have attacks of uncontrollable giggling and laughing, and had difficulty in holding her water, with numerous "accidents." She also complained of curious sensations in her legs, which felt numb and "too full." Her hands also became unsteady, especially the left, so that she could not play the piano and her writing deteriorated. No alteration of speech, but her singing master noticed that her singing voice was shaky. No ocular symptoms or vertigo. The condition has slowly got worse, but no fresh symptoms have appeared.

On examination, June 2, 1914: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: intelligent and observant; very sanguine and indifferent as regards her disabilities; defective emotional control. Vision and hearing, normal. Cranial nerves: inconstant nystagmus on conjugate deviation, slow jerks on looking to the right, rapid to the left; otherwise negative; no dysarthria. Motor.—Head and neck, normal. Upper limbs: no loss of power; moderate intention tremor, left much > right, with asynergia and dysmetria. Trunk: No weakness; combined flexion of hip and trunk well shown. Lower limbs: adducted and extended; considerable extensor spasm; weakness left > right, mainly of flexors at all joints and abductors at hip-joints; intention tremor present. Sensory.—Subjective: numbness of legs. Objective: cutaneous sensibility perfect; impairment to compasses and passive position and movement left lower limb; complete loss to vibration in lower limbs, profound loss in pelvis and lumbo-sacral spine, impaired in lower thoracic spine. Sphincters: urgent micturition. Gait: slighly spastic, left > right; Rombergism doubtful; general disequilibration, tottering and staggering; no synergic movement of arms; cannot bend back without losing balance. Reflexes: tendon jerks in arms exaggerated, in legs multiple; all abdominals absent; both plantar responses extensor.

Progress: Two months later impairment of deep sensation in lower limbs had increased, Rombergism was definitely present, and walking was impossible without support. Nystagmus was constantly present,

Note: Chronic progressive type with wide diffusion of lesions in brain, brain-stem and cord.

Case XXI.—I. W., woman, aged 25. Admitted to St. Thomas's Hospital on August 27, 1914.

Family and past history good.

History of present illness: Six years ago she suddenly became blind in the left eye; after a week the sight rapidly returned. Just over a year ago she had a "nervous breakdown," the chief symptoms being severe aching pains in the legs and back, lassitude and emotional instability; she has never been well since. Five months ago she was drenched in a thunderstorm and caught a

chill; her legs felt numb and painful and she had pins and needles in her fingers. After a few days in bed she got up to find that her walking was unsteady, and this has got worse; she reels about like a drunken person and is at times unable to walk without assistance. Quite recently she has had attacks of rotatory vertigo. No diplopia, dysarthria, or sphincter trouble.

On examination, August 27, 1914: Good type and physique. Visceral examination, negative. Wassermann reaction (blood) negative. Mental condition: unduly optimistic and sanguine; defective emotional control. Vision and hearing normal; visual acuity is $\frac{6}{6}$ in both eyes, and both optic discs are of good colour. Cranial nerves: nystagmus on lateral movements, slow to the left, rapid to the right; otherwise negative. Motor.—Head and neck: nodding tremor when unsupported. Upper limbs: no paresis; fine static tremor. Trunk: good. Lower limbs: no definite paresis; slight extensor spasticity. Sensory.—Subjective: paræsthesiæ in limbs, legs > arms. Objective, normal. Sphincters natural. Gait: very ataxic, reels about; profound asynergia, typical of cerebellar disease; no Rombergism. Reflexes: All jerks very brisk; all abdominals absent; both plantar responses extensor.

Progress: No change two months later. Six months later patient was reported to have developed difficulty in talking and severe tremor of both arms, but these findings have not been included in the statistical table.

Note: Remittent type; no objective evidence of optic nerve lesion in spite of history of sudden amaurosis six years previously.

Case XXII.—G. R., male, aged 22. Admitted to St. Thomas's Hospital, January 19, 1915.

Family and past history, good.

History of present illness: Five years ago his speech began to drawl and he experienced tight feelings round his knees. Later he began "to get shaky all over," especially when excited, and he "got in a tangle with his words." His walking became unsteady as if he were drunk. In July, 1911, he was admitted to St. Thomas's Hospital, when the following note was made: Scanning speech, nystagmus, slight intention tremor of arms, cerebellar gait, exaggerated reflexes, double extensor plantar response. On discharge two months later he had much improved. He remained fairly well for three years, experienced no more paræsthesiæ, and his walking at times seemed almost normal. Some months ago he noticed the vision of his left eye to be failing, and six weeks ago all his symptoms gradually got much worse again. He became very emotional and excitable, his speech at times was barely intelligible, and his walking more unsteady than ever. He also got very sleepy and seemed unnaturally hungry. No vertigo, diplopia, or sphincter trouble.

On examination, January 19, 1915: Good type and physique. Visceral examination, negative. Wassermann reaction (blood) negative. Mental condition: excitable; laughs at his own tremor. Vision: acuity, $\frac{6}{18}$ left, $\frac{6}{6}$ right; scotoma to colours in left eye in nasal field, not quite reaching fixation point; temporal pallor of both discs, left > right. Hearing, normal. Cranial

nerves: horizontal nystagmus; weakness of right lower face, especially with emotional movements. Typical dysmetria, slow syllabic, tremulous, monotonous, with overaction. Motor.—Head and neck: to-and-fro tremor, accentuated when he talks. Upper limbs: no paresis; slight intention tremor, especially with rapid movements; dysmetria and dysdiadokokinesis well marked; breaks pencil when writing. Trunk: combined flexion of hip and trunk; some tremor in sitting position. Lower limbs: no paresis; tremulous and awkward. Sensory: subjective and objective, normal. Sphincters, natural. Gait: staggering and reeling; gross asynergia; no Rombergism. Reflexes: all tendon jerks exaggerated; abdominals brisk and equal; right plantar response extensor, left indefinite.

Progress: Unchanged four weeks later.

Note: Remittent type with little tendency for development of fresh lesions. Cerebellar inco-ordination a prominent feature.

Case XXIII.—E. C., woman, aged 27, nurse. Admitted to St. Thomas's Hospital on February 1, 1915.

Family history: Father paralysed in legs for thirty years.

Past history good.

History of present illness: Seven months ago suddenly developed diplopia, which persisted for four days. A month later she suddenly lost the use of her left leg and fell down in the street; the leg seemed absolutely numb. Two weeks later the power and sensation began to return, and in another two weeks her walking was almost normal again. About this time she began to notice curious sensations in both legs and round her waist, "tight feelings," cramps, tinglings, &c. Three months ago she experienced urgency of micturition and the left leg again suddenly became weak. No tremor, dysarthria, or vertigo.

On examination, February 1, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition normal; first-class witness. Vision and hearing normal, except for a very doubtful temporal pallor of both discs. Cranial nerves: slow nystagmus on looking to left, otherwise negative. Motor.—Head and neck, trunk and limbs, normal. Lower limbs: slight extensor spasticity with weakness of flexors on left, power good on right, no ataxia. Sensory.—Subjective, paræsthesiæ. Objective: normal in every particular. Sphincters: slight urgency of micturition. Gait: weak and spastic, no Rombergism. Reflexes: all tendon jerks exaggerated, legs > arms; all abdominals absent; both plantar responses extensor.

Progress: Two months later both legs were more spastic and weaker.

Note: Early case; remissions after acute exacerbations.

Case XXIV.—H. W., man, aged 26, soldier. Admitted to St. Thomas's Hospital on February 3, 1915.

Family and past history good.

History of present illness: Ten weeks ago patient had a seizure and was

unconscious for an hour; on regaining consciousness he complained of severe headache and retro-ocular pain. A few days later he noticed that he was nearly blind in his right eye. He remained in bed for a month owing to severe giddiness every time he moved, accompanied by vomiting. He also had difficulty in holding his water and had to answer the call the moment he felt it. Four weeks ago he noticed that his hands were unsteady, and he also had cramp-like pains in his legs. His general condition has recently improved.

On examination, February 3, 1915: Fair type, good physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: intelligent; unduly sanguine and distinctly emotional. Vision: acuity, $\frac{3}{60}$ right, $\frac{6}{6}$ left; field in right eye is greatly contracted and there is no colour vision; there is a central scotoma involving the fixation point, spreading out into the temporal field more than the nasal; the field in the left eye is normal; the right disc is pale all over, the edges are slightly blurred, but there is no measurable swelling; the left is normal. Hearing normal; no vertigo now. Cranial nerves: except that the right pupil reacts rather sluggishly to direct light the pupillary reactions are normal; weakness of right external rectus; rotatory nystagmus on lateral movements, especially to the right; otherwise negative. Motor.—Head and neck, nodding tremor, when unsupported. Trunk and limbs: no paresis, hands are a little unsteady, but there is no true intention tremor or inco-ordination; writing is good. Sensory: no objective impairment. Sphincters: urgent micturition. Gait natural. Reflexes: all tendon jerks exaggerated; abdominals present and equal; both plantar responses flexor.

Progress: A month later vision was unchanged. He feels depressed, but laughs when spoken to. Urgency of micturition has increased with several "accidents." Numerous fleeting paræsthesiæ, especially in arms. Gait a little uncertain, but not definitely cerebellar.

Note: Early case; acute onset with loss of consciousness; wide dissemination of lesions.

Case XXV.—C. W., woman, aged 37, married. Admitted to National Hospital, Queen Square, on February 15, 1915.

Family history: Mother is "nervous."

Past history: Always of a nervous disposition.

History of present illness: When pregnant fifteen years ago she noticed that her legs frequently twitched; this has persisted, and she has never been able to walk fast since, although not regarding this as a disability. Ten years ago her left eye rapidly became nearly blind; after a few weeks the sight returned, and she believes it is now quite good. Four years ago she had three severe attacks of rotatory vertigo, associated with vomiting and headache. Three weeks ago, after a thorough wetting, she had severe tingling followed by coldness and numbness extending up the legs to the waist; she also felt as if a tight band were round her waist. These sensations have gradually diminished. Recently she has had slight frequency of micturition, but no urgency.

On examination, February 15, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, vision, and hearing normal; visual acuity is full in both eyes and there is no pallor of the discs. Cranial nerves negative. Motor.—Head, neck, and upper limbs normal. Trunk: weakness of muscles below umbilicus. Lower limbs: slight extensor spasticity and weakness of flexors. Sensory.—Subjective: numbness from waist downwards. Objective: no definite impairment; vibration not tested. Sphincters: natural. Gait: spastic. Reflexes: arm jerks brisk; leg jerks greatly exaggerated; upper abdominal reflexes present, lower absent; both plantar responses extensor.

Progress: Six weeks later the gait had greatly improved, and the numbness had almost disappeared.

Note: Remittent type extending over a long period; very little actual disability.

Case XXVI.—R. T., man, aged 29, porter. Admitted to St. Thomas's Hospital, April 23, 1915.

Family history negative.

Past history: Typhoid fever, aged 25.

History of present illness: Nine months ago he began to see double; this has persisted. Five months ago, when out walking, he suddenly became unsteady on his legs and nearly fell down; he had considerable difficulty in getting home. The same evening his left hand began to shake so that he could hardly feed himself. Since then his walking and tremulousness have got worse, and his head shakes when he moves about. During the past month he has been subject to sudden attacks of rotatory vertigo without tinnitus or vomiting, in which he tends to fall to the left. Never dysarthria, paræsthesiæ, or sphincter trouble.

On examination, April 23, 1915: Fair type, good physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: no loss of emotional control, but undue optimism and indifference to his disabilities. Vision: acuity, right uncorrected $\frac{6}{60}$, corrected $\frac{6}{18}$; left $\frac{6}{9}$; fundi normal, except for myopia in right eye. Hearing good. Cranial nerves: pupils normal; slight ptosis on right, and weakness of right external and internal recti with diplopia; coarse slow nystagmus in all directions; otherwise negative; no dysarthria. Motor.—Head and neck: nodding tremor of head, increased by excitement and when he walks. Upper limbs: no paresis; well marked intention tremor, left > right, with dysmetria and dysdiadokokinesis; all movements clumsy and laboriously slow; no sensory ataxia. Trunk: combined flexion of hip and trunk well shown. Lower limbs: a little extensor spasticity; no paresis; intention tremor, left > right. Sensory.—Subjective: normal. Objective: slight astereognosis in right hand, with lowering of compass threshold (2·5 cm.); no definite loss of passive posture and movement; otherwise negative; vibration normal. Sphincters natural. Gait: tremulous, unsteady and reeling; well marked asynergia;

Rombergism negative. Reflexes: all tendon jerks exaggerated, legs > arms; all abdominals absent; both plantar responses extensor.

Progress: Three months later his walking had enormously improved and his hands were much steadier.

Note: Early case; remittent type; cerebellar manifestations prominent.

Case XXVII.—M. F., woman, aged 21, servant. Admitted to St. Thomas's Hospital on May 19, 1915.

Family history: Both parents, two brothers and one sister all died of phthisis.

Past history good.

History of present illness: Eight years ago her right hand suddenly became useless; she could not grasp things properly nor feel what she held in her hand. Ten days later the right leg was affected and she stumbled when walking. This was shortly followed by the appearance of tremors in the arms, especially the right, which rendered dressing and feeding very difficult. Her speech also was said to have altered. In ten months all symptoms had entirely disappeared and she felt perfectly well. Four years ago she had precisely similar symptoms, though not nearly so severe; after four months she again got quite well. One year ago she noticed curious sensations in the right arm and leg, which began to shake when she moved them; she could not identify objects in the right hand, and her speech became slow and stammering. She improved for a time, but six months ago got much worse and has gone downhill ever since. Her gait has become unsteady, she has difficulty in passing her water, and has become very emotional and unable to control her feelings. Recently she has had attacks of vertigo. No ocular symptoms.

On examination, May 19, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition intelligent; profoundly emotional and laughs inordinately at her own tremor. Vision: acuity normal; no ophthalmoscopic examination. Hearing good. Cranial nerves: fine nystagmus on lateral movements: typical ataxic dysarthria, slurring, staccato, monotonous, breathless. Motor.—Head and neck: well-marked nodding tremor. Upper limbs: no paresis; well-marked intention tremor and asynergia, right > left; tabetic athetosis of right hand. Trunk: combined flexion of hip and trunk well marked. Lower limbs: no paresis or definite hypertonia; intention tremor, right > left. Sensory.—Subjective: numerous paræsthesiæ. Objective: definite impairment of sense of position and movement in right hand with raised threshold to compasses (3·5 cm.) and partial astereognosis; otherwise normal. Sphincters: hesitancy of micturition. Gait: no spasticity; tremulous, reeling, and staggering: profound asynergia; no Rombergism. Reflexes: all tendon jerks exaggerated: all abdominals absent; right plantar response flexor, left extensor.

Progress: No change four weeks later.

Note: Remittent type; cerebellar manifestations prominent.

Case XXVIII.—M. S., woman, aged 30, married. Admitted to St. Thomas's Hospital on June 14, 1915.

Family history good.

Past history: Always of a nervous disposition.

History of present illness: Nine years ago she had an illness diagnosed as chorea, during which "her right arm shook whenever she used it"; in three months' time she was quite well again. Three years ago she noticed that she frequently laughed and cried for quite inadequate reasons. At about the same time her walking became unsteady, as if she were drunk, and she had difficulty in holding her water, with frequent "accidents." After about twelve months these symptoms disappeared, but eight months ago they reappeared in a somewhat exaggerated form, together with a coarse tremor of the right arm, so that she had difficulty in writing and in feeding herself. Recently she has had attacks of rotatory vertigo without tinnitus, and the unsteadiness of gait, emotionalism, and loss of control over the bladder have become more pronounced. Never ocular symptoms, dysarthria, or paræsthesiæ.

On examination, June 14, 1915: Good type, fair physique. Visceral examination: slight visceroptosis; otherwise negative. Wassermann reaction (blood) negative. Mental condition: intelligent; very sanguine and facile; laughs at her own tremor; "my expression does not reflect my feelings." Vision: acuity, right $\frac{6}{12}$, left $\frac{6}{6}$ partly; fields not tested; whole of right disc pale compared with left, especially in temporal half; left disc physiological. Hearing normal. Cranial nerves: no ophthalmoplegia; coarse nystagmus with lateral movements; no dysarthria. Motor.—Head and neck: to-and-fro tremor when unsupported. Upper limbs: slight weakness on right compared with left; no spasticity; typical intention tremor, right much > left; asynergia and dysdiadokokinesis, right > left. Writing shows pronounced dysmetria. Trunk: combined flexion of hip and trunk present. Lower limbs: slight extensor spasticity on right, with slight weakness of flexors; no definite paresis on left; no tremor. Sensory: subjective and objective, normal in every particular. Sphincters: precipitate micturition; frequent "accidents." Gait: can just walk without help; not obviously spastic, but reeling, titubating and very unsteady; no Rombergism. Reflexes: all tendon jerks greatly exaggerated, right > left; all abdominals absent; both plantar responses extensor.

Progress: Two months later she could walk round the ward without assistance, but was otherwise *in statu quo*.

Note: Remittent type tending to chronic progression in later stages; no sensory disturbances in spite of wide dissemination of lesions.

Case XXIX.—F. O'B., woman, aged 48, dressmaker. Admitted to St. Thomas's Hospital on June 16, 1915.

Family history: One of ten children; first three were stillborn, all others alive and well except patient and a younger sister, who is undeveloped both physically and mentally.

Past history: Always "suffering with her nerves"; neurasthenia twelve years ago with numerous phobiæ and apprehensions.

History of present illness: Ten years ago her "nerves" were bad, the sight of the left eye was affected and she had difficulty in holding her water. She improved after a few months, and remained fairly well for nearly three years. Seven years ago her left arm suddenly became useless; it was not paralysed, but she dropped things without knowing it and could not feel properly; her gait became affected shortly after and she walked as if drunk. In six months time she had completely recovered, but a little later her right arm became weak, she developed a squint in the left eye and saw double, she had frequent attacks of vertigo, her right leg dragged, and she lost control over her bladder. The diplopia and vertigo disappeared after a year, and although her walking improved, the other symptoms have more or less persisted, but her condition has varied a great deal from time to time. One year ago she had a "nervous breakdown," became unduly emotional, and lost control over the rectum. Six weeks ago she suddenly lost the use of both legs completely and has been in bed ever since. No dysarthria or intention tremor.

On examination, June 16, 1915: Neurotic type, good physique. Small superficial bed-sore over sacrum. No pyrexia. Visceral examination: slight albuminuria; otherwise negative. Wassermann reaction (blood) negative. Mental condition: introspective; poor emotional tone. Vision: acuity, right $\frac{6}{6}$, left $\frac{6}{9}$ partly; fields full; right disc normal, left shows temporal pallor. Hearing normal. Cranial nerves: fine nystagmus on lateral movement; otherwise negative. Motor.—Head and neck natural. Upper limbs: slight weakness and spasticity, right and left; no intention tremor or ataxia. Trunk: weak with some rigidity of abdominal muscles. Lower limbs: almost complete spastic paralysis in extension with frequent flexor spasms. Sensory.—Subjective: girdle sensation. Objective: cutaneous sensibility perfect; vibration abolished in both lower limbs and pelvis; no loss of deep sensation in arms or hands. Sphincters: incontinence of urine and fæces; feels "call" and passage. Gait: impossible. Reflexes: all tendon jerks greatly exaggerated: all abdominals absent; both plantar responses extensor.

Progress: Two months later *in statu quo*.

Note: Duration ten years; remittent type; recent complete paraplegia.

Case XXX.—A. K., girl, aged 16. Admitted to St. Thomas's Hospital on June 22, 1915.

Family and past history good.

History of present illness: Five weeks ago in the course of three days she developed shaking of the hands, drunken gait, attacks of vertigo and headache. The left thigh felt numb and she had pins and needles in both feet. During the past week the tremor of the arms has nearly disappeared. No ocular or sphincter trouble.

On examination, June 22, 1915: Good type and physique. Visceral exami-

nation negative. Wassermann reaction (blood) negative. Mental condition, vision and hearing: normal. Cranial nerves: fine, rapid nystagmus on lateral movements; otherwise negative. Motor.—Head and neck normal. Upper limbs: slight weakness of left grip; no spasticity or wasting; coarse static tremor of hands; no true intention tremor or ataxia. Trunk good. Lower limbs: good tone; some weakness of dorsiflexion at both ankles; both limbs show tremor on sustained efforts. Sensory.—Subjective: numbness of both legs, right > left. Objective: normal except for diminution of vibration sense below right knee. Sphincters natural. Gait: a little reeling and lurching; steps unequal in length and direction; no spasticity or Rombergism. Reflexes: all tendon jerks exaggerated; upper abdominal reflexes present, lower absent; right plantar response indefinite, left extensor.

Progress: One month later the gait was almost normal, but the reflexes were unchanged. After-history could not be traced.

Note: Early case; sudden onset tending to recovery.

Case XXXI.—A. C., girl, aged 20. Admitted to St. Thomas's Hospital on June 24, 1915.

Family and past history: Nothing to note; patient is an only child.

History of present illness: Two years ago she suddenly developed a squint in the right eye with diplopia, headache, vertigo, and a tight feeling round the waist. A fortnight later she was well again. Six months later she had a precisely similar attack of the same duration. Two weeks later she had severe pain in the back of the neck and vomited; the following day the the right arm and leg were weak, she saw double, and when she closed her eyes felt as if she were moving round and round. She also had difficulty in holding her head straight, and in passing her water.

On examination, June 24, 1915: Poor type and physique; bad teeth, adenoid facies; pulse and temperature normal. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition and vision normal. Hearing: normal on right; watch heard at 6 in. on left; bone conduction > air; perforation of left drum; no mastoid tenderness; no tinnitus. Cranial nerves: weakness right external rectus with diplopia; fine nystagmus on looking to left, slow and coarse on looking to right; slight tenderness right lower face. Motor.—Head and neck: the head is carried down with chin to the left; the head can be lifted but quickly assumes this "forced" attitude; no weakness or rigidity. Upper limbs: slight weakness with some flexor rigidity of right arm; all movements of the right arm are remarkable for the slowness both of their initiation and execution; attempts at rapid movements slow intention tremor and hypermetria; left arm normal. Trunk good. Lower limbs: slight extensor spasticity on right, with weakness of dorsiflexion at ankles; left normal. Sensory.— Subjective and objective, normal. Sphincters; definite hesitancy of micturition. Gait: spastic weakness of right leg with circumduction at hip. Reflexes: all tendon jerks exaggerated,

right > left ; abdominals absent on right, just obtained on left. Right plantar response extensor, left flexor.

Progress: Two weeks later the attitude of the head was normal, and the right hemiparesis was less marked. The diplopia persisted.

Note: Remittent type with acute exacerbations.

Case XXXII.—F. L., man, aged 37, ex-soldier. Admitted to St. Thomas's Hospital on June 27, 1915.

Family history good.

Past history: Always enjoyed good health. Fourteen years ago he had a soft chancre, for which he was treated, but not with anti-syphilitic remedies ; married ; wife has had two healthy children, and no miscarriages.

History of present illness: Eighteen months ago while out walking the left foot became numb and weak, and his left hand useless, so that he could not distinguish articles in his left hand trousers pocket. The next day he had diplopia, which persisted for two weeks. The condition of the left arm improved, but his leg got worse, his walking became unsteady, and he lost control over his bladder, and to a less extent over his rectum, sometimes having incontinence and at others retention ; he was also unable to feel the passage of urine but was conscious of a "call." Three months after the onset he rapidly improved, and could walk two or three miles without feeling anything amiss in the left leg ; beyond that distance his leg would drag. The sphincter trouble almost disappeared. Nine months ago he relapsed again, his left arm and leg became weaker, he got progressively more unsteady on his legs, and again lost control over his sphincters. He also experienced various odd sensations ("tight feelings") all over his body and limbs, fleeting in character, and became subject to attacks of rotatory vertigo without sickness or tinnitus. A month ago his condition underwent temporary improvement, but his walking is now worse than ever, especially in the dark.

On examination, June 27, 1915: Good type and physique ; no evidence of past syphilis. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: vision and hearing normal. Cranial nerves: no ophthalmoplegia ; rather coarse nystagmus on lateral movements ; slight but definite dysarthria, slurring, halting, staccato. Motor.—Head and neck normal. Upper limbs: right normal ; slight weakness of extensors on left, but no rigidity ; no tremor or cerebellar ataxy ; slight sensory ataxy on left with tabetic athetosis. Trunk good. Lower limbs: slight extensor spasticity with weakness of flexors on left ; sensory ataxy of both legs ; no loss of power on right. Sensory.—Subjective: girdle sensation and numbness of left leg. Objective: cutaneous sensibility is lost or impaired down back of left lower limb, sacral segments 1 to 5 ; otherwise normal. Deep sensation: slight loss of passive position and movement in left hand and wrist, compass threshold raised on left (1·5 cm. left palm, 0·75 cm. right palm), partial astereognosis left hand. Moderate loss of sense of position and movement, especially peri-

pherally in lower limbs, left > right, but not sufficient to account for the high degree of inco-ordination. Vibration impaired in left pelvis, but within normal limits elsewhere. Sphincters: difficulty in feeling passage of urine and fæces; hesitancy of micturition alternating with urgency; anal reflex present; absolute loss of sexual power. Gait: can just walk a few steps unaided; Rombergism present; the gait is ataxic and reeling and combines the features of both tabetic and cerebellar inco-ordination. Reflexes: all tendon jerks increased, legs > arms. All abdominals absent. Both plantar responses extensor.

Progress: Three weeks later *in statu quo*.

Note: Remittent type with little tendency to the formation of lesions in fresh localities; involvement of cord in sacral region.

Case XXXIII.—F. T., man, aged 30, policeman. Admitted to St. Thomas's Hospital on July 7, 1915.

Family and past history good.

History of present illness: Two years ago he noticed a mist in front of his left eye, which has persisted. Nine months ago his legs quite rapidly became weak and he had difficulty in getting about. His walking has varied considerably since then, but on the whole it has got worse. Eight months ago he developed urgent micturition with occasional "accidents." More recently he has noticed numbness down his legs and his speech has got slow and jerky. Recently the sphincter trouble has improved; no "accidents" lately. Never diplopia, tremor, or emotionalism.

On examination, July 7, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition and hearing normal. Vision: acuity, $\frac{6}{6}$ right and left: large central scotoma in left eye, involving fixation point, especially to colours; left disc is pale all over, edges clear; right disc normal. Cranial nerves: no nystagmus or ophthalmoplegia; slight ataxic dysarthria, slow, staccato, and explosive. Motor.—Head and neck, trunk, upper limbs, normal; no tremor. Lower limbs: slight extensor spasticity and weakness of flexors, left > right; no ataxy. Sensory.—Subjective, numbness in legs. Objective, normal. Sphincters; urgent micturition. Gait: spastic; no Rombergism or ataxy. Reflexes: all tendon jerks exaggerated, legs > arms; all abdominals absent; both plantar responses extensor.

Progress; No material change four weeks later.

Note: Remittent type in early stages tending to become slowly progressive.

Case XXXIV.—C. R., woman, aged 25, married. Admitted to St. Thomas's Hospital on November 16, 1920.

Family history unimportant.

Past history: Since the age of 14 has been subject to attacks of headache and giddiness, with vomiting, diarrhœa and faintness.

History of present illness: Four years ago a few hours after having had

some teeth out under gas she "came over queer" and was unable to see or speak for some minutes: the next day her walking was unsteady. This unsteadiness has persisted off and on ever since, but varies a great deal; for weeks together she will walk as if drunk, and then get nearly well again. She is always much worse in the dark. Three years ago the right hand suddenly became useless; she could move it but could not feel things properly with it. After six weeks it improved, but has never got quite well. Twelve days ago she woke up to find that she was cold and numb all down the left side, and her left arm was useless although not paralysed: the left leg seemed weak and her walking more unsteady than ever. She also felt as if she had a tight band round her waist. Four days later she felt as if hot water were being poured down her left side. Recently she has had attacks of rotatory vertigo. Never speech disturbance, diplopia, or sphincter trouble.

On examination, November 16, 1920: Good type. General condition good. Thoracic and abdominal viscera negative. Wassermann reaction (blood) negative. Mental condition: rather sanguine and optimistic, but no loss of emotional tone; condition is not abnormal. Vision normal in every particular. Hearing normal. Vertigo: objects move from left to right. Cranial nerve normal, no nystagmus. Motor.—Head and neck normal. Upper extremities: no loss of power on right or intention tremor; slight tabetic athetosis of right hand and some sensory ataxia; power on left is subnormal, but with eyes shut this defect is greatly accentuated; wild sensory ataxia on left. Trunk: good. Lower extremities: right normal except for slight spasticity; left, considerable spasticity with weakness, especially of flexors. Sensory.—Subjective: paræsthesiæ trunk and left arm and leg. Objective: cutaneous sensibility, everywhere perfect. Profound loss of deep sensation in left upper limb; she has no idea of the position of the limb and loses it in bed; no threshold to compasses, complete astereognosis; localization perfect, vibration impaired below left elbow. Slight astereognosis in right hand and raised threshold to compasses (2·5 cm.). In the left lower limb there is some disturbance of sense of passive posture and movement with loss of vibration reaching up to the left pelvis; vibration much diminished in right pelvis and lower extremity. Sphincters natural. Gait: spastic and ataxic; Rombergism present: no cerebellar inco-ordination. Reflexes: all jerks increased, especially in legs; abdominals all absent: both plantars extensor.

Progress: Two months later (January, 1921) the condition had greatly improved; the loss of deep sensation in the left arm was diminishing, she no longer loses the limb, and could use a fork in the left hand and dress herself. Reflexes unaltered. April, 1921: improvement maintained; no loss of passive position and movement is demonstrable in left arm, there is no sensory ataxy, and the patient says that this limb is now better than its fellow. The gait is much improved, the right plantar response is flexor and the left extensor.

Note: Remittent type, lesions appear almost confined to spinal cord; remarkable recovery from most recent lesions.

Case XXXV.—L. H., woman, aged 25, domestic servant. Admitted to St. Thomas's Hospital on November 10, 1920.

Family history: Mother very "nervous"; one sister has had chorea.

Past history: Nothing of importance.

History of present illness: Ten years ago she woke up one morning to find that her right arm was useless and her right leg was weak. The leg got well in a few days, but the arm remained bad for four months; it was not paralysed, but felt numb and cold, and she could not use it properly. Ever since she has been subject to paræsthesiæ in the right arm and leg. Six years ago she suddenly developed an internal squint in the left eye and saw double: this condition persisted for three weeks and then passed off. Five years ago after an attack of influenza her legs became weak and her walking unsteady; complete recovery in six weeks. Three years ago her legs began to get weak again, and she had pain in her legs and pins and needles round her ankles. Her walking gradually became worse, so that her feet dragged and she had to go about with the aid of a stick. The weakness of the legs has varied considerably in the past three years, but has never entirely disappeared. Latterly the legs have felt cold and numb. Two months ago she again saw double, and a little later experienced pain behind the eyes, especially the left, which rapidly became blind; the vision is now returning but things "look black out of the left eye." During the past three weeks she has been subject to attacks of rotatory vertigo. No affection of speech or sphincters.

On examination, November 10, 1920: Thoracic and abdominal viscera negative. Wassermann reaction (blood) negative. Mental condition normal, perhaps a trifle sanguine. Vision: right, acuity $\frac{6}{9}$, fields normal, temporal pallor of disc; left, acuity $\frac{6}{18}$, large scotoma, disc edges all blurred, swelling 1·5 D.; no hæmorrhages (retro-bulbar neuritis). Hearing normal. Cranial nerves: pupils normal; weakness left external rectus; well-sustained horizontal nystagmus; otherwise negative. Motor.—Head, neck, trunk, and upper extremities, nothing to note. Lower extremities: slight spasticity, weakness of all flexors; loss of power is greatly accentuated if legs are screened from view during testing; considerable ataxy of tabetic type. Sensory.—Subjective: numerous paræsthesiæ, especially in lower limbs. Objective: cutaneous sensibility everywhere normal; no loss of deep sensation in upper limbs; vibration—complete loss below knees, profound loss in femora and pelvis; sense of passive posture and movement gravely disturbed in lower limbs, especially peripherally. Gait ataxic and spastic; Rombergism present. Sphincters natural. Reflexes: arm-jerks brisk; knee-jerks greatly exaggerated; ankle-jerks diminished; all abdominals absent; both plantars extensor.

Progress: Two months later the vision in the left eye was $\frac{6}{12}$, the scotoma had contracted, and there was no œdema of the disc, which was pale all over. The diplopia had disappeared, the legs were stronger, and the walking had improved. The right plantar response was less definitely extensor than on admission.

Note: Markedly remittent type with exacerbations and recoveries.

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