

Th. Sect.

P O R E W O R D

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RATS, WATER, AND DISSEMINATED SCLEROSIS

Mr. Porter Phillips, Physician Superintendent, Bethlem Royal Hospital, for work in that Hospital. Dr. Lovell in the Pathological Laboratory and Dr. Levey in the Out-Patient Department.

An Ætiological Study

by

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Dr. Porter Phillips, Physician Superintendent,
Bethlem Royal Hospital, has given me every facility
for work in that Hospital. Dr. Lovell in the Patho-
logical Laboratory and Dr. Danvers Atkinson in the
Out-Patient Department have also given me constant
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and for some advice on dealing with the figures.

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patients or in other ways are mentioned in the text,
and I appreciate their courtesy. I should like also
to thank members of the laboratory, nursing and office
staffs who made the carrying out of the practical work
so pleasant.

INTRODUCTION.

THE following pages embody some observations bearing on the possibility that a water-borne infection, perhaps a spirochaete with the rat as host, may be the cause of disseminated sclerosis.

The investigations have been directed deliberately towards the finding of evidence for and against that theory; and even so the ground necessarily covered is sufficiently extensive to show what a tremendous task the serious consideration of all known etiological possibilities would have been, and to bear out the belief that more hope of profit may be entertained if a certain definite path be followed.

Since this work, then, resolves itself into a study of facts to see how far they will fit in with a given theory - notoriously a bad principle - a little may be said as to the facts from which that theory had its origin in the first place. If the legitimacy of the deduction be acknowledged, the further outcome need not necessarily be looked upon with grave suspicion.

Having occasion to re-read in 1924 "The

Histology of Disseminated Sclerosis" (Dawson)¹⁸ I noted without any exceptional interest the fact that the patient whose case is fully described (in the reprint from the Edinburgh Medical Journal) had fallen into water. It is recorded of her that she "was employed at one of the baths in Edinburgh" and on one occasion she "stepped too far back and fell into the deep end of the bath". This was in March 1908, and by June she had begun to show signs of the disease from which she died.

The Sydenham Society's translation of Charcot's Clinical Lectures fell into my hands within a month after I had read Dawson's work. This translation contains the following note. "A patient, according to Baerwinkel, experienced a difficulty in executing movements with the right leg, three days after having fallen into water. The action of moist cold has a reality in this case, because the patient allowed his wet clothes to dry upon him."

To find, first in one classic and then in the other, the statement that a patient who afterwards

developed disseminated sclerosis had suffered the rather unusual accident of a fall into water was certainly striking, and I tried at the time to find some explanation, but did not succeed. It was not until early in this year that another article threw sudden light upon hitherto hidden possibilities. I mean Manson Bahr's article in the Lancet of 1922, (which I did not see at the time of publication), on a case of Spirochaetosis icterohaemorrhagica in London. Describing his patient, the author says "A seaman, aged 39.....one of the crew of a coastal petrol ship..... Both the patient and his captain were emphatic that no rats had ever been seen aboard their ship, indeed it was their opinion that, on account of the smell of petrol, a rat, once introduced, would instantly leave it. On March 23, 1922, a week before admission to the Albert Dock Hospital, he fell into the Thames at Gravesend; being unable to swim he got a good ducking, and swallowed a considerable quantity of Thames water, but after two minutes immersion he was rescued, dried, rubbed, and put to bed on the ship. Three days later he developed excruciating pains in his limbs..." He developed undoubted spirochaetosis icterohaemorrhagica.

This man, who later suffered from infective jaundice, fell into water - so did two patients who later suffered from disseminated sclerosis. Was this latter disease then caused by an organism which inhabited rats, was cast by them into water, and penetrated from thence the damp skin of the future invalid?

Spirochaetosis ictero-haemorrhagica, water, and rats; described spirochaetes of disseminated sclerosis, water, and possibly rats - the factors fell into place like the key-words of a cross-word puzzle. Fitting perfectly into the scheme was the clinical history of wet feet in a rat-haunted kitchen, given by my patient (No.1) whom I had seen in 1923. It remains to be said however that the scheme was hypothetical, and still is hypothetical, in spite of my attempts to establish or demolish it. The few words I have been able to add still appear to fit into their appropriate squares, but future work in medicine, bacteriology or statistics may prove the essential unsoundness of the beginning. But although the very grave difficulties (such as the obscurity of the incidence of the disease on only a few out of many exposed to the "causal" factors, and the lack of

full bacteriological corroboration) in the way of acceptance of the theory of rat-water and spirochaete as a possible means of spread of insular sclerosis, are only too obvious they are not destructive of that theory, since they do not consist in negation, but rather in lack of proof thereof. Moreover, very similar difficulties are encountered in the consideration of other diseases where an analogous view is entertained.

This thesis, then, consists of a preliminary clearing of the ground by a consideration of the history, symptoms, and pathology of disseminated sclerosis, followed by a discussion of relevant bacteriology, of old views of etiology and the present view, and finally by records drawn from the study of patients, of literature, and of the statistics of the Registrar General, in support of the theme that the association of the patients with water and rats is too frequent to be left unconsidered from the etiological standpoint.

HISTORICAL

To avoid covering the same ground twice, the beliefs of the various writers on multiple sclerosis about its nature - whether inflammatory or not - will be mentioned in the course of this outline.

Charcot, speaking in 1868, said "Even to-day I do not believe that disseminated sclerosis is known in England." This statement, made in his celebrated "Clinical Lectures",¹² was preceded by some reference to Cruvielhier's "Atlas d'anatomie Pathologique", wherein disseminated sclerosis is found mentioned for the first time, and followed by reference to the work of German writers, who, from 1855 onwards, took up the question again after the lapse of some years. He mentions Turck, Ferichs, Valentine, Rindfleisch, Leyden and Zenkler as contributing "elements towards the solution of the problem", which they discussed under the names of "sclerosis of the brain and spinal cord" and "grey degeneration of the brain and spinal cord."

Notwithstanding these works, and the recording of some examples from the Saltpetriere by Charcot and Vulpian in 1862 - some forty years after the early description by Cruvielhier, it was not until Charcot's lectures of 1868, already mentioned, that the disease fully established its identity. In these lectures, not only the clinical signs and symptoms but the morbid anatomy and histology were described and discussed; and considering the vast amount of work that has been done since then it is astonishing not that there is so much difference, but that there is so much agreement between the beliefs of the great Frenchman and the beliefs of to-day, both from the bedside and from the laboratory. Here one may mention his idea of the process at work. He says, "In what consists the affection of the neuroglia which marks the beginning of this series of derangements? It is easy to discover there all the characteristics of formative irritation. But, after recognising the fact that disseminated sclerosis as a primary and multilocular chronic interstitial myelitis or encephalitis, it remains for us to determine the histological characters..."

Once a start had been made, it was easier for physicians to recognise the illness, and piece by piece clinical and pathological observations were added to the literature. In 1884 Marie published a long serial contribution in the Progrès. Médicale³⁰ giving many examples of the occurrence of "sclerose en plaques" after infectious illnesses, amongst which typhoid figured prominently, and laying down his proposition that the disease was "not a real illness of the nervous system".....it is "nothing else than.....the medullo-encephalic localisation of the vascular disorders of diverse general illnesses which seem constantly to be of an infectious nature."

In 1898 Sachs wrote a critical digest of opinions up to that date. In the course of that digest, which appeared in the Journal of Nervous and Mental Diseases,⁴⁶ he makes the pertinent remark, "But, strangely enough, whenever any data are collected in favour of proving the existence of some special etiological factor that special factor, in the minds of many, becomes the sole cause of the disease." Indeed it is

difficult to avoid such a habit of seeing that which is expected, and one can only hope that the multiplicity of etiological factors which have to be sought in the present instance will to some extent obviate any tendency to obsessive thinking. Sachs himself thought that disseminated sclerosis might arise from many causes, and he said, "Some slight defect in the original development of the central nervous system must be held responsible for the outbreak of the disease." Muller, reviewing the subject again in 1904, was of much the same opinion.

Strangely different in tone is the next important contribution - that of Bullock (Lancet)⁸ in 1913, who not only experimented on the transmissibility of the disease (by injecting subcutaneously into rabbits the cerebro-spinal fluid of patients suffering therefrom) but believed that he had proved his contention, for he succeeded in producing paralysis in some rabbits so treated.

Three years later Dawson wrote "The Histology"¹⁹ of Disseminated Sclerosis", of which it has

recently been remarked "This work sets the standard" in the pathology of the disease. The findings in this monograph will be referred to later. Here one may quote the first "Conclusion" thereof - "That the process underlying disseminated sclerosis is a subacute disseminated encephalo-myelitis which terminates in areas of actual and complete sclerosis".

By this time thoughts of a specific organism were more freely expressed. In 1917 Kuhn and Steiner successfully repeated Bullock's transmission experiments, and although Marinesco failed to produce disease in animals so treated, he found spirochaetes in the blood, liver and cerebro-spinal fluid of his experimental animals. Kuhn and Steiner (whose experiments already quoted had included the passage of a virus through four guinea-pigs) corroborated this, and almost at once, in 1918, Siemerling found spirochaetes in the cerebrospinal fluid of a patient who had died of disseminated sclerosis. This latter observation was repeated by Buscher in 1920.

W.E. Gye,²³ (who had formerly worked as W.E. Bullock,) published in 1921 an account of

further experiments in transmission, and again he had succeeded in producing a paralysis which he believed to be due to multiple sclerosis in its early stages. He admitted, however, that control observations should be made on the effect of injection into rabbits of cerebro-spinal fluid of patients not suffering from the disease in question. That same year saw the publication of a careful report "Multiple Sclerosis"⁵ produced in America by various writers on behalf of the Association for Research in Nervous and Mental Diseases. The conclusion of this work declares inability to come to any decision as to whether multiple sclerosis is of one or of two clinical types, and whether it is inflammatory, or degenerative, or both. Individual contributors, however, have sufficiently well-marked opinions which will be quoted later. Of very special interest with regard to the subject of this thesis are the findings of the association on the geographical spread of the disease. These findings are compared with my data for England and Wales in the statistical section of the present observations.

Work since then has, I think, tended to confirm the general belief that a spirochaete will be found at the heart of the trouble.

In 1922 Mouzon and Pettit published separately papers on the infectious nature of disseminated sclerosis, and in 1923 Adams, Blacklock², and others investigated again the question of experimental transmission, coming to the conclusion after careful experiment that the disease was transmissible to animals, while in the same year Collins and Noguchi in America carried out analogous experiments, without finding anything more startling to communicate than a warning to the investigator to beware of certain artefacts. This, however, is sufficiently important to justify much work, for the traps for the unwary in bacteriological work are of course innumerable.

The following year Siemerling wrote on the pathogenesis and etiology of the malady, and Marinesco⁵⁵ published a paper on the histopathology. The Revue Neurologique^{4, 5, 13 etc} devoted a

large amount of space to articles written by contributors from many countries, of whom Gillian, André Thomas, Babinski, and Monrad Krohn formed a proportion.

In 1925, Adams, Blacklock and McCluskie dealt again with the spirochaete, incidentally describing spirillar bodies occurring naturally in experimental animals and likely to cause confusion of diagnosis. Marinesco, in the Revue Neurologique⁵⁷, wrote a detailed neuro-chemical study.

This year - 1926¹⁸ - has seen the appearance in the Journal of Neurology and Psychopathology¹⁷ of an article by Cottrell and Kinnier Wilson on the affective side - the increase, decrease and perversion of emotion.

SYMPTOMATOLOGY AND DIAGNOSIS.

Between 1868, when Charcot chose nystagmus, intention tremor and slurred, scanning speech from among many symptoms as a diagnostic triad, and 1926 when Cottrell and Kinnier Wilson¹⁷ declared change in prevailing emotional disposition, change in emotional expression and control, and change in the sense of physical well-being to constitute "a diagnostic triad of greater value than any neurological symptom complex", stretch many years in which conceptions of the symptomatology of disseminated sclerosis have widened, narrowed, and contradicted each other. Even now the state of affairs is such that two neurologists will hardly agree upon what constitute adequate grounds for the diagnosis in the early stages, though agreement upon the diagnosis of well-marked cases is of course almost uniform.

To both of the triad-syndromes mentioned there is one objection - they are syndromes each of one mechanism, physiological if not anatomical. Nystagmus, intention tremor, and scanning speech are all disorders of co-ordination. The Cottrell-Wilson triad shows disorder of a distinct enough

mechanism not only of function (the affective) but also of structure (the paleothalamus). Dependent as both these syndromes are upon the characteristic periventricular sclerosis, one would yet rather stress as typical a mixture of symptoms in a disease where "dissemination" is sufficiently noticeable to be incorporated in one of its familiar names. To choose a sample of such mixtures, one might mention that of nystagmus (extra-pyramidal - co-ordination) euphoria (thalamic affective) and extensor plantar response (pyramidal somatic reflex).

Fine points of diagnosis do not concern us here, however, for any conclusions I have formed have been based upon the study of patients as to the diagnosis of whose illness there was, in my own mind at any rate, no doubt. The way in which a decision was reached as to the admission of cases into the group of the definitely diagnosed will be indicated at the end of the following review of known symptoms and signs.

3. Of Center Muscles.

Definite paralysis giving rise to diplopia,
which is often an early and transient symptom.

1. MOTOR.

A. WEAKNESS.

of my patients was diplopia persistent,
although it was fairly often recurrent.

1. Of Limbs.

This is very often an early symptom. I have the impression, though I have not worked out the figures on this point, that weakness of the left leg is more often the first motor complaint than weakness of any other limb. The great length of the pyramidal tract invites attack from a widely-spread process involving white matter by preference.

2. Of Facial Muscles.

This is mentioned in "Multiple Sclerosis"³ as a very frequent symptom. It is not so marked as the weakness of the limbs as a rule - though there is always the variability of the disease to reckon with - and causing less disability it does not attract the attention of the patient in the same way.

3. Of Ocular Muscles.

Sometimes only a paresis which can be overcome on putting forth greater effort, and sometimes a

definite paralysis giving rise to diplopia, this is often an early and transient symptom. In only one of my patients was diplopia persistent, although it was fairly often recurrent.

4. Of Muscles of Deglutition and Respiration.

This, the characteristic symptom of the bulbar type of insular sclerosis, and a stage to which types beginning otherwise may develop, has long been known and is associated with localisation of sclerosis around the fourth ventricle. It may be responsible for death in advanced cases.

B. SPASTICITY.

Whether this, which Charcot called "a pseudo-tetanic state of the limbs", is to be looked upon as a motor symptom, dependent upon involvement of the corpus striatum, much as the spasticity of Parkinsonism is dependent thereon, or whether it is to be looked upon as a failure of co-ordination in the sense of lack of balance and reciprocity between the "movement fibres" and the "fixing fibres", is doubtful. Spasticity while at rest would favour the former, and spasticity only arising on efforts to move would favour the latter, view point. Whichever be true, spasticity is

common as a symptom, usually expressed as "stiffness" by the patient, and sometimes inextricably confounded with the paraesthesiae which often affect the same limb. Thus, one patient (No. 6) complained that she felt as if a rubber band were wound around her knee, with rubber projections or mounds which made her knees feel twice the normal size (so that she had to feel her knee with her hand to assure herself that it was not so enlarged); she also complained that when she tried to move the joint this apparent band stiffened and tightened so that she was not able to move the limb at all comfortably.

Spasticity is common too as a sign, whether felt on attempting passive movement, or seen as producing a spastic or the spastic component of a mixed, gait.

C. INCO-ORDINATION.

Dawson¹⁹ quotes Kinnier Wilson to the effect that inco-ordination is associated with the disturbance of a) the cerebello-rubro-thalamo-cortical path and b) the lenticulo-rubro-spinal system.

Inco-ordination is manifest as:-

1. Dysarthria, which may take the form of scanning or staccato speech, or slurring and drawling, which elements may be distinct or interwoven with each other, and with the further disabilities arising from bulbar involvement or advanced mental enfeeblement. Sachs⁴⁶ has said that almost any form of dysarthria is possible in multiple sclerosis, and quotes Leube, who found a disturbance of innervation of the vocal cords in one instance.

2. Intention Tremor.

This, one of the old classical signs, is given third in order of diagnostic importance by the American authors of "Multiple Sclerosis".³ Sometimes the tremor is bilateral, sometimes unilateral, the excursions may be large and obvious to the patient on attempting voluntary movements, sometimes smaller and elicited by the "finger-nose test"; and sometimes very fine and only elicited by careful observation, as of the picking up of a pin from a smooth surface with the tip of a finger and thumb. Such a fine tremor was the chief

diagnostic point in a most interesting case I was fortunate enough to see, under the charge of Dr. Danvers Atkinson. This case is not quoted here, because there were many unusual points and it was not one where the diagnosis was at once obvious.

3. Nystagmus.

Unilateral or bilateral; vertical, lateral or rolling; spontaneous or only demonstrated on looking in a given direction, this is a third type of inco-ordination, and is given second place both by Charcot and by the American Association for Research above quoted.

Some of these disorders of co-ordination may be associated not only with the lesions already quoted but with involvement of the dorsal longitudinal bundle, which lies so close to the floor of the spinal canal and the central ventricles.

4. Adiadochokinesis.

Common in the cerebellar type of insular sclerosis, and might perhaps be found more often in mixed types if it were more often sought.

D. APOPLECTIFORM ATTACKS.

These are a rare but quite definite accident.

Noted by Charcot to be "occasionally encountered several times in the course of the disease" they are exemplified also in the following, quoted by Cadwalader and McConnell¹¹ "Case vi. M.S. white, male..... The history of his present illness was to the effect that about a year before coming to the hospital he had a sudden attack of what was believed to have been an apoplectic stroke, which resulted in paralysis of the right arm and right leg". Ormerod⁵⁸ also describes a patient who had "what she calls a stroke on the right side of the body". This lasted 24 hours. One patient in the present series (No. 15) began his illness by a fall from the table on which he worked as a tailor, and under which he was later found with a hemiplegia from which he recovered.

C. MUSCULAR ATROPHY.

This must be very rare. Charcot says, "in several cases which were otherwise well marked I have seen an atrophy of certain muscles supervene". He compares this to progressive muscular atrophy. In the one case in my series in which this occurred,

it was the first symptom of illness; the patient (No. 16) herself, who was an experienced nurse, used to say laughingly that she was suffering from infantile paralysis, which was at that time rife in America. The patient was in England, however, and was able to finish her walking tour and afterwards continue with her work for some months without interruption. Symptoms of disseminated sclerosis developed gradually after this. It is impossible to say whether the patient did have a slight unrecognised attack of poliomyelitis of Heine Medin type, or whether the invasion of a group of anterior horn cells was the first effective inroad of the "virus" of insular sclerosis. There seems little reason to doubt the possibility of the latter occurrence.

II. REFLEX

A. SOMATIC.

1. Pupil.

Disturbances of the pupil reflexes are so rare that their presence tends to throw doubt upon the diagnosis.

2. Tendon Reflexes of Arm, Biceps, Triceps, Supinator.

Frequently exaggerated, and sometimes more active on one side than on the other.

3. Reflexes of the Trunk.

Epigastric, Abdominal, Upper and Lower.

Weakness and absence of one or more of the abdominal reflexes in a patient with firm abdominal walls is one of the most useful diagnostic points. Its mechanism is obscure, but such loss is associated with pyramidal tract lesions. The integrity of some cortical component seems necessary for the performance of these reflexes.

4. Cremasteric Reflexes.

Sometimes lost.

5. Tendon Reflexes of the Leg. Knee Jerk. Ankle Jerk.

These are very frequently exaggerated, such exaggeration taking its place with spasticity and motor weakness as evidence of pyramidal tract lesions. Knee and ankle jerks may be more active

on one side than on the other, and patellar or ankle clonus may be present.

6. Plantar Reflex.

"Positive Babinski" or extensor plantar response is very common indeed, on one, and often both sides. Some of its variants, as Foix's or Chaddock's signs, may be elicited.

B. VISCERAL.

1. Micturition.

Various disturbances of this function may arise, such as delayed or difficult micturition, but the commonest effect is lack of cortical control as a result of which the reflex becomes more urgent and incontinence of urine and precipitate micturition occur.

2. Defaecation.

"Difficulties in defaecation as a symptom are a cause of controversy. Charcot mentions them; Sachs and Friedman³ say definitely that these do not occur in disseminated sclerosis. On the other hand, out of a series of fourteen

cases described by Adams, Blacklock and others,² no less than four showed this symptom, and I have seen in a comparatively limited experience two patients who suffered therefrom.

III. SENSORY.

A. EXTEROCEPTIVE GENERAL SENSATION.

1. Light Touch.

This is seldom lost to a great degree, though scattered patches of loss may be found. Patients show uncertainty often, and will sometimes respond to a light touch and sometimes fail to do so, in an apparently haphazard manner. By the time that actual loss of sense of light touch is established, it is sometimes apt to be difficult to demonstrate - possibly because by the time that the disease has advanced to this stage the patient's mental state is such that he has difficulty in concentrating upon such an insignificant stimulus as a touch with cotton wool.

2. Pain (pin-prick) and Temperature (moderate degrees).

May be irregularly lost; such loss is often

Very transient and is by no means a diagnostic feature of the disease.

3. Pressure.

As with other senses, this may be affected by a process which, after all, may pick out any white matter in the nervous system, but pressure appreciation is not often lost until the disease is advanced, and then only in small patches as a rule.

PARAESTHESIAE.

These are very much more common than any of the foregoing and are quite characteristic. They may take the form of numbness, tightness, formication, feeling of pins and needles and other anomalies such as the feeling of enlargement of the knees to which reference has been made. The same patient stated that she sometimes felt as if her abdomen were much enlarged, and at others would believe that she had gone to sleep with a book on her chest because of the sense of weight and oppression of which she was conscious on waking.

Pain is not uncommon. It may take the form of headache, or of more generalised pains. One patient (No. 6) complained of aching over the right half of the body and in the right limbs, and it was not easy to make up one's mind whether this distribution signified thalamic involvement, or, a "functional" element.

HYPERAESTHESIAE.

Occasional. Tenderness over the spine is referred to by American authors - I have not noticed this in the present series.

On the whole, though disturbances of skin sensibility are often present on examination, they are seldom definite enough to attract the patient's notice except where they take the form of paraesthesiae.

B. INTEROCEPTIVE.

1. Kinaesthetic.

Very frequently impaired or lost. This may be due to posterior column involvement implicating the central fibres of the receptor neurones concerned, when the spinal type of ataxia will result. It may also be due to cerebellar

involvement presumably of some part of adjustor neurones or their synapses, when the cerebellar type of ataxia is produced - this I think is commoner. But it is probable that very often both components are responsible for manifestations such as ataxic gait, the ataxic part of spastic-ataxic gait; ataxia of hands (finger nose test), ataxia of legs (heel to knee test) and Rombergism either with closed eyes, or open eyes, or both.

2. Vestibular.

Closely associated functionally with the last, the vestibular mechanism may show disorder of which the most common symptom is Vertigo. Vertigo is present in many cases. Other disturbances of vestibular function are found from time to time.

3. JOINT SENSE.

Now and then a patient will be found who is unaware of the position of some of his digits, or even limbs, after these have been moved in such a way that the movement is not visible to him. "Miss V" of the "Clinical Lectures"¹² showed this sign, and it was present in one of the cases I have seen.

SPECIAL SENSES.

A. SIGHT.

1. Disturbance of vision.

This is very common, often early and often transient "A sort of haze", "blurring", "a film over my eyes", and "things look all misty" are familiar phrases on the lips of patients. Alterations in the visual fields, such as peripheral or central scotomata, or both, may be found. Dawson¹⁹ associates the fleeting early visual symptoms with sclerotic patches in the optic radiation; Charcot¹² believed them to arise from the presence of early turgid patches in the optic nerves.

2. Discs.

Associated with later visual failure, and sometimes without any visual defect arousing attention, is pallor of the optic discs, particularly of the temporal halves.

3. Diplopia)
) Have already been mentioned.
4. Nystagmus)

B. HEARING.

This is sometimes impaired. Such impairment is of particular interest in those cases simulating eighth nerve tumour. Aural hallucinations occasionally occur.

IV. MENTAL.

A. AFFECTIVE.

The recent work of Cottrell¹¹ and Kinnier Wilson on this aspect has been mentioned, and the headings here given are taken from their paper.

1. Changes in prevailing emotional tone.

This is common, at any rate in well marked cases - Charcot¹² speaks of the "cheerful indifference" of his patients, and a history of such a change can often be obtained from observant relatives or friends, if not directly from the patient.

2. Changes in emotional expression and control.

Under this heading come various symptoms such as "forced laughter" and "forced crying". The

former is much more common than the latter, and while it is often associated with emotional excitement, such excitement is not by any means always concerned with amusement. One patient, (No. 3) who laughed so much when interviewed that it was difficult to get a complete sentence from him in reply to the most mundane questions, said, between snorts and giggles of laughter, that he was not in the least amused, and that he always laughed when he was excited. A relative standing by explained that his present excitement was due to nervousness when sent to see a new doctor. Another, (No. 14) complained in the most bitter tones of the discomfort of forced laughter to which he had at one time been subject. "I did wish the doctors could stop it. I felt so silly. There was nothing to laugh about. I could not help it. I used to laugh at anything; at things not at all comic. Also sometimes I would burst out crying for nothing at all". It was interesting to find a patient who had been subject to both laughter and crying, involuntarily, during the same period. This patient was under the care of Dr. Yealland, at the West End Hospital for Nervous Diseases.

3. Change in the sense of physical well-being.

"To-day I feel like a king, but I don't know what I'll feel like tomorrow", said a female patient to me (No. 16) and many others have shown very great changes from great malaise to much bodily content, when seen at intervals of a week or more.

Cottrell and Kinnier Wilson¹⁷ believe that these symptoms are dependent upon a paleothalamic invasion. In this connection it is interesting to note that Taylor⁵⁰ describes one of his patients as "Emotional. Sensitive to noises", thus once again linking up the sclerotic affective syndrome with the thalamic syndrome so fully described by Head. Of this thalamic syndrome many illustrative examples are to be found in Head's "Studies";²⁵ such is one from which the following excerpt is taken: "Serious music is so intolerable, owing to the sensations it produces through the right side of her body, that she is obliged to leave the room."

I am not in a position to throw doubt upon the work of experienced observers, but in the

present series I have been unable to find emotional changes in such a great proportion of cases as did Cottrell and Kinnier Wilson; and particularly in early cases. Most early cases declare that they feel in no way different emotionally; and a fair number of the later ones acknowledged nothing less logical than was suggested by remarks like, "I have been depressed since I got ill - I hate to lie here and wonder if I shall be able to work again"; or "I don't worry a bit. What's the use? Worrying never helped anybody to get better". But while I have not found such an overwhelming number of affective changes, these have been well enough marked in a good many instances; and I do not doubt that more careful investigation would have revealed slight changes in many more. In passing, one may remark that it is difficult to know what could be called a normal, and what an abnormal affective attitude to the advance of a more or less incurable disease in a patient who might have one of half a dozen different temperaments. I heard an experienced statistician say the other day that the great fallacy of in attacks lasting for a few days at a time, in a fair number of patients. It is not easy to

devotion to vital statistics was the fact that nobody had as yet decided whether it was in fact truly desirable that life should be prolonged. He was not, so far as I am aware, suffering from multiple sclerosis!

B. OTHER MENTAL DISTURBANCES.

These, like the other manifestations of the disease, may be infinitely varied. They may range from mild dementia to well-marked insanity; they may be narrowed to a small amnesia or spread out to generalised intellectual degeneration, and almost any form of insanity may be reproduced. They are, however, not particularly characteristic of the disease and need not be enumerated in detail. Out of the patients 688 recorded in the statistical section as dying of disseminated sclerosis in 1925, 4 spent their last days in Mental Hospitals.

V. MISCELLANEOUS.

A. VOMITING.

1. This occurs from time to time, sometimes in attacks lasting for a few days at a time, in a fair number of patients. It is not easy to

assign a cause to it, and as a symptom it cannot be placed with certainty in any other class than the present.

2. Pyrexia.

Slight degrees of pyrexia are an occasional but not constant accompaniment of acute onset or exacerbations.

B. COURSE.

1. Onset.

This may be acute, with generalised aches and pains which may lead to a false diagnosis. I have little doubt that some of the many cases reported as following on after rheumatism or influenza were in reality chronic illnesses following on after an acute onset. It is to be noted that the patient in "The Histology of Disseminated Sclerosis",¹⁹ of whom mention has already been made, began her attack with swelling and tenderness of both legs, and shooting pains and that she sent for her doctor "who thought the symptoms were due to muscular rheumatism". Very similar, to quote only one instance, is a case

described by Adams, Blacklock, Dunlop and Scott.²

"Case VI Aged 18. Female". Symptoms began
"two weeks prior to admission and followed on
an attack of subacute rheumatism".

One would go a little further, and say that perhaps a few of the patients who began their troubles by falling down may just possibly have fallen because of the sudden onset, comparable to the sudden onset of the occasional apoplectiform attacks noted. One would not push these views too far, however. It is notorious that one illness predisposes to another, and that shock and injury are also predisposing. Who knows ^{but} that fright and sudden emotion, pace James, may so alter the vascularity of the thalamus as to stir up a hitherto quiescent organism?

However that may be, while a sudden onset of disseminated sclerosis is accepted as a clinical fact by many, by almost equally many the possibility is denied, and I do not think the argument can be decisively settled yet. A gradual onset is in any case much more common.

Variability.

2. REMISSIONS.

These, which may be anything from slight alleviation to apparent total cure (with or without a later recurrence) are most misleading to the patient, tending to make him entertain quite false hopes from this or that treatment, but they are most helpful to the physician since they so greatly strengthen a tentative diagnosis. It is difficult to account for these remissions, though easy to guess about them. Dawson¹⁹ says "Remissions and relapses necessitate the assumption of the latent presence of the morbid agent in the body, or, if this is an autogenous toxin, either its intermittent evolution or its accumulation from deficient elimination". In a sense, their presence helps to bear out the suggestion of a spirochaetal origin for disseminated sclerosis, since they may be looked upon as having at least a possible analogy with the long unexplained remissions in that other chronic spirochaetal encephalitis, general paralysis of the insane.

3. Variability.

Not only are there remissions in the disease

as a whole, but variability of symptoms in themselves is a very striking feature. An original leg stiffness will pass off; a month or two later dimness of vision and diplopia will appear; presently there will be vertigo, and perhaps a return of the spasticity with weakness affecting both leg and arm. Almost any pattern may be traced as the advancing disease jumps from point to point of attack.

SUMMARY OF SYMPTOMS.

The more prominent symptoms, then are an acute or gradual onset of weakness of limbs or face, with exaggerated tendon reflexes, positive Babinski's sign, impaired or lost abdominal reflex; loss of posterior column sensation with ataxia; inco-ordination with nystagmus, intention tremor and dysarthria; euphoria with forced laughter or crying; paraesthesiae particularly numbness and formication; vertigo; difficulties of micturition; visual dimness and diplopia; vomiting; and above all a haphazard non-system incidence with variability in individual symptoms and remissions in the whole.

DIAGNOSIS OF THE PRESENT SERIES.

For this purpose, after the symptoms and signs had been noted upon a case sheet designed for the purpose, a summary was made giving a rough indication of the more common manifestations. A "rough" indication because to give precise definition was merely to repeat the case-sheet statements, and a more or less uniform diagnostic standard was aimed at. Thus, "ataxia" might mean anything from slight uncertainty of placing in the finger-nose test to full-blown cerebellar Rombergism, and "mental" change ranged from slight euphoria to a disturbance which sent the patient to a mental hospital. Opposite the particular item in the summary (which was the same in every case) was placed a plus or minus sign according to the presence or absence of the symptom in question.

The summary was as follows:-

Weakness of Arms

" " Legs (i.e. patient's complaint of these)

Paraesthesiae

Vomiting

Visual disturbance

Disc changes

Vertigo
Micturition difficulties.
Positive Babinski (on one or both sides)
Absence of Abdominal Reflexes (or of epigastric reflexes)
Ataxia
Nystagmus
Intention tremor.
Speech change.
Mental change.
Transience of symptoms, and remissions.

This very imperfect scheme was found to cover enough ground for the purpose of making diagnosis sufficiently certain for acceptance in an etiological discussion - where it is important that it should not be said "But this was not disseminated sclerosis, but some other disease". Of course the whole range of symptoms was not demanded, but no patient was admitted unless he or she manifested at least four of the symptoms detailed above, distributed in such a way as to exclude the suggestion of an alternative diagnosis. Thus, one patient, (No. 14) was admitted to the list because he added to a selection of symptoms that would just as well have meant acoustic nerve tumour as insular sclerosis, the very characteristic forced

laughter, forced crying, and remissions, and he did not show papilloedema, and another was excluded from the list because although she had shown various symptoms with remissions, and had been diagnosed by an experienced neurologist, she could not muster up four unmistakable signs or symptoms when I saw her. Apart from this no other selection was exercised, and the cases were consecutive in the sense that they were those to whom my attention was consecutively directed, although the dates of onset and of application for treatment at the various hospitals were very different.

PATHOLOGY.

In view of the controversy and uncertainty which occupies the field of bacteriology in the disease under consideration, it is satisfactory that the pathology at least is so clearly defined, and that pathologists agree in the main as to what changes they see in those parts of the nervous system which are affected, even though they still quite fail to agree as to the meaning of these changes.

NAKED EYE CHANGES.

The brain and cord do not show any obvious change in size, but the patches of sclerosis which are near the surface are usually visible to the naked eye. These are grey in colour, both untouched and on section - an appearance which led the earlier German writers to describe the disease under the name of "grey degeneration". Some writers have recorded also patches which were reddish and prominent, and they look upon such patches as being recent and acute in type. Dawson¹⁹ says that the pia over the patches may appear thickened, and Buzzard and Greenfield¹⁰ refer to the "curious knobby sensation" felt on

passing the hand along the cord. Older patches are white in colour.

No changes which can be attributed to the disease are to be seen either microscopically or macroscopically in other organs though the findings are often complicated by the presence of signs of disease such as cystitis, pneumonia or other intercurrent trouble from which the patient ultimately died. Changes in endocrine organs have been described, but these are not constant.

DISTRIBUTION OF PATCHES IN THE CENTRAL NERVOUS SYSTEM.

While the patches may be anywhere in brain, cord, and sometimes nerves, there are certain areas where patches are more frequent although they are not distributed in any regular order.

1. IN THE HEMISPHERES.

Here the localisation of the sclerosis has been the subject of comment by almost all authorities, for the most striking feature is the periventricular sclerosis. This is seen

around the lateral ventricles, and usually extends into the horns of these ventricles; the third ventricle has also its lining of sclerosis. The meaning of this distribution, although suggestive at first sight of toxicity or infectivity of the cerebro-spinal fluid (a possibility which again is discussed in nearly every writing on the pathology of multiple sclerosis) is, as has been shown by Dawson,¹³ capable of another interpretation, when he says "The absence, however, of any change in the ependymal epithelium seemed to contra-indicate the possibility of a simple soakage of the cerebro-spinal fluid into the periventricular tissues. The terminal branches of the central arteries ramify on the ventricular walls, and this localisation of the areas, therefore, might equally be related to the vascular richness of this region." Neither Dawson nor any other author whose work I have read has come to a finally conclusive opinion on this point, however, and if bacteriology is to help it must go further than it has yet done, and tell us whether the suspected organism is distributed by blood-vessels, cerebro-spinal fluid, or lymph.

Such a periventricular sclerosis, however caused, involves the thalamus and encourages the appearance of some of the symptoms already noted.

White matter in the rest of the hemispheres is involved in a much less constant way, the patches being situated anywhere and anyhow, without regard to anatomical structure. The precise location of any one of these spots is attended by symptoms more or less definite according to the functional importance of the area involved.

2. The Mid-brain.

This is very frequently diseased, with the result that the tracts from cerebellum to red nucleus, and from red nucleus to telencephalon and to cord, as well as the dorsal longitudinal bundle and sometimes the tracts of the oculomotor and sixth nerves, are attacked, presumably in virtue of their proximity to the aqueduct. The results of this in nystagmus, tremor and dysarthria are well known.

3. The Pons and Medulla.

Here the sclerosis follows its usual course, and may be involving the lower cranial nerves produce a type of bulbar paralysis simulating

glosso-labio-laryngeal paralysis, or by settling as sometimes happens around the eighth nerve nuclei may cause those occasional but very puzzling syndromes of deafness, vertigo, nystagmus and facial paralysis on one side with symptoms of pyramidal involvement upon the other, which so strongly suggest acoustic nerve tumour.

This ponto-bulbar spread has its manifest dangers to life, and often ends it.

4. The Cerebellum.

The white matter is frequently attacked; according to Buzzard and Greenfield the lobes of the cerebellum are rarely attacked. Many of the symptoms - the ataxia and perhaps the nystagmus and some forms of the speech defects, are of cerebellar origin.

5. The Cord.

Patches are scattered up and down the cord with very little indication of systematisation. The common pyramidal lesions are rather to be attributed to the length of the tracts, (which, like a long line of communications, form a vulnerable element,) than to any predilection of the disease

process for motor fibres; similarly the comparative freedom of the fibres of common sensation is to be attributed to the different and devious paths by which they ascend rather than to any native distastefulness to the "virus". On similar structural grounds is to be explained the fact that tendon jerks are far oftener increased by patches which cut their cortical connections at one of many possible levels than lost as the result of destruction by a patch at the actual reflex arc level. Another factor (the integrity of cells) has some concern with this, and will be mentioned shortly. These are general considerations - but disseminated sclerosis cannot be properly described under a general rule. In the cord, as elsewhere, patches may appear anywhere and everywhere, with the most varied results.

6. In the nerves.

Patches may occupy the central portions of the nerves, and one or two cases have been described where they occupied the peripheral nerves. One of the nerves most frequently suffering from the advance of the sclerotic process is the optic nerve; a condition which may

well be explained on the basis of the familiar periventricular distribution, since the optic nerve arises as an outgrowth from the brain and has its own vestigial ventricular prolongation. It is easy to see how central scotoma arises from a sclerosis which, radiating from the sulcus chiasmatis, will just catch the decussating central fibres. The explanation of the typical pallor of the temporal halves of the discs is less straightforward. It may result secondarily from lesions of the lower visual centres.

Should the disease-process be localised mainly in the cerebrum, cerebellum, pons-and-medulla, or cord, symptoms will be produced which will perhaps justify the clinician in labelling the case as of cerebral, cerebellar, bulbar or spinal type for the sake of convenience, but it is seldom that such a localisation persists, and indeed it is very often a diagnostic point between disseminated sclerosis and such lesions as tumour, that one or more symptoms appear which are referable to lesions in some other locus. The divisions of the central nervous system are in themselves arbitrary and artificial and the same can be said of the divisions between the

different forms of multiple sclerosis.

MICROSCOPIC CHANGES.

1. Methods of investigation.

For the ordinary worker, who cannot undertake special investigations, Marchi's method of staining will give information on recent patches and the state of structures therein, and the method of Weigert-Pal will give clear differentiation between healthy tissue and diseased patches of long standing, and will demonstrate very well, even in sections examined with the naked eye or with a lens, the irregular dissemination of the disease. The specialist will find descriptions of stains for different structures in pathological works. Dawson's work was based upon serial sections stained by the two methods stated, and by special elective stains to show cells, the axis cylinders, and the neuroglia respectively, as well as by diffuse stains for general observations.

2. Types of Areas.

Different pathologists have described the patches according to the recency or otherwise of the invading process, and the number of stages into which the process is divided for this

purpose varies greatly. Dawson describes six stages, but for the purposes of this thesis it will be sufficient to outline the changes in the different histological structures and then to state briefly how these changes are noted in two types of area - a "early area" and an "actual sclerotic area" (to borrow titles).

3. Changes in the Myelin.

Charcot¹² believed that the change in the neuroglia was primary but I think that now most authors are agreed that the change in the myelin is entitled to that designation. Buzzard and Greenfield¹⁰ begin with a description of this change in their histological study; Hassin²⁴ in America, beginning with a remark on fat accumulation in the pia, puts "neural degeneration" before "glia proliferation"; André-Thomas⁵² in France believed that myelin degeneration and less severe but definite changes in the axis cylinders went hand in hand, the neuroglial reaction being secondary, while Dawson¹⁹ says "the change in the myelin sheath must be looked upon as the most constant, the most uniform, and in many cases the primary one".

These myelin changes take the form of initial degeneration with droplet formation (stainable by Marchi's method) and later disappearance. Babinski⁴ compared them to the alterations in the central end of a cut nerve in the neighbourhood of the section. On this myelin degeneration Bullock⁸ based his belief that he had produced early lesions of insular sclerosis in a rabbit, and while this is open to question (for reasons which will be stated) it is certain that such degeneration is found in this disease.

4. Changes in the Axis Cylinder.

According to Buzzard and Greenfield,¹⁰ the axis cylinders may be "swollen, varicose, fusiform, or generally thinned and atrophied in places"; and André-Thomas¹², as mentioned, describes changes of the nature of hypertrophy, accentuation of fibrillary appearance, and dissociation and rupture of a certain number of fibres, as occurring early. With this belief in early axis cylinder change Dawson is in agreement - he and other workers from the time of Charcot, however, note the persistence of axis



cylinders, in spite of this attack, long after the myelin has gone and sclerosis has begun. Finally, however, axis cylinders may be choked and deformed by the increasing glia fibres, and when this stage is reached the patient is clinically worse and probably incurable.

5. Changes in the nerve cells.

The obstinate health and survival of the ganglion cells with so much disease around them has been indicated often as the prime factor (along with persistence of axis cylinders) in the comparative functional integrity of neurones starting in or running through sclerotic patches. Hassin²⁴ comments on "the absence of significant ganglion cell changes". Later on, however, the cells do suffer showing "chromatolytic alterations" and more rarely "an obvious diminution in the number of cells" (Buzzard and Greenfield)¹⁰; these changes being due to 1. increasing sclerosis; 2. loss of function and 3. somatic disturbance (Dawson)¹⁹. A remark of the former authors in this connection may be quoted. They say "The absence of lower motor neuron disturbances - in other words the absence of muscular atrophy - is due to the

integrity of the ventral horn cells even when they are included in a diseased area."

I personally believe that it is consistent with the capabilities of this protean disease for it to attack as an occasional freak these anterior horn cells; such an attack would explain the muscular atrophy of case No. . It is a point on which one cannot be dogmatic, however, for there is remarkably little evidence either way. Epidemic encephalitis, which typically attacks the brain, similarly strikes occasionally at anterior horn cells - here the fact if rare is beyond controversy. I have personally seen two such cases, and quite a number of others have been described. What the orthodox encephalitis can do is surely well within the reach of the blatantly non-conforming sclerosis.

6. Changes in the Neuroglia.

The glial proliferation is the most striking, if it is not the primary, histological change. Charcot and the early writers placed it first, Charcot¹² saying "the affection of the neuroglia which marks the beginning of this series of derangements." The glia cells increase and

form fibrils, and these fibrils, as shown in the illustrations to "The Histology of Disseminated Sclerosis"¹⁹ arrange themselves at first longitudinally, so that they replace the myelin sheath by a glia fibril sheath. In this way the general structure of the tissue is retained. Later the glia fibres spread in all directions, there being in older plaques "a thick network of neuroglia fibres and a sparsity of glia cells" (Buzzard and Greenfield).²⁰ Whether the neuroglia proliferation be regarded as irritative and hypertrophic, and so analogous to inflammatory tumour such as tuberculoma, or whether it be regarded as reparative and compensatory for loss of other tissue - a kind of scar formation - it differs from other tumours in producing in most cases no projection and from scar tissue in producing no retraction. The general effect is one of replacement with absence of deformity.

7. Other Cells.

a) Lymphocytes. These may be found in the perivascular spaces, and form one of the arguments on behalf of the inflammatory theory. Cells of similar appearance - "small round cells" - may be found in the pericellular lymph spaces also.

The mere presence of these cells round the large nerve cells cannot be taken as proof of inflammation, for most observers are agreed that a few such cells are normally present; an increase of these cells, however, is taken by Dawson to be one of the most characteristic signs of affected patches in the cortex.

b) Leucocytes of other types.

These may be found, though not in such numbers, in the perivascular spaces.

c) Fat-granule cells, or Gitterzellen.

Scattered in the tissue in the affected patches, and more particularly aggregated round the vessels of capillary size and over, are these large cells with granules of myelin or corresponding vacuoles where the myelin has been dissolved out, according to the method of treatment. Again, while these cells appear in inflammation of the nervous system, they also appear in degenerative processes, the products of which they engorge and remove so that here also little help is obtained in the solution of the inflammation or degeneration problem.

8. Changes in blood vessels.

Some observers, notably Charcot, report changes in the smaller blood-vessels, such as that "the parieties of the vessels appear much thickened". However, now nearly everyone is agreed that though changes in the blood vessels may appear, they are very slight; so slight as to be almost negligible in comparison with other changes. The argument that Dawson uses as contrary to the opinion that the peri-ventricular sclerosis is not due to soakage of toxic material, through the ventricular wall, when he says that there is no evidence of damage to the ependymal cells, can be used, also, against the probability of soakage of toxic material through the vessel walls, because the cells of those walls show so little damage.

The chief change in relation to the vessels is the perivascular infiltration with cells; definite, but by no means so striking as that seen in encephalitis lethargica.

7. Lymphatics.

The path of the lymphatics is to a certain extent in dispute. Many observers who have investigated this have used the injection of coloured particles and subsequent microscopical examination as a method of search, and while this is useful, it seems to me to be open to much fallacy when, as sometimes happens, the particles are injected under artificial conditions of pressure. However, there is little dispute on the path of the perivascular lymphatics above noted to be infiltrated with cells, and probably these lymphatics communicate with the pericellular lymphatic spaces also. The cellular infiltration is the chief change to be noted.

8. Other changes.

a) Oedema.

Oedema of the tissues around the vessels and cells is often noted.

b) Lipoids.

²⁴Hassin speaks of the increase of lipoids

in the pia arachnoid and the choroid plexus, and fatty granules may be found scattered in the affected patches.

c) Pigment.

There may be an increase of pigmentation in the cells, but it is impossible to attach much weight to this, since its significance is not known. Certainly it is seen both in chronic inflammatory conditions such as general paralysis of the insane and in degenerative conditions such as senility; but in how far paresis is a degeneration and senility an intoxication is again disputable.

TYPES OF AREAS.

1. "Early areas."

These have been described by Dawson¹⁹ as follows. They "consist largely of closely arranged fat-granule cells between which lie the large, protoplasmic, proliferated glia elements of dilated vessels, with fat-granule cells and other nucleated elements in their adventitial spaces; of markedly altered persisting axis cylinders;

and of a gradual transition zone in which these changes are less marked and in which degenerating myelin fibre may be found."

2. "Actual sclerotic areas."

To quote from the same author, these may be described also as showing "complete absence of myelin; the presence of a dense fibrillar tissue; the persistence of numerous axis cylinders; the presence of numerous blood vessels with condensed sclerosed walls; and the complete absence of any evidence of myelin degeneration; and finally, a nucleated transition zone which gives frequently an abrupt passage to normal tissue."

The foregoing, as is obvious, has been based chiefly on work done before 1922. Since then, the pathology has been added to, so far as I can judge, more by the careful working out of minute points of microscopy and bio-chemistry than by the declaration of any striking new features.

In 1924, this advance was shown by the papers published in the Revue Neurologique^{32 etc} of that year; and also by the work of Marinesco, in the

Annales de Medicine.⁵⁸ Of this interesting work one cannot here say very much, but there are some aspects of it which may be quoted. For instance, he says that the essential lesion consists in the infiltration of the venules of the pre-capillary and capillary vessels.... that in one of his cases the infiltration of the venules was very considerable, it formed an extremely thick perivascular sleeve, such as one sees in the most definite inflammations.

The localisation explains itself by the fact that the virus of sclerose en plaques is carried to the neuraxis by the lymphatic vessels, it spreads itself through the arachnoidal space and in the ventricles, from whence, on account of the numerous vessels which are found in the white matter, it directs itself from the deep parts towards the surface along the adventitial space of the vessels.

Talking of the cerebellum, he says, "The lesions of the Purkinje cells are not considerable. The granular layer having disappeared, there remains a tangle of neuroglia fibres.

The propagation of the pathogenic agent by the cerebro-spinal fluid seemed indisputable to him.

Finally he says, in spite of the negative results obtained by some authors and the uncertainty which rules as to the nature of the pathogenic agent, the transmission of the virus of disseminated sclerosis to animals... seems to demonstrate that the nervous system of the subjects attacked by this malady contains an active virus.

In 1925 Marin⁵⁷esco produced a further publication on this disease, in the shape of a careful study of its bio-chemistry as this was shown in the central nervous system. Of particular interest is his emphasis on the importance of the morbid predisposition. I shall have occasion to refer to this in considering the etiology, but it is to be noted in the meantime that he looked upon this morbid predisposition - as that found in hereditary and familial diseases - as a disturbance of the acido-basic equilibrium of the neurone.

THE CEREBRO-SPINAL FLUID.

There has been no very great change found in this in disseminated sclerosis; sometimes a slight pleocytosis, but not constantly; sometimes a small globulin increase. The one frequent pathological finding is a paretic type of curve to Lange's colloid gold sol test. In "Multiple Sclerosis"³ the proportion of paretic curves is given as "50 per cent of all fluids"; Adams' states that 39 out of 41 patients seen by him gave a positive reaction of C.S.F. to colloid gold; and my own experience in pathological laboratories, though by no means extensive, fully confirms my belief in the accuracy of these findings. The degree of precipitation varies very considerably in different cases.

THE INTERPRETATION OF THE PATHOLOGICAL CHANGES.

It has been indicated through this paper how great and lasting is the difference of opinion on the meaning of the pathological changes. Dawson

believes them to be, as already stated, of the nature of encephalo-myelitis; Hassin¹⁴ in America came to the conclusion that the process was "conclusively degenerative"; Marinesco^{32 et al.} is equally convinced that what he sees means inflammation.

It is obvious that where the findings are substantially the same and yet opinions differ, the question is entirely beyond solution by the mere interested onlooker.

Stress has been laid upon the point of inflammation versus degeneration, because it has a very obvious bearing upon the question here mooted - a question involving spirochaetosis. Pathology can take us no further than this - that while to some the changes appear to be degenerative, it is at least equally likely that they may prove to be inflammatory.

PROBABLE BACTERIOLOGY OF DISSEMINATED SCLEROSIS
WITH NOTES ON THE BACTERIOLOGY OF APPARENTLY
ALLIED CONDITIONS.

The organism most suspected as the probable cause of disseminated sclerosis is a spirochaete, and therefore it seems wise to begin with a discussion of the spirochaete group and in particular of the leptospira variety. This step is justified not by the findings of workers on nervous diseases only, but by the general impression in favour of the spirochaete which has found its way into systematic textbooks of medicine. Thus in Price's Textbook of the Practice of Medicine, of 1926, in the section on Nervous Diseases (Collier and Adie)¹⁵ we find the remark "The course of the disease as well as the inflammatory nature of the early lesions points to an infective origin, and recent research suggests that the causative agent is a specific transmissible virus, to wit, an organism resembling the spirochaete pallidum".

CLASSIFICATION OF SPIROCHAETES.

In 1919 Muir and Ritchie³⁶ stated that it was uncertain whether spirochaetes were to be regarded as bacteria or protozoa but said "The balance

of opinion is now distinctly in favour of the latter". The position at the moment does not seem clearer, although the subject has been much discussed. Probably the spirochaetae are in fact as they appear to be - a class by themselves, not to be accurately placed in either group, though having some of the characteristics of both.

The type species is the *Treponema pallidum*.
In 1923, the Committee on Classification of the Society of American Bacteriologists made the following arrangement, described by Thomas.⁵⁷

"The fourth" (of the Schizomycetes) "the Spirochaetales, are simply placed in the class because there seems to be no other convenient place for them in the classification of living things.....forms which are not ultra-microscopic which cannot be definitely classed as either plants or animals. These are spirally shaped organisms, with rigid or undulating bodies. Reproduction is usually by transverse division, though in some types longitudinal division apparently takes place....."

1. Genus Spirochaeta.
2. Genus Cristispira.

3. Genus *Saprosira*. Non-parasitic forms similar to *Cristispira*, but without the flattened ridge of "crista", which is, if present, here replaced by a straight columella or thickening of the periblast.

4. Genus *Spironema*.

5. Genus *Treponema*.

The type species is the *treponema pallidum*.

6. Genus *Leptospira*.

Parasitic forms. Sharply twisted cylinders with flagelliform tapering ends, one extremity being sharply curved into a hook".

This extract (which has been slightly abridged) shows one state of opinion - the other one which definitely includes the Spirochaetae with protozoa, has been noted. Whatever be the proper place of the order, interest as far as disseminated sclerosis is concerned centres mainly on the genus *leptospira*, and it is consistent with that view that the work which suggested the theory at the root of this present investigation concerned an illness caused by a member of the same group - the *leptospira* of *spirochaetosis icterohaemorrhagica*.

A few remarks on the leptospira of this type of jaundice may be made, and in passing, one may say that the dispute as to the identity or distinctiveness of Weil's disease and spirochaetosis icterohaemorrhagica need not concern us at all, and for our present purpose they will be treated as synonymous, and their causative organisms likewise.

SPIROCHAETOSIS ICTERHAEMORRHAGICA.

This type of jaundice occurred during the war in the French, German, and British troops on the Western front; it arose in certain mining areas later, in Midlothian, where the offending organism was found in the slime of the mines and in the local rats by Buchanan; it occurs in Japan and elsewhere, and in 1922 Manson-Bahr reported the case whose history is given in the beginning of this paper.

The organism is found in rats in Japan, and has been found in the same animals in America, England, and Flanders. It is described by Dawson (of Penn) in The Medical History of the War,²⁰ his article being illustrated by a very beautiful microphotograph of the spirochaete, from Pettit,

showing the terminal hooks and flagelliform and bead-like bodies. The leptospira is 4 μ to 25 μ long, it has a hooked extremity, and the clubs and flagellae mentioned above have been described by other workers; it has large and small waves. Stitt⁴⁹ notes that it has no undulating membrane. It can be grown on Noguchi's blood agar media, and while it will live at 37° C, the optimum temperature is below that - as might be expected in an organism which survives with such apparent ease in river water.

Life-cycle.

I have found no description of a life-cycle of differing phases in this organism, but it is reasonable to suppose that there is such a cycle. Noguchi, after "almost innumerable series of unsuccessful cultivations" of different strains of *Tr. Pallidum*, succeeded in growing that organism. He gave the results of his experiments in the Journal of Experimental Medicine,³⁷ and showed diagrams and microphotographs of the young spirochaetes, and what is of more interest, of

round refractile bodies to which these young creatures were attached. Riddell and Stewart, writing in the Journal of Neurology and Psychopathology,⁴⁵ describe the finding of the spirochaete in cerebrospinal fluid obtained by lumbar or cisternal puncture from a General Pareitic, on six successive occasions, after which the spirochaete abruptly disappeared, but there were present for a time instead, bodies similar to those described by Noguchi, which had been seen earlier attached to the spirochaetes. The authors say "The refractive power appeared to be higher than that of the body of the organism, and gave the impression of a brilliant "head lamp" as the Spirochaetes moved rapidly across the field."

Talking of a different type of organism, the "Borrelia berbera (of North African Relapsing Fever)" as he calls it, Stitt,⁴⁹ after talking of the spirochaetes which are at first found in and then disappear from the louse which spreads the disease says, "A striking fact is that infection can be brought about a day before spirochaetes appear, and that after a few days these spirochaete-containing lice lose their power to

infect.....Wohlbach has shown that certain spirochaetes will pass through a Berkefeld filter as such, but this would not affect the possibility of some granule or chlamydozoal stage."

Muir and Ritchie,³⁶ discussing the work of Leishman on *Sp. Duttoni*, make some statements which are so pertinent to the question now considered that I shall quote at some length. They say, "On the other hand Leishman has failed to find any evidence of spirochaetes in the tissues of ticks later than ten days after ingestion of blood containing them, or in the ova laid by the ticks, or in the young ticks when hatched, though these were proved by experiment to be infective. After ingestion of blood by the ticks he found that morphological changes occurred in the spirochaetes, resulting in the formation of minute chromatin granules which traverse the walls of the intestine and are taken up by the cells of the Malpighian tubules... Similar granules are to be seen in the Malpighian tubules of the embryo ticks, where they are also found in the subsequent states of their life. He has proved that infection of animals may be produced by inoculation with

crushed material containing the granules, but no spirochaetes. He accordingly considers that the granules in question represent a phase in the life-history of the parasite, and that infection occurs by inoculation of the skin with the chromatic granules voided in the Malpighian secretion and not by unaltered spirochaetes from the salivary glands. A similar view is taken by Hindle, who has found that when infected ticks, in which the spirochaetes have disappeared, are heated to a temperature of 35° C the spirochaetes reappear in the organs and coelomic fluid. It is also interesting to note that Balfour has found similar granules in ticks....infected with *Spirochaete Gallinarum*."

Adams, Blacklock, Dunlop and Scott² make the following interesting remark - "There are many striking analogies between disseminated sclerosis and neurosyphilis. The similarity of the ocular manifestations in respect of optic atrophy and diplopia is striking, and the vast majority of cases showing clinical symptoms of spinal sclerosis fall under the heading of one or either of these two diseases. It is of interest to note that in

another known spirochaetal disease, viz, East African Relapsing Fever, Manson and Thornton state that third, fourth and sixth nerve lesions are encountered."

I am not familiar with these various types of Relapsing Fever, occurring as they do in different parts of the same countries, and answering to an assortment of different names, several to each variety. But the point is that they are spirochaetal. Here is another - in the most recent publication which I have seen, the Bulletin de la Societé de Pathologie Exotique³¹ for June of this year, there is an article on the receptivity of the rabbit to the "spirochaete de la musaraigne." Here the following remark is made. "But while the parasites were not discoverable on direct examination, we have seen that the blood is not the less infectious for sensitive animals like the grey mouse."

There is, then, plenty of evidence that not only do variations exist in the infectivity of spirochaetes, but also that different phases of these organisms can be found. The variability in the incidence of spirochaetosis icterohaemorrhagica suggests the possibility of the same sort of thing,

and considering that there is a likelihood that the variabilities in incidence and development of disseminated sclerosis may be due to similar etiological factors (a likelihood borne out by a certain amount of circumstantial evidence) - it is worth while going a little further into the study of the infectivity of *spirochaetosis icterohaemorrhagica*.

To return, then, to life cycles and the *leptospira ictero-haemorrhagiae*, one may quote Manson Bahr²⁹ on the incidence of the jaundice. He says "It is difficult not to assume that the infection originated from immersion in contaminated water....Reiter in 1919 definitely associated the occurrence of Weil's disease in the German army with bathing in certain pools in Maddeburg and Brunswick, while Uhlenhuth and Zeuler.....succeeded in stopping the epidemic by preventing the men from bathing in certain spots. They were led to connect the source of the infection with the presence of putrefying material in the water. An almost identical case to the one reported above is reported by Schürer (1922) in a canal labourer, who, 14 days after falling into a sewage contaminated pool in Germany, developed typical Weil's disease". In what way

do these facts suggest a life cycle? Because the infection comes from stagnant water containing putrefying material; it is suggested that the organism in the rich quiet of such a pool, develops a form or stage which, in contradistinction to the form of the hurrying waters, is infective. Such at least, is my own tentative interpretation, and one or two facts will be given presently to show how this may relate to multiple sclerosis and its alleged cause. Whether the infective form is developed because of the conditions in these pools per se, or because of the rats which are likely to congregate there, is another and an unanswered question.

DISSEMINATED SCLEROSIS.

Like spirochaetosis icterohaemorrhagica, this disease occurs in many countries. Evidence will presently be brought forward from the geographical side to show its relation to waterways, and from the clinical side to show its relationship to damp and rats.

SPIROCHAETE ARGENTINENSIS.

The above is the name given at first to the supposed organism of disseminated sclerosis. Noguchi⁶ quotes the following description of it. "In length, from the fraction of the diameter of a red cell to a whole red cell, while in width more delicate than leptospira icterohaemorrhagiae of Weil's disease. There were often highly refractile balls at both ends. Some specimens showed a loop at the end or along the course of the body. The movements were somewhat wormlike, moderately active, but seldom rotatory as in the case of leptospira icterchaemorrhagiae. In stained preparations a small delicate straight projection of varying size was observed, resembling a flagellum". Gye²³ says, "The organism was described as resembling closely the leptospira of Weil's disease; it could be stained with Giemsa's stain and with Loeffler's flagella stain, and was blackened in tissues by Levaditi's silver method."

It is stated, though I have been unable to find the original paper, that the first suggestion that a spirochaete might be the infecting organism appears to have been made by Buzzard in 1911 (Adams, Blacklock etc). The claim on behalf of

the spirochaete argentinensis was made by Kuhn and Steiner.

In 1913 Bullock⁸ injected the cerebrospinal fluid from a patient with multiple sclerosis subcutaneously into a rabbit, the rabbit developed paralysis on the eighth day, it died of cystitis, and was found to have a recent patch of degeneration of the cord, visible by Marchi's stain, and it was believed to have had the disease under consideration. Two points may be noted on this work. First that the work of Orr and Rows³⁹ would make one chary of accepting as of the nature of insular sclerosis a spinal patch of myelin degeneration in a rabbit with severe cystitis; and secondly, it is of interest that this and similar results were obtained with tame rabbits, whereas further work with wild rabbits was negative. Spirochaetes of some types are found in wild rabbits, whether they are found in tame ones I do not know. Whether the wild rabbit, in common with the wild rat, is or is not susceptible to disseminated sclerosis is a question of great interest.

This work of Bullock's set the ball rolling, and other investigators followed. I may quote a work published by Adams, Blacklock, Dunlop, and Scott,² on behalf of the Medical Research Council. They produced nervous symptoms in five out of sixteen animals injected with the cerebrospinal fluid of patients; the patients numbered nine, and positive results were obtained from five; some of the rabbits showed leg paralysis and some cerebellar symptoms; and the following series of passages was carried out.

Cerebro spinal fluid of patient into rabbit, which became paralysed; Central nervous system of rabbit on to Noguchi medium; Noguchi medium after 14 days into rabbit, which became paralysed; nervous system of rabbit into Noguchi medium for 18 days; Noguchi medium into rabbit, which became paralysed 13 months after inoculation.

Various changes were found in the central nervous system of the experimental animals; degenerative changes were to be found in the myelin sheath in only one animal and "it is to be noted that this animal had lived for over a year after the onset of the paralysis". Spirochaete-like

Structures were seen in 7 out of 42 rabbits inoculated; not in others. Inoculations of normal blood and C.S.F., as well as C.S.F. from patients with other diseases; intraperitoneal injection of killed bacteria, protein or milk all alike failed to produce nervous symptoms, and spontaneous paralysis was never seen in all the 200 rabbits housed in the laboratory.

This is given as a type of a careful experiment, well controlled.

Another experiment, equally careful, was performed by Noguchi,⁶ working with Collins in America, inoculated animals intracerebrally and intraperitoneally with material from patients suffering from disseminated sclerosis. His results were entirely negative both as regards the production of the disease in the animals so treated, and in the search for spirochaetes in them. He failed to find these organisms in "the blood, C.S.F., liver, spleen, kidney, suprarenal glands, lymph nodes or brain" of his experimental animals. Moreover, he described "Morphological elements present in the defibrinated blood", which, being "delicate tremulous beaded filaments of varying length"

behaved under dark field illumination much like the leptospira group of spirochaetes. Such a report, from one who is admittedly an expert in this work, enforces the need for caution.

The results of various workers on the bacteriology of disseminated sclerosis, are summarised in the following table, mainly compiled from a full resume by Guillain in the Revue Neurologique for 1924.^{52, 4, etc.}

INOCULATION INTO ANIMALS OF C.S.F. OR OTHER MATERIAL FROM PATIENTS.

SEARCH FOR PRODUCTION OF PARALYSIS.

1. Positive.

Bullock (1913) Steiner (1914) Kuhn and Steiner (1917) Simons (1918) Marinesco (1919) Kuhn and Steiner (1920) Bullock i.e. Gye (1921) Adams (1921) Pettit (1922) Jarlow and Rud (1923) Adams, Blacklock, Dunlop and Scott (1924) Adams, Blacklock and McCluskie (1925)

2. Negative.

Siemerling et Racke (1914) Hauptmann (1918) Olsen (1919) Guillain, Jacquet, et Lechelle (1920)

Rothfeld, Freund and Hornowski (1921) Birley
and Dudgeon (1921) Von Magnus (1921) Teague
(1921) Achard (1922) Claude, Schaeffer,
Alajouanine (1922) Laroche et Lechelle (1922)
Noguchi (1923).

INOCULATION INTO ANIMALS OF MATERIAL FROM PATIENTS.

SPIROCHAETES SOUGHT.

1. Positive.

Kuhn and Steiner (1917) Marinesco (1919)
Kalberlah (1921) Pettit (1922) Stephanopoulo
(1922) Paraf et Lermoyez (1922) Adams, Blacklock,
Dunlop and Scott, (1924) Poussep (1924).

2. Negative.

Simons (1918) Bullock - now Gye - (1921),
Rothfeld, Freund und Hornowski (1921) Von Magnus
(1921), Teague (1921) Claude, Schaeffer,
Alajouanine, (1922) Bertrand (1922) Jarlow and
Rud (1923) Noguchi (1923) Marquezy (1924).

ATTEMPTED PASSAGE THROUGH ANIMALS, OR CULTURE
AND ANIMALS.

Positive Kuhn and Steiner (1917) Adams (1921)
Stephanopoulo (1922)

EXAMINATION OF C.S.F. OR BRAIN OF PERSONS DYING
FROM INSULAR SCLEROSIS SPIROCHAETES SOUGHT.

1. Positive.

Siemerling (1918) Buscher (1920) Kuhn and
Steiner (1920) von Speer (1921) Schuster (1923)

2. Negative.

Church (1920) Achard (1922) Claude, Schaeffer,
Alajouanine (1922) Laroche et Lechelle (1922)
Stevenson (1923) Barré et Reys (1924).

But those whose experiments fall into the
scales on the negative side are not always
convinced that there is nothing to find bacteriolo-
gically. Thus, Birley and Dudgeon,⁷ whose transmission
experiments failed, say that in examining the
deposit from the C.S.F. obtained by precipitation
with absolute alcohol and stained by Giemsa's method
they saw "Numerous small bodies resembling cocci,"
and that in two cases "small granules resembling
fat were observed by the dark-ground method" and
"our own investigations support the view which
regards the process underlying this as inflammatory."
Gye,²³ on the positive side, quotes Rothfeld, Freund,
and Hornowski, who found "the frequent occurrence
of coccidiosis".

These may or may not be observations on the non-spirillar phase of the spirochaete argentinensis. In searching for these things myself I became aware almost at once after beginning the search that what I looked for, i.e. small refractile granules, were like so many other things - cocci - fat droplets - bubbles in the dark-field - that it seemed absurd to hope that they would be recognisable for what they were. I think that one must wait for the development of bacteriology which shall bring us some elective staining method for the granule phase of the spirochaetae.

One of the most interesting of this series was the work of Adams, Blacklock, and McCluskie⁵⁶ seen in two consecutive articles published in 1925. In the first of these, they write on Spirochaete like structures in experimental animals, and conclude "that spirillar structures have been found practically constant in the cerebro-spinal fluid of monkeys, rats and guinea-pigs, which must be recognised as a source of confusion with true spirochaetes". In the second article, on spirochaetes in the ventricles

of inoculated monkeys, they say that "these organism appear to be similar to those previously found in rabbits inoculated under similar conditions, but that no conclusion can be drawn as to their causal relationship to the disease". The article is illustrated by plates showing vague wispy spirillar bodies referred to in the first article; rabbit spirochaetes for comparison, and finally the spirochaetes from the inoculated monkeys.

Amid all this welter of work, what is one to believe? I think the situation can be summed up as follows.

There is not complete proof that an organism is the cause of disseminated sclerosis, but there is at least a possibility that this may be so, and that the organism may be a spirochaete of the leptospira type.

In the laboratory of Bethlem Royal Hospital during the last few months, I have spent some time searching for "Noguchi bodies" in various samples of cerebro-spinal fluid. I cannot lay claim to any success therein. Much time was taken up in

experimenting with various techniques and becoming familiar with those adopted. Some interesting and suggestive forms were seen, but the chances of deception by artefacts were so great that i have not considered it worth while to give these any but a very tentative place in the appendix to this paper. Bacteriology is a realm where experience is of paramount importance, and the results of investigations carried on without wide experience must be looked upon with caution.

ETIOLOGY.

FORMER THEORIES.

1. Inherited predisposition, and familial incidence.

This factor has been cited, as in almost all diseases, as being of importance. Cases have been quoted, such as that given by Reynolds, where disseminated sclerosis has occurred in several members of a family. Sometimes it is "disseminated sclerosis", sometimes is it "A familial disease resembling disseminated sclerosis." Recent investigations throw doubt upon the likelihood of

the disease being inherited. Regarding familial incidence, opinion in 1921 was summed up by the Association for Research in Nervous and Mental Diseases (America)³ as follows. "Far and away the commonest condition of recurrence of the disease in the family is that of two or more affected persons in the same fraternity". The bearing of that upon the theory of the present paper will be shown immediately in its relation to a common exposure by the persons affected to the suggested etiological conditions. The aspect of predisposition may first be reviewed.

Taking as an example Reynolds⁴⁴ patients, we may note what they showed, in order of their place in the family.

Father suffered from delusions.

Cousin had disseminated sclerosis.

Cousin had exophthalmic goitre.

Aunt had melancholia.

1st in family - sister - died in asylum - melancholia.

2nd in family - sister - Mary - had disseminated sclerosis.

3rd in family well, apart from occasional sciatica.

4th in family - brother - John - had disseminated sclerosis.

5th in family - brother - well (went abroad).

6th in family - Edward, had disseminated sclerosis.

This terrible record may be read in two ways. It may mean that this family had a disposition to nervous diseases, and that view is almost inevitable. I do not doubt that this factor operates in disseminated sclerosis, as in other diseases. An excellent comparison can be found in the etiology of General Paralysis of the Insane. Much has been written of an incontestable kind, showing the incidence of this disease in members of the same family infected from different sources. Here is the predisposition. Much, however, has also been written on the incidence of the illness among members of different families infected from the same source. Here is the organismal factor. I cannot but think that both must be operative. It is all very well to talk about the seed and the soil - but it is blatantly obvious that to grow good plants both must be suitable. As far as this predisposition goes - in disseminated sclerosis - I think one may postulate that there are families the members of which, once exposed to infection,

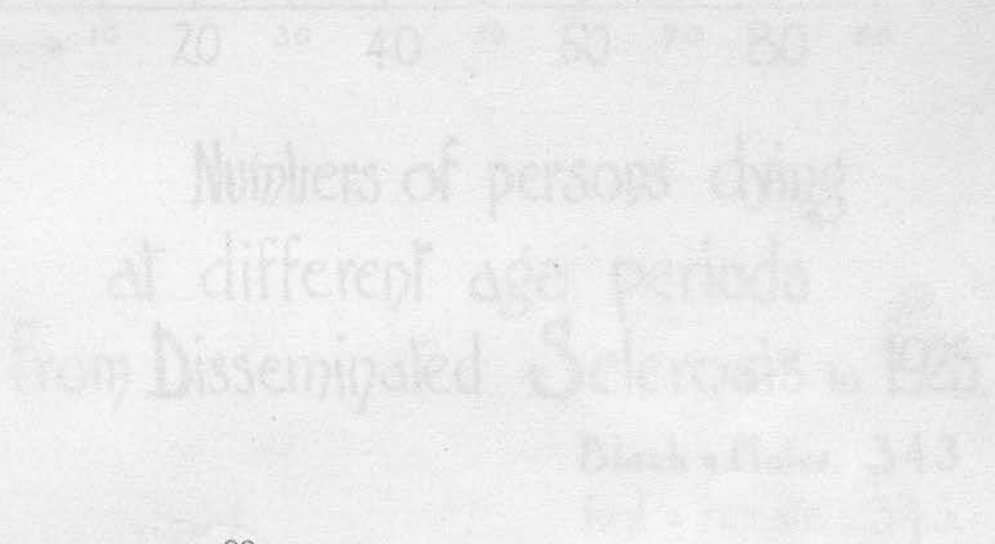
will be more likely to fall victims of the disease than the members of other families. One of the most striking demonstrations of what appeared to be susceptibility to attack in the nervous system was given by a patient whom I saw who had congenital deformity of the fingers (a stigma of degeneration); who had suffered in early childhood from anterior poliomyelitis; and who came for treatment in middle age for encephalitis lethargica. In much the same way I think one should regard the occurrence of anterior poliomyelitis in the patients who later develop disseminated sclerosis; a combination of which one definite and one possible example are to be found in the series here investigated.

Possibly the biochemical disturbances cited by Marinesco may have something to do with predisposition to attack alike by anterior poliomyelitis and by disseminated sclerosis.

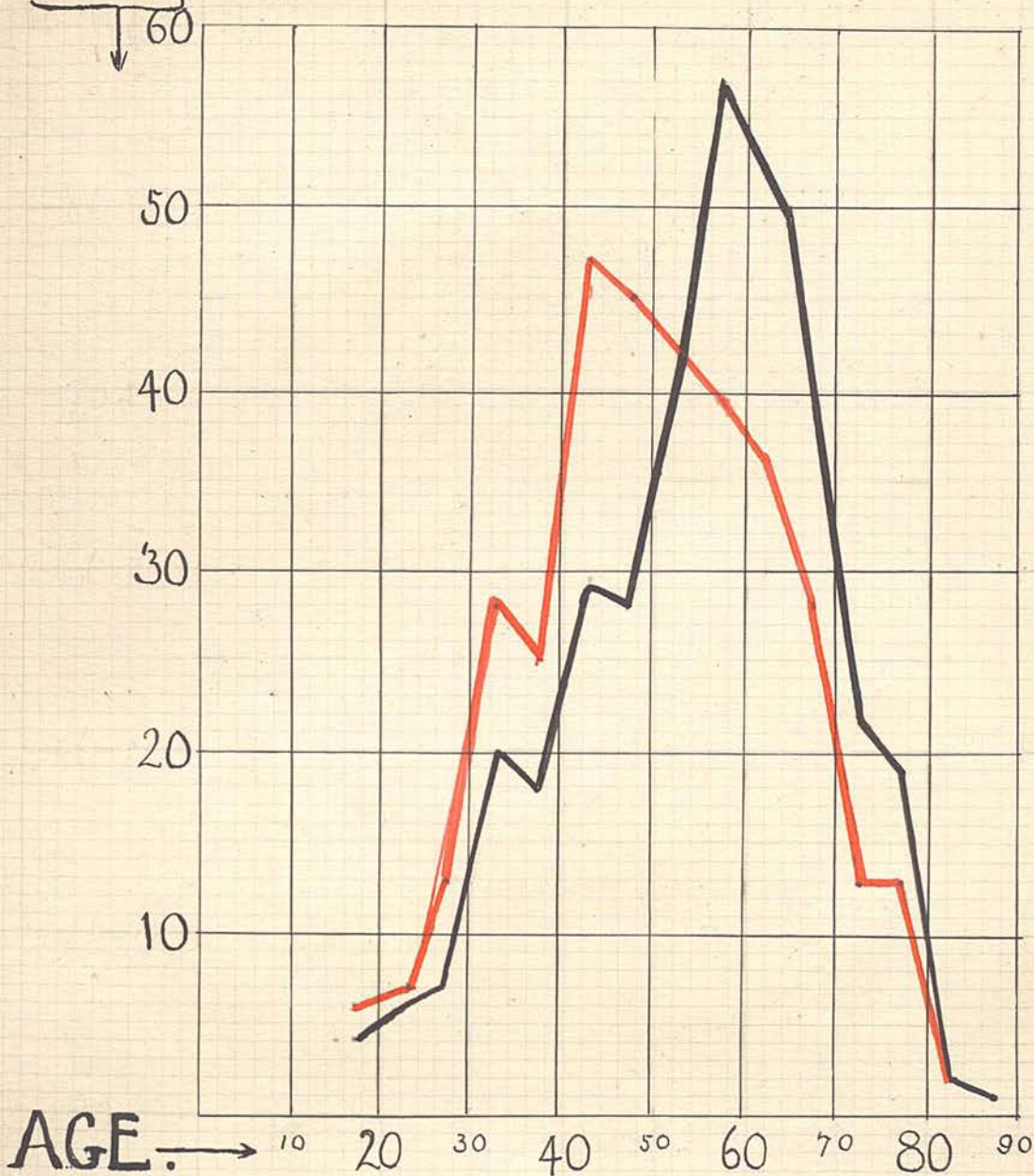
To look at the second aspect - that of common exposure to the alleged predisposing causes, there is one argument above quoted from the etiology of General Paralysis of the Insane. Then, there is the known relationship (to get nearer to the rat and water theory) between degeneracy, insanity, and poverty. That family, as to whose lives there was little information given, might well have lived in squalid surroundings, damp and rat-haunted, along with the tuberculous, the alcoholic, and the feeble-minded, whose family histories often display a somewhat similar battered scutcheon. However, it is quite certainly stretching hypothesis too far to allow any great force to this particular argument. It is simpler to note the obvious fact that brothers and sisters growing up together and living together are more than likely to be exposed to the same conditions, whatever they may be. In the present series there are two couples, one of two sisters who were both swimmers who occasionally swam in fresh (q.e. not salt) waters; and the other of a brother and sister, both of whom were children on the same water-side farm, over-run, according to the statement of one of them, with rats.

2. Age.

Age is gradually being regarded as a factor of less importance in the etiology than was formerly thought. Disseminated sclerosis used to be looked upon as a disease of the twenties and thirties - now it is stated that it has occurred in children of four or five and in adults of anything up to 81. Some of the reported cases are not fully authenticated, but undoubtedly the disease is not uncommon at any age between thirteen or fourteen and seventy or over. The age of death in patients dying in England and Wales in 1925 is shown on the accompanying table.



DEATHS. (England & Wales.)



Numbers of persons dying
at different age periods
from Disseminated Sclerosis in 1925.

Black = Males 343

Red = Females. 345.

Males

	All ages	5	15	25	35	45	55	65	75	85
Population	9,184,004.8	17,242,243	16,640,112	15,230,483	12,457,618	10,966,048	7,298,780	3,823,120	1,166,193	129,994
Deaths	1,702	4	54	119	254	363	499	306	98 → 103 ←	5
Rate per million	18.5	0.2	3.2	9.0	20.4	33.1	68.4	80.0	84.0	38.5
									79.5	
Population	10,034,980.6	17,064,580	17,542,412	15,932,900	14,389,047	11,903,901	8,065,877	4,735,642	1,794,660	264,025
Deaths	1,792	6	61	187	321	426	411	261	107 → 118 ←	11
Rate per million	17.9	0.4	3.5	11.7	22.3	35.8	51.0	55.1	59.6	41.7
									57.3	

Females

Rate per Million



Death rates per million at different ages: 1921-1925.
Disseminated Sclerosis.

(The figures from which these curves were drawn were kindly given to me at Somerset House)

Comparing this death-rate table with the previous table showing, for 1925, actual numbers of deaths at different ages, it is seen that the slight fall between 35 & 40 has disappeared. The death-rate for both sexes shows a continuous though not proportional increase up to the age-period 75-85 and over (the figures for which have been taken together). At this period there is a very slight decrease in the male death-rate. If disseminated sclerosis only lasts, as is believed, for an average time of about 8 years, one would expect the highest death-rate to be at about 45, putting the average age of onset even so late as 37. The figures suggest that either the onset is later or the duration longer.

The differences between the death-rates for Males and those for Females are very striking. Curve for Males, Black; for Females, Red.

It is to be noted that the death-rate for both sexes at all ages here given of about 18.2, is not comparable with the rate of 17.7 per million for 1925, shown on Map D (Appendix) since the figure upon which the latter was based was obtained by taking only certain diagnoses on death-certificates, as explained in the text.

3. Occupation.

This has hitherto excited much discussion; various theories have been put forward, but the general opinion seems to be that this has little bearing on the etiology of the disease. That it has a very definite bearing indeed is part and parcel of the rat-water-spirochaete hypothesis, as will be shown in another section. Here one may quote a few opinions. Jelliffe, writing in the journal of Nervous and Mental Diseases,²⁶ said "Our own statistics bear out those of practically every worker in the field that the type of occupation plays no important role. Hoffmann has well said that often the particular type of clientele of a hospital or clinic seems to show a certain preponderance of one type of occupation, but this is more a matter of locale than anything else. Thus in his own studies he has found a large number of farm workers among his cases, at least 37, but to conclude that work in the garden or field was a predisposing or contributory factor would be nonsense". The authors of "Multiple Sclerosis" (1921)³ said, "It occurs in persons doing skilled

investigated, will be discussed more fully in the following pages.

manual work more often than in ordinary labourers or in brain workers." Medea, Milan,³⁴ wrote in 1924 "Pas de rapports sûr avec les differents metiers". An analysis of occupations of persons dying in 1925 in this country will be given later, and its significance commented upon.

4. Geographical distribution.

Disseminated sclerosis has been noted as occurring in almost every country. The most full work on this side of the problem which has come into my hands has been that of the American Association for Research in Nervous and Mental diseases in 1921.³ They say, "In the United States it seems to occur more in the region of the Great Lakes, at least among young males, while in Europe it prevails more in Northern parts than in Italy and about the Mediterranean Sea". The European distribution I have not considered. A map of the American distribution is to be found in the appendix, and this also, with the distribution of cases dying in England and Wales in the year investigated, will be discussed more fully in the following pages.

5. Sex.

According to American theory, it occurs more often in males than females in the ratio of 3 to 2. In England and Wales, the following sex incidence was noted for deaths in the years indicated.

SEX	YEARS.				
	1921.	1922	1923	1924	1925
M.	283	368	326	366	359
F.	349	348	370	351	374

It is to be noted that notifications of doubtful meaning, if not elucidated in reply to a letter of enquiry sent by the Register Office to the certifying doctor, are classified in what seems to be the most appropriate group. Thus, patients said to have died of "Cerebral Sclerosis" or "Spinal Sclerosis" are classified under disseminated sclerosis. In going through these returns for 1925, I disregarded those two diagnoses altogether, and only took into account "Cerebro Spinal Sclerosis", "Multiple" Sclerosis, "Insular Sclerosis" and "Disseminated Sclerosis", as being in all probability the same disease. The figures thus corrected show -

Males dying of disseminated sclerosis in 1925	343
Females " " " " " "	345

I may say here that I have not been able to attach any particular importance to sex as a factor, except in so far as the occupation was influenced by sex.

6. Race.

The Americans noted a high incidence among Scandinavians and Finns in America, but note that these peoples are aggregated around the Great Lakes. Jelliffe²⁶ says "Certainly our figures would justify Dr. Bramwell's assertion that multiple sclerosis is more common in England than in the United States, and it seems reasonably certain that we make a diagnosis on much the same lines as our English confreres. He quotes figures from Germany, in Jolly's Polyclinic. "1 in every 118 patients suffering with general nervous disorder" and says, "This is a figure double our figure and half that of Bramwell". On this question there can be none but an open verdict at present.

7. Shock and Trauma.

It is almost habitual for patients to start at once to hunt for some cause for their troubles, and the latest shock, mental or physical, is sure to be blamed, with or without cause. Of the series given by Adams, Blacklock and McCluskie, one patient had suffered from chill; had "had a severe fall", and one had been torpedoed. One of Dawson's cases had fallen into baths - a psychic shock certainly; and very many cases of analogous type can be found in the literature. But I do not think that present information warrants the supposition that shock and trauma are determining causes of the disease, though naturally they may be expected to hasten the development of a latent process and excite exacerbations of a chronic one.

8. Infectious illness.

Marie was the great exponent of the view that "sclerose en plaques" was caused primarily by infectious diseases. His long series of cases described the development of the symptoms after different infectious illnesses; and such a sequence is not uncommonly found now. The latest

recruit to the ranks of the evil-doers in this respect is of course encephalitis lethargica. De Tomasi^{2/} published notes of a case where a girl of 8 developed "encephalomyelitis" after influenza, and this in turn was succeeded by multiple sclerosis. One is disposed to look with some scepticism upon such descriptions. Certainly it is disputed that disseminated sclerosis can begin acutely, but I am much inclined to think that the "influenza" so often quoted, along with the "subacute rheumatism" which also crops up, is in truth the early stage of invasion of multiple sclerosis, with malaise and generalised aches and pains. As to the encephalitis lethargica, more than one author has noted an occasional strong resemblance between disseminated sclerosis and this disease. Barré⁵ in particular, after discussing the possible part played by encephalitis lethargica as a factor, says "Nos recherches personnelles sont jusq'à maintenant negatives. Plusieurs fois nous avons observé de malades qui s'étaient plaints de somnolence..... et qui avait à ce moment de la diplopie et des vertiges Cet ensemble reproduit trait pour trait

celui qu'on trouve si souvent au debut de l'encephalite epidemique".

Further remarks on the place of other diseases of an infectious type need not be quoted here; almost everyone who has made any recent contribution of note to the literature is of opinion that infectious diseases do not play a specific role in the genesis of multiple sclerosis, but only act in much the same general way as trauma and shock.

9. Damp and chill.

A suspicion of dampness has long clung to disseminated sclerosis, nor has it completely evaporated in spite of the most ardent scepticism on the part of investigators. Dawson,¹⁹ who grouped cold, fatigue and psychical influences together as factors tending to lower the vitality or favour the emergence of a toxin already circulating in the blood, noted that Krefft Ebing traced a history of chill in forty out of a hundred cases. American opinion was in 1921³ that "the evidence available is strongly against - its being caused by - electrical, chemical, or thermal influences." In general, authors as a

rule mention damp and chill as possible contributing factors, but are disinclined to lay any special stress on them.

ETIOLOGY - THE PRESENT HYPOTHESIS.

This hypothesis may be fully stated as follows. It is suggested that disseminated sclerosis is caused by an organism of the spirochaete type; that variations in the life-cycle of the organism may account for the small total incidence of the disease on the population and for the failure of some investigators to find the organism; that this organism is carried by rats; that it is excreted by rats into water and develops its infective phase in stagnant pools or other collections of water; that it gains entrance to the future invalid either by penetrating the nasal mucous membrane of those patients who develop the disease after falling into water or early efforts to learn to swim, or through the skin of some part of the body, especially the arms, in those patients who develop the disease as the result of

occupational exposure; and that the entrance through the skin is facilitated by continuous dampness of the skin, and very probably also by the existence of dermatitis, occupational or otherwise.

The work of bacteriologists, clinicians and pathologists which formed the grounds of this hypothesis have been discussed. My own share therein concerns the rats, the entrance through damp skin, and the factor of dermatitis; the possibility of entrance through the nasal mucous membrane was suggested to me by Dr. Lovell, of the Bethlem Royal Hospital Laboratory, when I was discussing the hypothesis with him and speaking of the clinical findings.

THE INHERENT PROBABILITY OF THE HYPOTHESIS.

From what has gone before it seems probable that disseminated sclerosis is caused by a spirochaete, and that the organism may have two phases; Rats are known to carry many diseases, they are ubiquitous, they are found in the neighbourhood of water. Professor Beattie⁶ in Liverpool in 1924 suggests that they might be carriers of foot and mouth disease, and it is

known that the wild rat harbours spirochaetes in plenty. Only a few days ago there was published in the British Medical Journal¹⁴ the following very interesting annotation on the report of Sir Alex!Houston on London waters.

"Sir Alexander Houston, on the available evidence does not regard the presence of leptospira as of paramount significance, whether on scientific or commonsense grounds. Leptospira are found to be almost universally present, not only in the raw sources of supply, but also in filtered waters and in pure deep wells. All cultures have been proved to be non-pathogenic, except the cultures from one well, the supply from which has now been chlorinated; and it is satisfactory to know that leptospira are easily killed by minimal doses of chlorine. At the same time, as Sir Alexander Houston says, the possibility of a change from a saprophyte to a pathogen opens many disquieting possibilities. He thinks that rats have something to do with poisoning water and slime, and rendering possible the production of jaundice by leptospiral water. At all events, he cannot believe that infection comes simply from saprophytic leptospira occurring in water, soil, or

foodstuffs. On such a hypothesis the whole world would be jaundiced."

There is another point. The spirochaetes of other diseases - the relapsing fevers, for instance, have a great predilection for a verminous host and an entrance via the skin.

CLINICAL - NOTES OF CASES.

The following is the record from this point of view already stated, of the histories of those patients whom I have seen. Notes on the symptoms, signs and remissions of the disease in these patients are given in the appendix.

Case No. 1, Woman, aged 30, Kitchenmaid.

Doctor, R.C. Turnbull, Severalls, Colchester.

History: She had been employed as kitchenmaid in a hospital equipped with steam ovens; the floor of the kitchen where she worked was temporarily defective and water from sinks and steam pipes used to collect thereon. Rats were frequently seen in this kitchen, especially at night, and persisted in spite of efforts to get

rid of them. When the question of damp was mooted as regards this patient, it was remarked "She was always in trouble with the cook because she wore thin shoes, and did not change her wet shoes and stockings when she had finished her work."

Rats, water, damp skin - present as factors.

Case No. 2, Woman, aged 27. Saleswoman, dry goods.

Doctor Worster Drought, West End Hospital for Nervous Diseases.

History: Nothing in her occupation or her history suggested exposure to the factors under consideration, except the following incident. In August 1924 she was in a punt at Bedford with a friend; they were overtaken by a thunderstorm, and for three hours (owing to some difficulty of navigation of which I have forgotten the details) she sat in the punt in a downpour of rain, being soaked to the skin through thin summer clothing. She does not remember having put her hands into the water, or having wet her feet with river water when getting into or out of the punt. If, however, she had once wet her skin with river water in any way, the maintained dampness of her skin from rain (except where the rain struck forcibly) would encourage the entrance of a skin-

permeating spirochaete. When she reached the town, she had a hot bath and changed all her clothing. In November, 1924, her symptoms developed.

History: Here was water infested with rats (there are rats in Bedford around the river); and persistently damp skin. Whether the patient came into contact with rat-infected water is unknown.

Factors suggested - possibly present.

Case No. 3. Man, aged 30. Engineer's storekeeper.

Doctor, Worster Drought.

History: He was in France during the war. He says that he spent months in the trenches, where there were "dozens of rats". He was there in wet weather. He was wounded by "a bullet across the spine" in 1918, and was paralysed as the result of this. He recovered from these effects, and in 1922 developed symptoms which it is reasonable to attribute to the disseminated sclerosis from which he now suffers. He himself believes his illness to be "the effects of the wound come back". This patient was so overcome with pathological laughter when questioned, that it was difficult to be certain of the accuracy of the answers, but there is no doubt about the fact that he was in the trenches as he says.

Rats, wet, damp skin - all present.

Case No. 4. Male, aged 54. Visitor under Health Insurance Scheme.

Doctor Worster Drought.

History: He was in France during the war, and was employed in road-making, and "pumping water to G.H.Q. and the Hospitals". In some of his billets, he says, "the rats would run over your bed, but you took no notice of them". He was often standing in water at his work. He complained first of the symptoms of his illness in 1925. He was in France till 1919.

Rats, wet, damp skin - all present.

Case No. 5. Man, aged 40. Postman.

Doctor Danvers Atkinson, Hospital for Nervous Diseases, Lambeth Road.

History: He carried on his work as a postman till 1916, and in October of that year he went to France. There he was not in the trenches or in any way exposed to wet in places where there were rats; but in December 1916 he went to Salonika, and there, in trenches and dugouts, he was often very wet. There were rats in these places. On the 16th December - the same month - he had to fall out from a route march on the third day, owing to weakness of the left leg. He recovered from this, and went to Egypt in June of the same year, being able to remain in the army, at work, until March 1918, when he

had to "go sick" with a return of his leg weakness, and other symptoms. If the suggested origin be true, the short incubation period in this case (a fortnight or less) is of interest. One is inclined to think that the real incubation period may be very short, though it may be long before symptoms develop so as to attract attention. Baerwinkel's patient developed symptoms three days after falling into water; and another patient - a small boy who developed nystagmus within a fortnight after his first efforts to learn to swim (in fresh water) - confirms this view. The history of this small boy is not included in the present series, since the diagnosis only rested on nystagmus and increased tendon reflexes.

In the present case, No. 5, wet, rats, and damp skin were present.

Case No. 6. Woman, aged 41. Employed in cable factory.

Case No. 7. Doctor Danvers Atkinson.

History: She was employed latterly as charwoman in a cable factory, but at the time when she developed her symptoms, she was employed as a factory hand. She says that she did not get damp at her work, and did not come into contact with rat-infected water. Closer questioning, however, revealed the fact that it was from time

to time her duty to take her turn at handling, for stretches of an hour or more at a time, a cable in a tank of water. She could not make clear the precise nature of the process, but it appears that she stood by a tank, up to her elbows in water; and that the water of the tank was seldom, if ever, changed, being merely filled up from time to time. There were many rats in this factory at night, and they could be seen running along the pipes during the day. It is interesting to know that she suffered at this time from what she called a "rubber rash" and a "rubber throat", due to the chemicals used in other parts of the works. If the organism be a spirochaete or a stage thereof which gains entrance through the skin, it is likely that a cracked, irritated skin would favour the process.

Factors, rats, water, damp skin - all present.

Case No. 7. Young woman, cork brander in a bottling factory

Doctor Danvers Atkinson.

History: This patient was seen early in the investigation, although placed No. 7 here inadvertantly, and I was not at the time clear enough as to the details of the probable mode of infection, to make sufficiently precise enquiries. I have not been able to see her since. When questioned, she laughed at the idea of

exposure to damp, saying that her work was particularly warm and dry, and that there were no rats in the room in which she worked. Formerly, however, when she first began to complain of illness, she had been working in the damp cellars of the factory, where there were rats and mice. (The omission in my questioning concerned the nature of her work, and the chance of damp feet or hands.)

Factors of damp and rats present. Wet skin - not known.

Case No. 8. Man, aged 28. Decorator.

Doctor Alexander, Prince of Wales Hospital, Tottenham.

History: From 1915 till June 1919, he was in France. He was in a cavalry regiment. He frequently slept in barns, etc. with rats running round, and while dry and comfortable as a rule, was sometimes thoroughly soaked by rain, and once or twice his billets - of the kind described above - were damp. He complained of weakness in one foot and leg in 1925.

Factors, rats, water and damp skin, present.

Case No. 9. Woman aged 19. At home

Doctor Porter Phillips, Bethlem Royal
Hospital.

History: She lived on a farm close to an Essex
river. Her doctor informs me that there is no place
where she would bathe in the river. As she devel-
oped the disease at the age of 18, and a brother at
the age of 14, they may have become infected about
the farm; the patient tells me that the farm is
"over-run with rats".

Rats present. Water present. Damp skin, no
evidence.

Case No. 10. Man, aged 47. Baker's van driver.

Doctor Worster Drought.

History: He has suffered from disseminated
sclerosis for 17 years. Though now unable to work,
at the time when his symptoms began he was driving
a horse van for a large bakery. He did not go into
the stables, his horses being cared for by other
workers, but he went daily to the bakery, and though
he says he was not particularly exposed to damp, he
"might have got wet in the yard in bad weather."
The bakery was "right down by the water side" in the

locality in which he then worked, and he says "The place was running with rats, all over the bakery." The only way in which this man appears to have been exposed to the type of infection sought, was either by standing with wet feet in the yard where rats ran, or by handling in wet weather the sides or cover of the van, which might have been contaminated while it stood in the bakery sheds at night. He was out driving all day.

Factors, rats and water present - damp skin, no evidence.

Case No. 11. Man of 40. Coal carrier before the war.

Doctor Worster Drought.

History: Well until the war. Joined up in 1914, was a horse ambulance driver for the R.A.M.C., and states that when there was comfort to be had he was one of the first to get it. Was never in the trenches, and was hardly ever wet. Slept "in comfort" - in barns with rats running round and over him and his comrades "so long as they were not Germans, we didn't mind them." He was gassed in 1918, and demobilised the same year. His symptoms began in 1920.

Factors, rats, close contact. Wet, and damp skin, no evidence.

Case No. 12. Man. Age 30. Clerk in motor
delivery department.

Doctor Worster Drought.

History: He was in an infantry regiment in France from May 1915 till August 1915. He was in the trenches, and of course often wet with no opportunity of changing his clothing. "Yes, there were any amount of rats there" he said, "They were good pals. We used to feed them when we had our own food; they came quite close. If you didn't give it to them, they took it."

Factors, rats, wet, damp skin, all present.

Case No. 13. Boy of 19. Motor engineer.

Doctor Worster Drought.

History: This boy denied any suggestion whatever of his having come in contact with water where rats might have been; he said that he got petrol and grease on his hands, but nothing more. However, it transpired that his illness first attracted his attention when he was fifteen years old. A year previously, he had learned to swim (doubtless with the usual swallowing and snuffling up the nose of water - which occurring in the early stages of a swimmer's education, may, in my opinion, provide a means of entry for an organism via the nasal mucous membrane) He said

the baths were clean, and there were no rats. The town in which he lived was a familiar Thames-side place; he said that the water was supplied to the baths from a fresh water reservoir, which was a favourite haunt of schoolboys on Sunday afternoons. The boys went there with the object of chasing and throwing stones at the rats which were abundant. This boy had a brother - healthy - who never swam, or attempted to learn. As noted, public baths, while as a rule, fairly clean from the point of view of the swimmer, are doubtless splendidly contaminated with organic material, from the point of view of the organism, by the time the days for renewing the water come round. They would appear to provide a good nidus for the development of a secondary infective phase, if such there be.

Factors, rat-contaminated water, and damp nasal mucous membrane, or swallowing of such water - present.

Case No. 14. Man aged 34. Master furrier.

Doctor Yealland. West End Hospital
for Nervous Diseases.

History: This patient was of foreign birth.

He was not a swimmer, but said several times "I did

dip in the sea, when I had a holiday." The etiological factors were not active then, but presumably when from time to time he helped with the work in his shop. He only did this on occasions when business was very pressing; the skins which he handled were worked in a damp state, and he admitted with reluctance that there were rats in the shop. "Not more than two," he said. When I saw him, he was suffering from an irritative rash on his lip and chin; and his skin reacted easily to irritants, its unhealthy state and probably increased susceptibility to organismal penetration would counterbalance the scarcity of opportunities for infection. That his ectodermal tissues were none too immune is borne out by the fact that he had at one time conjunctivitis. Wassermann negative. His business address was within 1500 yards of Regent's Canal on one side, and 1600 yards of the Thames on the other.

Factors, rats, water, damp skin - all present.

Case No 15. Man aged 36. Occupation, Tailor.

Doctor Yealland.

History: This patient had suffered from disseminated sclerosis since the age of twenty; he had been

for that reason unfit for war service; He did not swim, nor bathe except in the domestic type of bath; he was employed as a tailor in a dry warm room with no rats; he never damped the cloth with which he worked; he spent his holidays by the seaside, mostly on promenade and beach; there had never been rats in any house in which he lived. The only suggestive fact was that the street in which he lived was crossed by a canal and ran alongside docks for some distance - it's greatest distance from water of one or other of the docks in the neighbourhood was half a mile. Otherwise there was no sort of evidence in favour of the etiology suggested.

Factors, water, rats, damp skin - all denied.

Case No. 16. Woman aged about 30. Occupation, Nurse.

Doctor Worster Drought.

History: The patient's family history, given in the appendix, suggested a neuropathic inheritance. She was interested in the questions I put to her, and understanding fully the points at issue, was most anxious to give every help and furnish all the information she could. She had never been particularly robust, and for that reason, her swimming was limited. But she did swim occasionally in fresh waters of rivers

or lakes when opportunity offered. She was "not a good swimmer." Her sister, who also had disseminated sclerosis which had developed considerably before this patient showed symptoms, was a keen swimmer in salt and in fresh water. There was no sort of evidence beyond this, in spite of the patient's willingness to discuss small details of her history. Unless it were that as a family they were particularly susceptible to attack upon the nervous system, nothing can be said in favour of the hypothesis under consideration.

Rats , water, damp skin - not sufficient evidence, but not impossible on history.

Case No. 17. Woman aged Mantle maker.

Doctor Danvers Atkinson.

History: It is of interest to note that this patient had anterior poliomyelitis in childhood, leaving her with a damaged left leg. She was under out-patient treatment for "tiredness", according to her own diagnosis, in a hospital for Nervous Diseases, when she had what was presumably the first symptoms of her present illness. (See Appendix) She said that she never got wet or damp. Her work as mantle maker was carried on in dry, rat-free surroundings. When questioned, however, she informed

me that she had been doing most of the work of the house at home for some considerable time before her illness began; the work included domestic washing and washing of floors, etc; she lived in a London district "right on the river" i.e. Thames; and there were "lots of rats" in the house and very many in the garden. Susceptibility to infection, along with exposure thereto, may be suggested as etiological elements.

Factors. Rats, water, damp skin - all present.

Case No. 18. Woman aged 55. Librarian.

Doctor Worster Drought.

History: At the time of onset of her illness she was supporting herself, after the death of her husband, by daily work, cleaning and charing. She did a great deal of washing, both of dishes and floors, for various employers, but never worked in cellars, never saw a rat in her own or any employer's house, and did not live in a particularly well-watered district. There was a small brook some mile or more away - nothing more. The most that can be said is that the operation entailed frequent and constant dampness of the skin of hands and arms.

Factors, damp skin, present. Rats and water - no evidence at all.

Case No. 19. Woman aged 35. Domestic work at home.
 Doctor Yealland.

History: Patient's mother, seventy years of age, suffered according to the statement of the patient, from the delusion that she had no money and was going to be ruined financially. The patient lived in Bow, in an area roughly rectangular, a mile across and a mile and a half long, having on the North side Duckett's canal; on the West, Regent's canal; on the South, Limehouse Cut; and on the East, Bow Creek, these waterways joining one another to form a complete chain surrounding the area. The patient lived somewhere about the centre of this area - not at all close to the water. She lived in a basement house, very damp. The water used to run in from the street level and down the walls in wet weather. There were mice in the house, and rats in the neighbourhood. She once saw a rat in the yard, and believed it had come from a certain hole in the damp scullery, but she never saw a rat in the house. Patient's work in the house, to which she devoted much time and thought, included washing floors, and drying the damp walls.

 Factors, Water and damp skin present - Rats probable.

Case No. 20. Woman aged 38. Cook.

Doctor Macnamara, West End Hospital
for Nervous Diseases.

History: Patient was for eight years in service
in the same house, as cook, the house was on Wimble-
don Common, but "not near the marshy end." She
used to scrub the kitchen floor, etc, but the house
was dry and she states that there were no rats there.
The only point to note is that Wimbledon is also
between two waterways, and is a damp neighbourhood
on the whole. Patients died of the disease in 1925
in Wimbledon, Croydon and Mitcham.

Factors, damp skin present. Water doubtful,
Rats, no history.

In analysing these case-histories there are
several points of interest. In the first place,
it seems to me that the possibility of infection
in the wet, rat-infested dugouts and trenches
inhabited by soldiers during the war, is one which
needs careful handling. While it occurs in the
history of those patients noted above to have
developed disseminated sclerosis, it also occurred
in the history of thousands more who did not develop
sclerosis. While there is ample suggestion from

the bacteriological side there may be an explanation in the change in the infecting organism; it seems sounder to me to base any hypothesis of infectivity on the histories of the female patients, and on those of the men who were not in the fighting forces. I am sure myself that many men did begin their disease as a result of infection in France and elsewhere, but I can find no note of the incidence of disseminated sclerosis in the war in our official Medical History of the War; nor have I found notes of papers on this in medical indices of published work. Certainly this has been done in Germany, but I have only seen the fact mentioned, and have not been able to see the publication nor find any precise reference thereto.

Therefore, leaving out this very important factor, we come to the incidence on other people. It is to be noted in the first place that out of 14 cases without a history of active service before the onset of the disease, 10 of them admitted that rats were in their houses, or places of work. Of these said 14 patients, the occupations of 10 were either for gain or in domestic duties at home were such that their skin was exposed to damp in one place for a considerable time. Some of them showed a

neuropathic family history in addition. There is also the interesting patient who began shortly after his first efforts to swim - a case that I classify with those of Dawson¹⁹ and Baerwinkel,¹² who has fallen into water. Two or three - the patient with rubber rash, the furrier, and the ex-charwoman, gave a little evidence of the dermatitis element.

STUDIES OF THE HISTORIES OF PATIENTS
DESCRIBED BY OTHERS.

Here I propose to bring forward some evidence from writings over a long period, to support the hypothesis. To simplify and shorten this, I shall note here not only the factor of exposure to damp, but also any suggestive occupations which I have been able to find in recorded cases. This factor of occupation is the subject of further study in the statistical section of this work, and I shall not now make any comment on the occupations mentioned on this and the subsequent page.

In searching for this evidence I have been confronted by very many articles and annotations where the patients are described with such brevity that nothing can be known about their exposure to

the factors for which I sought. Thus, I Marie³⁰, in his series of 20 cases following infectious illness, says little about them except in four, whom he describes as Government employee ("employé d'administration"), workman, "artist lyrique", soldier, and baker. The others are described by a mere note of sex and age. The following are some exceptions to this rule of brevity, however.

II Charcot¹².... Baerwinkel's patient who fell into water.

III Dawson¹⁹.... Patient who fell into baths (the swimming baths in Edinburgh are fresh-water baths)

Occupations. - Dawson

Nine patients described, amongst whom were - Kitchenmaid; woman in poor home surroundings; trained nurse; baker's shopwoman; cabinet maker; typist; healthy girl fond of games.

IV Moxon³⁵....

Occupations.

Wife of a coachman, apparently living where he was employed, since she assisted in his employer's house.

V Spiller.....⁴⁸

Patient described as follows:

Labourer. "Two years ago last winter he worked four or five hours one night in the hold of a vessel with nothing on but trousers, drawers, shoes, and stockings. Four days after this exposure he had to work seven hours in the hold of a ship shovelling wet coal. While shovelling, he stood in the wet coal, and afterwards had to sit in the wet, shivering, while waiting for more coal"

A patient who said that illness began after residence in a damp house.

VI Adams Blacklock Dunlop and Scott.²

- 1 Clerk - following on a severe chill.
- 2 Female piano teacher.
- 3 Apprentice plater. In 1917, following trench fever.
- 4 Male.
- 5 Plumber.
- 6 Female, aged 18, following attack of subacute rheumatism.
- 7 Male, coal miner. Following being blown up by mine in 1918.

STATISTICAL

- 8 Clerk.
- 9 Purser. Following on a fall.
- 10 Engineer, torpedoed and dropped into the sea.
- 11 Miner. In Gallipoli in war.
- 12 Nurse.
- 13 Male. Following attack of influenza.
14. Chaffeur.

VII Sougus.

- 1 Commercial employee.
- 2 Plumber.
- 3 Woman
- 4 "Madame"

The histories given by Baerwinkel's, Dawson's and Spiller's patients need no comment. As regards occupation, one may note in this short list a cabinet maker, a baker and a baker's shopwoman, and two plumbers.

STATISTICAL.

These statistical investigations have been carried out at Somerset House, where by the kindness of ██████████, The Registrar General I was allowed to refer to the necessary books. Several factors militate against anything like accuracy, and it may as well be said quite definitely that no sound deduction can be made from ^{the} figures so obtained. It seems to me that the results are very suggestive - but beyond that one cannot venture to go. Some of the difficulties were, the doubt as to the diagnosis of all those cases returned as "spinal sclerosis" or "cerebral sclerosis" merely, who had consequently to be excluded from the study; the inability to compare patients with occupied males on one hand and unoccupied males on the other, since such a large proportion of those who had died of the disease were classed as "retired" without any indication as to whether they had retired before acquiring the disease or on account thereof; doubt as to whether a "dressmaker", "daughter of a farmer" was to be classed with the textile workers or with the agricultural population. As regards domicile at time of death, while the home address was

taken, and not the hospital or other institution in which the patient died, yet there was no means of knowing whether patients who had died in Bath, Hove, Brighton, and other places had been there when the disease was acquired or had moved there as invalids, so that this side of the work is rather unfruitful. The greatest fallacy of all lies in the smallness of the numbers dealt with. Without any doubt, unless some thousands of figures were studied, one could not say with certainty that disseminated sclerosis did or did not tend to occur in definite localities, or that it did or did not tend to affect those pursuing this or that occupation.

While the figures from 1921 onwards are noted by the Registrar General, they occur scattered through the registers in the haphazard order of time and place which corresponds to the inscrutable wanderings of death itself in the houses of England and Wales, and the task of dealing adequately with these figures would be very great. The figures for the year 1925 were found from two hundred books of register, and I do not think that the end to be gained by further search would

quite justify the means. The suggestion is present in these few records - confirmation can only come from the bacteriologist.

I may say that in dealing with these figures I tried as far as possible to choose in matters of doubt so as to give what advantage there might be to the opposition to the present theory, so as to enhance the value of what was positive. Thus the dressmaker to whom allusion has been made was classed as a dressmaker, though one imagined that she picked up her infection at home, on the farm.

OCCUPATION.

In the appendix to this paper is given a full analysis of the occupations of persons dying in England and Wales from disseminated sclerosis in 1925. When this analysis had been made, some of the figures where the numbers of deaths were high, were taken out, and the expectation of death of persons so employed was compared with the actual deaths. For instance, taking farmers as an example, the number of farmers over the age of twenty was compared with the total number of occupied and retired males over twenty. That comparison

was made from the figures given in the last census return (incidentally another source of error, for who knows how the number of farmers may not have varied since then?). Taking then the proportion of farmers to the male population, a calculation was made on this basis as to the expected deaths from disseminated sclerosis. To make the matter clear, had the proportion of farmers to the rest of the male community been one-twentieth, and the total numbers of death from disseminated sclerosis been forty, the expected deaths among farmers would have been two - that is to say that is the number that would have been expected to die if the disease had shown no special tendency to attack farmers. The calculation was:

<u>Farmers over twenty</u>	x {	Deaths from disseminated
Males over twenty		sclerosis over age of twenty.

The numbers under twenty were excluded because

the numbers of deaths from disseminated sclerosis during this period was so small that the comparisons were much more accurate as shown. Had it been possible to make further corrections for age, the figures would have had more value, but it was not possible to make further calculations when the initial number was so small.

The following list shows some of the results.

474	Carpenters	175,000	1	0.00057
532	Painters and Decorators	150,000	1	0.00067
012	Garbage	150,000	1	0.00067
735	Seaman	100,000	1	0.00100
253	Plumbers	90,000	1	0.00111
180	Moulders	80,000	1	0.00125
237	Grinders	70,000	1	0.00143
923	Window Cleaners	60,000	1	0.00167
	All Trades	11,000,000	10	0.000091
900	Domestic Service including Cooks	300,000	10	0.00333
	Female Clerks	200,000	10	0.00500
	All Females	10,000,000	10	0.000100

ENGLAND AND WALES

Census Code Number	Trade	Census Population, 1921 (20-Upwards)	Actual Deaths Registered	Expected Deaths
042,043,047	Miners, below Ground	042) 472,716) 043) 72,566) 623,618 047) 78,336)	20	19.17
939	Clerks	388,857	11	11.95
011	Farmers	242,812	16	7.46
022-24	Farm labourers	422,416	15	12.98
700-709	Railway workers	280,738	11	8.63
474	Carpenters	179,917	9	5.53
592	Painters and Decorators	141,951	7	4.36
013	Gardeners	173,272	8	5.33
735	Seamen	36194	3	1.11.
252	Plumbers	40,263	3	1.24
180	Moulders	62,980	3	1.94
237	Grinders	13,870	2	.43
923	Window Cleaners	12,528	2	.39
	All Males > 20	11,062,292	340	340
900	Domestic Service including cooks	826,219	10	21.97
	Female Clerks	265,522	6	7.062
	All Females > 20	12,820,898	341	341.

MINERS show just about the number of deaths that would be expected from their proportion in the community. Reference to the occupation table in the appendix will show that many of them were actual hewers of coal, as would be expected. For the purposes of calculation, only the underground workers were taken, to compare with the corresponding census group return.

CLERKS have a fairly heavy incidence, and here one must remember that clerical work is often the last occupation of the invalid. I can think of two or three instances - the Librarian of the present clinical series of cases, who before her illness was a charwoman; two ex-service men, who though disabled as wage-earners by cerebral wounds, occupy their better moments in light clerical work; and a mental hospital attendant who through some physical ailment not of the nervous system, left the wards and became a telephone operator and clerk. Such change of occupation must be very frequent.

FARMERS are affected in more than twice the degree which would be expected did they merely share incidentally in the disease. It is of particular interest to note that the FARM LABOURER does not

suffer nearly in so great a degree. Perhaps two things account for this - firstly that the farmer, I think, in England, is more likely to be working among his cows and horses than the average farm labourer. The damp of cow-sheds and byres and barns from the presence of rats and the neighbourhood of the farm water supply, is perhaps more likely to be infected than the damp of the open fields. Secondly, the age must be noted. A farmer's son working on a farm is more likely to be classed in England as a farm labourer than otherwise. There are more farmers at sixty than at thirty. In other words, a certain proportion of those who acquire the disease as "farm labourers" at thirty or forty will be farmers by the time they die of it at forty five or sixty. Reference to the appendix shows that there is a large number of FARMER'S WIVES who have died of disseminated sclerosis. This is very striking, and I think suggests infection from the rats around the farms and often in the farmhouse. But although comparison is not possible here, partly because there is no group with which to compare them, and partly because wives, widows and daughters of no other defined occupation have all been classed in

the disseminated sclerosis death group of Wives and other relatives. (See Appendix)

Other agriculturalists who suffer heavily are GARDENERS, who have eight actual deaths as against expected 5.3.

RAILWAY WORKERS form a rather indiscriminate group, with again a slightly raised incidence.

Next on the list come another section with half as many deaths as the expected number, added to their total - i.e. 9 actual deaths as against an expected death figure of 5.53. among CARPENTER'S. Why they should have such a heavy incidence is not at once easy to see. But many carpenters work in circumstances of damp. Carpenters work among ships and docks, and among the wet foundations of new houses. However, the explanation is not very obvious. A factor may be the possibility of some of those classed as carpenters taking their share in work of the nature which would induce dermatitis. A very striking group which it has not been found possible to analyse is that found in the appendix among those concerned with FURNITURE i.e. the two wives of furniture dealers, the wife of a furniture remover

the wife of an upholsterer and the wife of a cabinet maker. One does not know how many women there are attached to these industries who have no other registerable occupation, but they must be few compared with the rest of the population. Yet they have no fewer than 5 deaths out of a total female death-roll of 345. I can but connect this with the suggestion of dermatitis. Furniture-polisher's dermatitis is well-known. These women, though it is perhaps carrying speculation too far to suggest it, may have spent their time partly in domestic work and partly in furniture polishing, thus acquiring a spirochaete infection on roughened arms.

PAINTERS AND DECORATORS have also more deaths than their mere distribution in the population would account for, and one may suggest that this is linked to the frequent washing of walls and mixing of distempers with which these people are from time to time engaged.

The rest of the analysis concerns small figures and it might be said that the results were here particularly fallible. I understand, however, from those who deal with such things, that the chances of error are much less in dealing with a few deaths among any

reasonably large section of the population than in dealing with a large number of deaths in a small population. For some unknown reason these small figures - say two in a given section of the community, tend to vary very little from year to year.

SEAMEN, here, were abstracted as a matter of interest, but the result is really valueless, since on the one hand the death number could not include more than three of those shown in the appendix under "ships", for other persons were adjudged to other occupations. Thus, a naval officer is not a "seaman," but a member of the "defence forces." The other factor - the census return - is also here very false, for the census only counts the sailor in port, and takes no note of those upon the sea. But as far as the rest are concerned - Plumbers, Moulders, Grinders and Window Cleaners, who stand among drains, pour water upon iron where rats are attracted by the flour mixed with the sand in the mould, work with wet knives and tools to counteract sparks and dust, and clean windows all day (doubtless with their share of washerwoman's dermatitis) - as far as all these go, one may call the heavy incidence "co-incidence", - yet it is strange that each co-incidence should tell the same way.

Some of the other un-analysed figures may be noted. The appendix table shows a large number of engineering, cotton, woollen, and general labouring employees. These have not been analysed for reasons connected with census occupation groups. Into the details of all these I need not enter - one example will show the sort of reason. No census distinction is made between cotton and wool workers, and there is a separate class for spinners, another for winders, another for warpers, another for cloth lookers, and another for parcellers. No analysis is of value based upon an incidence of 1, and the question had to be left. Nevertheless, the general impression is left of heavy incidence in these trades. I understand that wool and cotton are both twisted wet - not only is the atmosphere humid, but the hands of the workers are engaged with wet material. I can only say that where it has seemed possible to make analysis, that analysis has been made, and that I have had the advantage of expert advice in this matter.

One or two of the "miscellaneous" occupations at death, while from their almost unique incidence they partake more than ever of the fallacies dependent on small numbers, coincidence and accidental variation,

are yet so suggestive that they bring pictures at once before the mind. One sees the "daughter of the captain of the barge," on a hot summer's day in some quiet canal, washing dusters in the stagnant water, not even hearing the quiet smack of the water rat as he slips into the canal. Or, the "foreman of the mineral water works" stands, his boots in holes, on the wet floor, arguing with the engineer, while the little bright eyes of *Rattus Rattus* look out from behind the pipes. Or, "the wife of the town hall attendant," with tired face, scrubs with wrinkled hands the great Hall floor for the fourth time in a week, - that floor where last night the rats made merry with the odds and ends of the Hospital Sale buns.

But these pictures are those of the imagination, and have I fear no right in a serious discussion, however attractive they may be as a relief to the monotony of statistics.

One more point only remains to be mentioned. Reading the "Introduction to Dermatology"⁵⁴ the other day, I was much struck by the list of those who suffered from occupational dermatitis. With the order

of the names changed, the list is as follows. Surgeons, pathologists, photographers, silver-platers, dyers, tanners, builders, plasterers, carpenters, housewives, packers, bricklayers, bakers, and washerwomen. We may take it that the first four work with solutions too strong for the comfort of the ordinary microbe. Of the remainder there is hardly one which is not represented in the occupational table in the appendix, and the part played by the rubber rash of one patient and the dermatitis of uncertain etiology in another of the present clinical series has been discussed.

Thus there is a mass of evidence, all of it flimsy but all of it pointing in the same direction, to the effect that occupation has a bearing upon the etiology of disseminated sclerosis. It is not "nonsense to conclude" that work in the garden or field is a predisposing factor when the wet and rats in those fields are considered. And it is easy to understand why the "clientèle of a hospital or clinic seems to show a preponderance of one type of occupation". In the Lancashire towns the cotton twisters will have more than their share; in London the labourers and plumbers, and in Lincoln the farmers.

GEOGRAPHICAL DISTRIBUTION.

Geographical distribution in America. (Map A, appendix.)

In "Multiple Sclerosis,"³ the Association for Research in Nervous and Mental Diseases published in America in 1921 a map, showing the distribution of disseminated sclerosis in the U.S.A. in that year. Their incidence rates are based on the proportion of cases of disseminated sclerosis to cases of nervous disease of other types, and are much more valuable than the rates which I have obtained for this country, which are merely death-rates. It is noted that the cases occur chiefly round inland waters. Of this the authors say, "It is of great interest that the states of high ratio for multiple sclerosis are adjacent states, bordering on the Great Lakes." "Various hypotheses are suggested for these facts. One is that there is some race inhabiting the Great Lakes region and the state of Washington that is especially subject to multiple sclerosis, as well as goiter, chorea, and cardio-vascular defects. One thinks of the big Swedes that live in this country."

Reference may be made to Map A, in the appendix. This is diagrammatic, based upon the map published in "Multiple Sclerosis." I hoped

to include an actual specimen of the original map in this work, but have as yet had no reply to my request for permission to do so. If the adapted map be studied it will be seen that the only considerable body of inland water in the neighbourhood of which there is no heavy incidence, is the Great Salt Lake. Whether the waters are too alkaline for the spirochaete or the surrounding country too arid for the rat, I do not know.

There is a heavy incidence around New York, on the Hudson River. It was said to me recently "Rats on the Hudson at New York? It is no exaggeration to say you meet them in flocks, moving along the banks and stopping to eat something, and then going on again." I have no reason to doubt this statement, made to me in good faith, though perhaps it is a little over-emphasised.

Referring to American waterways in 1906, Pratt⁴² says. "The St. Lawrence River and the Great Lakes whose waters flow through it into the Atlantic form a continuous waterway extending from the Fond du Lac to the Straits of Belle Isle.

Emptying into the St. Lawrence are the Ottawa and Richelieu Rivers, connecting with the timber forests of Ontario and Lake Champion."

And again "The Mississippi is navigable from St. Paul to New Orleans," and "The distributing points on the lower Mississippi were Memphis, Vicksburg, Natchez, Bayona Sarc, Baton Rouge, and New Orleans."

Comparison of an ordinary map of the U.S.A. with the map in the appendix will show that it is precisely in relation to these places that disseminated sclerosis is excessive not in number of cases (which might merely mean thickness of population) but in proportion of cases. One cannot help feeling that the most important races inhabiting those regions, from the point of view of the spread of disseminated sclerosis, are *Rattus Rattus* and *Rattus Norvegicus*.

Rat distribution.

Mr. Boulanger, of the Zoological Gardens, London, kindly discussed rat distribution with me, and I understand from him that these two types, while formerly rather sharply distinguished in distribution,

are now both found in places where formerly one or other alone might have been expected.

Where Spirochaetosis Icterohaemorrhagica is concerned, Manson Bahr²⁸ says, "The natural reservoir of infection would appear to be the Rat (*Rattus rattus* and *Rattus norvegicus*), ... The organism is found as a harmless parasite in the kidneys of wild rabbits and mice, and is excreted in their urine."

I have not been able to go into the question of actual numbers or proportions of rats in different places, but think that aggregations of them may be expected near water, especially in thickly populated areas.

Geographical Distribution in England and Wales

The distribution of patients dying from disseminated sclerosis in 1925 has been worked out in two ways. In the first place, the actual place of death was noted upon a map, (Map B. appendix). (These places of deaths were corrected for "transferable deaths" - but no knowledge was obtainable as to the former residence of patients whose illness might have induced them to move to

another part of the country years before death). This system of mapping has very little value. Numbers of cases in London may merely mean that London is thickly populated. But it was thought that some points of interest might emerge. In studying the Map of London (Map C. Appendix) it is seen that in spite of all the factors which might make a patient move from the place of incidence, there is a just discernible tendency for an aggregation of cases around stagnant waters. Not so much round the Thames as round the Canal Basins, especially at the St. Pancras and Hoxton Basins of the Regents Canal. Little stress can be laid on a tendency so slight, however.

The Map of England and Wales shows one or two interesting points. Why should Cornwall have so many cases? Why should Peterborough and Lincoln have many cases? These points will recur in considering death rates.

What is of much more value, the death rates per million of population have been worked out in certain areas. England and Wales for administrative purposes is divided up into

"Administrative Counties" and "Administrative Boroughs." The numbers of persons dying in those areas has been considered, and wherever it appeared possible to work out a death rate for such an area, this has been done. It was no use, for instance, working out a death rate on the strength of one death from disseminated sclerosis in a given area.

For advice on all these points, as well as for help with some of the calculations, I am greatly indebted to the staff of the Registrar General. Without their advice I should have fallen into many more errors than those which have doubtless involved me without my knowledge.

The results of these calculations are shown in the smaller map of England and Wales. (Map D. Appendix). This map shows only the death rates for 1925, and the figures are consequently liable to be affected by mere accidental variation. The highest death rate is in the Soke of Peterborough, where the rate is 103.3 per million instead of 17.7. There is certainly a canal in this area, and the chief industry I understand to be brick making. In Merioneth the high incidence is due to the occurrence of 4 cases in a

thinly populated county. Norwich city had 4 cases die of the disease in the third quarter of the year. Whether the heavy incidence in Cornwall is associated with primitive conditions and poor housing, those who know the county will be better able to judge than I. The Midlands perhaps because they have so many persons employed otherwise than in the exposed occupations, suffer unexpectedly little. On the whole, I find the results of these investigations very difficult to interpret, but it may be said:

1. England and Wales are small and patients may easily migrate from one district to another.
2. Death rates are probably not clearly related to incidence rates, on account of the long average, and longer possible, duration of the disease.
3. Figures based upon the returns for one year only are too small for anything approaching accuracy. I have indicated the amount of work which would be involved in searching further.

PRACTICAL CONSIDERATIONS.

If there be any truth in the suggested etiological sequence, a few practical points emerge. Clinically, in searching for this sequence, it seems advisable to enquire about wet hands or feet as much as about damp in general. The occupations at and before the time of onset should be enquired into with more care than the occupation at the time of seeking medical advice.

Bacteriologically, one would like to see experts attempt the transmission of disseminated sclerosis to animals via the skin - say by applying to the skin water to which the C.S.F. of a suitable patient had been added. Culture might be attempted, as suggested by Fischer²², by adding the C.S.F. of a patient to a culture of nerve cells. Fischer says that Smyth is right in supposing such methods to be useful, but adds "perhaps the complex technique frightens." And doubtless that is true.

Experienced workers are alert for changes of phase - one would like to see such possibilities kept in mind by every interested enquirer, experienced or otherwise.

Prevention of leptospira in the tanks of printers, cable-workers, and cotton-workers, and in the buckets of washerwomen and window cleaners may, according to Sir Alexander Houston,¹⁴ be easily carried out by the addition of chlorine. Whether the non-spirochaete phase would survive such treatment remains to be seen.

Rats are ubiquitous, and so long as there are ships, seem likely to remain so. Ordinary rat-destruction campaigns may well be continued, and perhaps the balance of nature in regard to bumble bees, old maids, and clover would not be unduly upset by the addition of cats to those factories where rats are worst. Of the "bête lunatique"⁵³ Van Vechten makes the following remarks.

"In England cats work for the Government in offices, barracks, docks and workshops. There are at least two thousand felines so employed, and they are all on the pay-roll, receiving a shilling a week..... The National Printing Office of France employs a large staff of cats to guard the paper from rats and mice.

Vienna has official cats and the Midland Railway in England has eight cats among its employees. Cats are kept in all the large United States Post offices and in the military magazines. A writer in the Spectator tells of the regret felt in a large London factory when the 'best foundry cat' died. The sand moulds for making casts in the foundry are mixed with flour. Mice eat the flour and spoil the moulds. Cats are kept to kill the mice but they have to be taught not to walk on the moulds or to scratch them up."

There is only one more point to mention. Are disseminated sclerosis and spirochaetosis icterohaemorrhagica variants of the same disease? This is perhaps a possibility, but there is no clinical evidence to suggest it.

SUMMARY.

In considering the development of knowledge about disseminated sclerosis it has been seen that there is a considerable body of opinion in favour of the view that the disease may be infective, although the question is not yet settled.

The various and intermittent symptoms, while not wholly like those of any other disease, show a certain resemblance in one of their common points of attack to those of one of the African Relapsing Fevers of spirochaetal origin; and in their remission to the quiescent or stationary periods seen in General Paralysis of the Insane, also spirochaetal.

From a study of the pathology it is found that many workers are in sharp opposition in the interpretation of microscopic appearances, some believing these to be degenerative and some believing them to be inflammatory in origin.

The most recent pathological work investigates the bio-chemistry of the affected tissues. I think it is not untrue to say that the opinion of the majority of experienced modern pathologists is becoming more

and more turned towards the validity of the inflammatory or infective origin.

Bacteriology is in a similar state of indecision. A review has been given of the results of experimental work by different investigators, from which it will be seen that many have failed to find any organism or to cause symptoms of disease in animals inoculated with material from patients suffering from disseminated sclerosis. On the other hand, among those whose results have been positive, there is considerable agreement in throwing suspicion upon a spirochaetal organism resembling that christened spirochaete argentinensis by Kuhn and Steiner, as the cause of the illness. This organism is described as being of the leptospira variety, and bearing a very close resemblance to the leptospira icterohaemorrhagica.

Having regard to the theory put forward in this paper, it has seemed wise to collect evidence on the existence of life-cycles, or variations of phase, in the spirochaete group. As Adams' has said, in speaking of disseminated sclerosis, "the non-discovery of spirochaetes in the media employed does not exclude them from an etiological role on account of the

difficulty of detecting so delicate an organism and our ignorance of possible phases in its life cycle." This question of non-spirochaetal phases in the life of organisms belonging to the group named as spirochaetes, has been gone into in some detail. Notice has been taken of the fact that many of the spirochaete group are maintained in verminous hosts and gain entrance through the skin of the patient, and that leptospira icterohaemorrhagiae in particular, being maintained in rats and reaching the skin of the patient through the medium of infected water or slime, provides an interesting parallel.

The older theories of etiology have been reviewed, and may be summarised by saying that there is no one theory which at present holds the field. There is some variation in the incidence of the disease in patients of different ages, race, or sex, but the meaning of this is not understood. Heredity, and previous shock, trauma, - are looked upon as exercising rather a general than a specific predisposing effect. Illness, which had a notable protagonist in Marie, is commonly placed in the same category. It is suggested that "influenza",

"subacute rheumatism" and rarely "encephalitis lethargica" may be in reality guises assumed by disseminated sclerosis at its acute onset.

Dampness and chill are mentioned by nearly every writer, but no precise interpretation of their action is given; occupation, varying in the patients of different clinics has not been found previously to have any ascertainable influence; the geographical distribution of the illness has not been explained although most interesting facts came to light in American work on this aspect.

In the present investigation attention has been directed to the factors noted in last paragraph. 20 patients were seen, and of those some 17 gave a history of such exposure to wet; as of hands feet, or of nasal mucous membrane in sudden immersion in water, as would give an opportunity for the entrance of a skin penetrating organism, and association with rats was traced in 15 out of the twenty.

An analytical study of the occupations of 688 patients dying of disseminated sclerosis reveals an unusually heavy incidence on farmers and gardeners, and, so far as may be judged from small

figures, on plumbers, window-cleaners, grinders, and others who work with wet materials. The predisposing effect of occupational dermatitis is suggested both clinically and statistically.

Geographically, the distribution in America around the Great Lakes, where rats are known to exist in large numbers, is very striking.

In England and Wales the distribution of deaths from this disease in 1925 has been worked out, but the figures are too small for any very precise inferences to be drawn, though they seem to agree.

Finally, a few practical suggestions are made, designed to test the validity of the theory and to counteract the workings of the etiological factors, if these be accepted as such.

CONCLUSIONS.

1. That a large proportion of patients suffering from disseminated sclerosis give a history of exposure to damp, especially of the hands and feet.
2. That a large proportion give also a history of association with rats at home or at work.

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3. That a study of the occupation of those dying of the disease in England and Wales in 1925 shows a heavy incidence in those occupations which would expose the worker to the above etiological factors.
 4. That the geographical distribution of cases in America, and to a lesser extent in London round inland waters is in keeping with the clinical and occupational findings.
 5. That bacteriological opinion suggests a leptospira related to leptospira icterohaemorrhagiae as the casual organism of disseminated sclerosis, and that there is a strong probability that these organisms have an infective and a non-infective phase.
 6. That in general the association of rats, damp, and disseminated sclerosis is too frequent to be dismissed as merely accidental, without further investigation.

APPENDIX

- I Clinical Notes
- II Bacteriological Work
- III Occupation Tables
- IV Maps.
- V Bibliography

I FURTHER CLINICAL NOTES ON PATIENTS ALREADY MENTIONED

Case No.1. Woman aged 30.

Transient dimness of vision, with central scotoma. Later numbness of left leg and heel, also transient. A year from first symptoms, vertigo, vomiting, and depression. Aching in left leg and difficulty in walking owing to spasticity; later, numbness in left hand. On examination Knee-jerks exaggerated, plantar reflex extensor on both sides; transient ankle clonus; absent abdominal reflexes, ataxia and Rombergism. Nystagmus developed later.

Case No.2. Woman aged 27.

Previous illnesses Diphtheria and Scarlet Fever. Chicken-pox. Pneumonia at age of 2. Pleurisy. Rheumatism.

Family history, nothing to note.

In Nov.1924, three months after three hours' exposure to wet, developed weakness and dragging of right leg. Later, numbness from the waist down.

Difficulty in walking. These all improved.
No sensory loss. On examination, absent
abdominal reflexes, right knee-jerk more active
than left; right extensor plantar reflex.
Bilateral nystagmus. Very slight intention
tremor. Has been treated as In-Patient at
West End Hospital for nervous diseases, and has
improved.

Case No.3. Man aged 30.

Following recovery from spine wound which
paralysed him in both legs, he was discharged
from hospital. Later complained of feeling
tired, and of laughing when he did not want to.
When seen, he was laughing too much for a full
history to be obtained from him, but the follow-
ing signs and symptoms were or had been present.
Visual defect - cannot read. Staccato speech.
Blushes and bursts into laughter of uncontrolled
and apparently unprovoked type. Too unsteady
to stand. Marked intention tremor, ataxia both
hands, exaggerated tendon reflexes, absent
abdominal reflexes, bilateral plantar extensor
response. At one time had attacks of vomiting.

Case No.4. Man aged 54.

Family history, nothing to note.

Healthy until onset of present illness.

Twelve months ago noticed his walk was staggering. Numbness on outer side of left thigh. Later, began to feel nervous "feels all tumbled to pieces." Speech drawling and hesitating. Left intention tremor, ataxia left hand, left arm tendon reflexes more active than right. Diminished right abdominal reflex. Slight nystagmus in left eye and marked nystagmus in right eye. The numbness has gone and the weakness improved, and he does not now suffer as he has done from precipitate micturition and nocturnal enuresis.

Case No.5. Man aged 40.

Nothing to note in family history.

Began a fortnight after entering trenches in Salonika, with weakness of the left leg, which only lasted a few days and then disappeared. Later, pain across the back.

Loss of power returned. Blurring of vision of left eye occasionally. Gait ataxic and spastic. Drawling speech. Occasional incontinence of urine. On examination, intention tremor in both hands, ataxia on heel to knee test. All four abdominal reflexes absent. Bilateral plantar extensor response. Left leg tendon jerks exaggerated as compared with right. No nystagmus. Pallor right optic disc.

Case No.6. Woman aged 41.

Family history.

Mother "always lost her voice when she was pregnant". Died of "Consumption".

Grandmother died at 102.

Father healthy.

Brothers, 5. One in Mental Hospital - depression.

Four suffered war injuries - otherwise well.

Sisters, 2. One nervous, and has had one breakdown.

One suffered from epilepsy. Died of smallpox.

Previous illnesses.

Nervous breakdown years ago. Measles.
Varicella. Pleurisy. All years before present
illness.

In 1924 had transient paralysis of right
leg, and had attacks of sickness at intervals
for two or three months. In August 1924 went
as out-patient to hospital complaining of
"depression and fluttering at heart." Now in
1926 she shows weakness of right leg and aching
pain all down right side, which is associated
with altered subjective response to stimuli
on that side "it feels different when you touch
me there". Complains of "skin over the eyes".
Spastic gait, intention tremor both sides,
specially right, absent abdominal reflexes,
bilateral extensor response. Pallor of both
temporal halves of discs. Mental depression.
Occasional incontinence of urine.

Blood Wassermann negative.

Serum surface tension range

38 to 41.5.

Case No.7. Young woman.

An advanced unmistakable case.

Marked weakness and ataxia, intention tremor, nystagmus and speech change. Fuller notes not available, as I did not note her name when I personally saw her first, and have not been able to identify her records and case notes since, and have not seen her again. Probably too ill and unsteady to visit hospital.

Case No.8.

Family history good, except for one brother with "weak chest".

Previous illnesses: rickets in infancy. Bilious at times.

Present illness.

Weakness of left leg began 12 months ago. Suffered from lenteric diarrhoea for twelve months. Nocturnal enuresis. Precipitate micturition in daytime. Has had pins and needles in legs and fingers - now gone. Weakness of both legs and arms. Gait unsteady....tends to fall forward. No speech change. On examination, intention

tremor left hand. Little ataxia. Sensory, slight loss over left leg - on one occasion burnt his left leg on a hot water bottle and did not know till morning. Pain in left shoulder. All abdominal reflexes lost. Double plantar extensor response, ankle clonus. Blurring of sight in left eye. Diplopia at one time, now gone. Nystagmus.

W.R negative. C.S.F., no increase of albumen or cells.

Case No.9. Girl aged 19.

Family history - brother had disseminated sclerosis. The diagnosis in this case was made by Dr. W.H.R. McCarter, (to whom I am obliged for notes) and confirmed by Dr. Gordon Holmes. His first symptom was an "influenzal" attack followed by diplopia at the age of 14.

Previous illness: Anterior poliomyelitis at the age of 14.

Case No. 10. 1918

Patient's Symptoms: At age of eighteen, complained of seeing double. No disorder of sleep or temperature. Followed by feeling of numbness in legs and arms. She became worried and fretful, and then agitated and restless, was sent to a nursing home, and was finally admitted as voluntary boarder to a mental hospital. She now shows nystagmus to both sides, exaggerated knee-jerks with patellar clonus, absent abdominal reflexes, and pronounced mental change.

Colloid gold test, 2,222,000,000

W.R. Negative.

Case No.10. Man aged 47.

Family history - one sister nervous and sometimes "does not know what she is doing."

Nothing else to note.

Previous illnesses: pneumonia and bronchitis, not associated with onset of present illness.

Present illness. Seventeen years ago noticed his right hand drag as he combed his hair. This "worked off". Then dragging of right leg. Now complains of dragging of right leg and weakness of right hand, numbness and tingling of fingers, pressure sensations right foot. Blurring of sight. Incontinence of urine at times. Gait spastic. Speech slurring - was formerly scanning. His emotional state is altered - his affective attitude changes rapidly, and is associated with some impairment of reasoning. Said angrily "I can't get up those steps. How am I to get up those steps?" and less than five minutes later said with marked gaiety and elation "I'll get up the steps all right. I don't need any help. Of course I can get up the steps, of course I can".

Reflexes altered - abdominal reflexes lost,
bilateral Babinski (was at one time only on right
side). Intention tremor of left hand and was in
right till that became too weak to move. Rombergism.

Case No.11. Man of 48.

Nothing to note in family history.

No previous illnesses.

Present illness began with dragging of the left
leg in 1918, two years after patient was demobilised
from the Army. Associated with this was cramp
in the legs, buzzing in ears as of aeroplane, and
giddiness. Finds it difficult to start to walk.
On examination, weakness of legs, slight intention
tremor in right hand (formerly present slightly in
left). Impaired right abdominal reflexes.
Bilateral ankle clonus and Babinski's sign.
Nystagmus.

Case No.12. Man aged 30.

Family history, nothing to note.

Previous illnesses: Measles in childhood.
influenza. Onset of present illness very indefinite.

ill for eight months before he knew what was wrong. Strength goes suddenly from arms and legs, so that he will stop in the middle of a letter and be unable to write any more "I can't push the pencil". Numbness from the waist down and pins and needles which die away and come back. Couldn't form words at one time - can now. At times he has no control over micturition. Loses control of the muscles of his face - a "sensation comes up the right side and holds the mouth". Transient blurring of sight. Nystagmus to right. Pallor of left optic disc (Diagnosed Primary Optic Atrophy by Dr Bishop Harman) Vertigo at times. "Nervy." "If I see a child near water it makes me so afraid I have to run, and yet if it fell in I suppose I should go after it. Wherever I am, I am always waiting for a crash. Something seems to be going to happen. I always used to pride myself on my pluck - I didn't use to be like that".

C.S.F., W.R., negative.

Case No.13. Boy aged 19.

Nothing in family history. notes.

Previous illnesses: said to have had "sleepy sickness four years ago and then meningitis". Began with diplopia, vomiting (patient states he vomited blood) and giddiness. Was very sleepy. This may well be an onset of disseminated sclerosis simulating encephalitis lethargica - (see etiological section) Cause of vomiting of blood, if true, not ascertained. Complains of right foot dragging, and seeing double. Thinks his speech may have altered. Seems distinctly childish for his years. Weakness and unsteadiness of left arm. Right foot drags. intention tremor both sides. Ataxia right hand, now, 1926. Showed slight Rombergism in 1923. Right upper abdominal reflex present, others absent, Right plantar reflex extensor; was left extensor formerly also. Sight blurred. C.S.F cells 11 per c.m.m. and a few R.B.C. Almost all small lymphocytes. W.R. negative. Colloid gold figure 43322100000.

Case No.14. Man aged 34.

Family history: nothing to note.

Previous illness: influenza in epidemic.

Began by "walking like a drunkard". Then complained of bursting out to laugh and couldn't stop - this was two years ago, and then he suffered from involuntary crying also. Now only has occasional involuntary laughter "anything makes me laugh". Now simulates acoustic nerve tumour - deaf left ear, weak left side of face, weakness of right arm and leg, one sudden attack of vertigo but has no evidence of intracranial hypertension, no disc change in spite of inability to read. Nystagmus in all directions. Intention tremor both sides. Ataxia on finger nose test, Rombergism. No headache or vomiting.

Blood and C.S.F. W.R negative on two occasions.

Cells 3 per c.m.m., total protein 0.0.6, globulin slight excess. Lange 233321000.

Case No.15. Man aged 36.

Family history nothing to note, previous illness, measles in childhood. Present illness began suddenly with an apoplectiform attack - he was at work on a table and fell off it, being found unconscious under it. Kept in bed for three days, and then was taken to West End Hospital for Nervous Diseases, where he was said to have hemiplegia. Recovered from this. Two years ago began again with weakness of legs and numbness of fingers. Gait spastic-ataxic. Speech, hesitating, as if impediment in speech. Not stammering or slurring, and more marked than ordinary staccato speech. Now has weakness in both arms and legs, intention tremor left hand, ataxia right hand, all abdominal reflexes absent, bilateral Babinski and other left reflexes exaggerated; Rombergism, nystagmus. Pupils react sluggishly.

Case No.16. Woman of about 30.

Family history.

Sisters, two well and strong.

One has DISSEMINATED SCLEROSIS.

Brothers, one died sunstroke and brain fever

one killed in war

one has diabetes

Previous illness, measles and pertussis in childhood. Septic arm; subject to septic throats.

Present illness began in 1916, pain in left thigh after walking, then wasting of thigh and 1 inch wasting in calf. She would trip on a stair unless she were attending to her walking. Tingling of fingers of right hand passed off and came back. Muscles felt tightened round the knee. Sensory symptoms of this patient have been described - feeling as if knees and abdomen were enlarged; feeling of weight on chest. Felt as if she were walking on wool or bristles. Mental changes marked - day to day fluctuations of affect. Weakness of legs, left more than right. Ataxia. Absence of abdominal reflexes. Bilateral Babinski. Exaggerated knee and ankle jerks. Nystagmus. Giddy if she turns quickly.

Case No.17. Woman aged

Family History nothing to note.

Previous illnesses, anterior poliomyelitis six years ago. In November of last year, was walking in the street when she was asked by her sister if she felt all right, for her "face was funny". She then became weak, and would have fallen if her sister had not caught her.

Taken to hospital paralysed down one side and unable to speak, but recovered completely in a few days, and after ten days holiday was back at work. Now complains of feeling depressed, could "scream for nothing". Has exaggerated knee jerk on right side (left leg old anterior poliomyelitis), with extensor plantar response, absent abdominal reflexes, intention tremor on both sides, and some ataxia in left hand.

Nystagmus.

Case No.18. Woman aged 55.

Sharp shooting pains, short in duration, worse now, off and on for three years, right side more often than left, no sharp localisation. Weakness of right leg, gradual in onset, causing

dragging of foot. No true nystagmus, but nystagnoid movements on looking to one side. Absent abdominal reflexes. Bilateral extensor plantar response. Spastic gait. Rombergism. Slight ataxia of right hand in finger nose test; slight terminal intention tremor. In conversation she seems apathetic and mentally slow - there is no evidence whether this has arisen since her illness.

Case No.19. Woman aged 35.

Paralysed since age of five - a spinal trouble of which she cannot give very definite information, treated by forcible extension of the spine, resulting in recovery, patient being able to walk. Patient's mother suffers from the delusion that she has lost all she had and will be ruined. Present illness began with difficulty in walking. Complains of "cold from knees down". Deaf, sometimes in one and sometimes in other ear - commonest in left. Sometimes very happy and sometimes very depressed. Bilateral intention tremor, attacks of vertigo, attacks of vomiting; alterations of sight - cannot see so well as formerly. Signs of pyramidal

involvement found in legs, perhaps old trouble.
C.S.F., Wassermann reaction negative, very
little change in Lange's colloid gold test.

Case No. 20. Woman, aged 38.

Nothing to note in family history.

No previous illness.

Present illness began with weakness of
legs and difficulty in walking. "Funny feeling"
in little finger - patient cannot describe it -
this has never improved. Curious sensory change -
double feeling, i.e., when washing plates, she
feels as if she held two in her left hand, when
in reality she holds one. Has twice has diplopia.
Gait staggering. Speech slightly slurred and
nasal. Mentally on the apathetic and simple side -
no evidence if this is new. Occasional retention
of urine. Exaggerated tendon jerks. Ataxia.

Three cases not noted in Etiological Section
owing to presence of few Diagnostic Signs only:

Case No. 21 Boy, aged 14.

Dr. Danvers Atkinson.

This boy showed nystagmus, loss of abdominal
reflexes, and exaggerated tendon jerks, within a

fortnight of beginning to learn to swim in
"fresh" London water.

Case No. 22 Boy aged 20.

Dr. Danvers Atkinson.

At the age of 16 he developed difficulty
in walking. A brother has "spinal trouble".
Patient complains of pain in legs, and has marked
spasticity and ataxia, with incontinence of faeces.
Diagnosis rests on presence of intention tremor,
seen once, and transient mistiness of vision. At
the time of onset he was washing bottles in the
cellar of a bottle factory. Rats present.

Case No. 23 Boy, aged 19.

Dr. Danvers Atkinson.

Loss of abdominal reflex on one side; numbness
of right hand, and dimness of left eye. Patient
works as washer of prints in a tank of plain water
in a factory where there were rats.


In compiling the foregoing, I have made full
use of the case-notes of these patients, which were
very kindly placed at my disposal. I have, however,
examined each patient myself.

II RECORD OF BACTERIOLOGICAL WORK DONE AT BETHLEM ROYAL
HOSPITAL LABORATORY ON THE SUBJECT OF THIS
PAPER.

Specimens of C.S.F. were examined fresh upon a film of tinted agar, and deposits were stained by Giemsa, sudan III and Osmic Acid. Patients from whom the C.S.F. was obtained were suffering from dementia paranoides, G.P.I. (3), encephalitis lethargica (2), chorea (3), cerebral tumor (specimen sent from another hospital), Disseminated sclerosis (3).

Films were examined from old culture of Vincent's angina; dental films were made from patients with mouth spirochaetes, and various control examinations of distilled water, etc. were made.

Cultures were made with serum and Tyrode's solution with the addition of animal tissue. The latter were seldom obtained sterile.

The following were the only results of note. In an old culture of Vincent's Angina, a triangular body about as large as an R.B.C., with refractile margin and a notch in one edge  apparently motile.

II C.S.F. In a case of disseminated sclerosis, similar appearances changing in aspect.



III In a dental culture, spirochaetal infection



IV C.S.F. In a culture from early d.s., in Serum heated to 70° C. in Buchner's Tyrodes sol., anaerobic method, showed small round organisms as follows:



Successive changes in shape.

V C.S.F. Another culture from early disseminated sclerosis

An actively motile spirochaete was seen wending its way among other organisms, but this culture was so contaminated, probably from the spleen extract which was added to it, that the source of this spirochaete was uncertain.



These 'organisms' in I, II, & III, IV appeared to be sluggishly motile.

III OCCUPATIONAL TABLES

Industry		Males Employed		Females of No Occupation associated with these Classified Industries, Wives, etc.	
<u>AGRICULTURE:</u>					
Farmers	16	Farmers	15	Farmers	14
Cowkeepers	3	Cowkeepers	3	Cowkeepers	2
Labourers	12	Farm labourers	12	Farm bailiff	2
		Small holder	1	Farm labourer	
		Corn mill) labourer)	1	Miller	1
		(Corn merchant's (foreman	1	Shepherd	1
				(Miller's trolley man	1
				Gamekeeper	2
Gardeners	8	Gardeners	8	Gardeners	6
				Veterinary) Surgeon) (1 son, 1 daughter, diff.)	2
<u>LABOURERS</u>					
		General	18	General	11
		(Lab. Plumbago works	2	Gasworker	1
		Brewery	1	Docks	3
		(Skilled, at (Bult Point (Devon	1	Chem. Works	1

Industry	Males Employed	Females of No Occupation Associated with these Classified Industries, Wives etc.	
<u>LABOURERS, continued.</u>	Steel works 2 Machine works 1 Engine Fitters 1 Engineers 1 Gas Company 1 Biscuit Factory 1 Lead Works 1 Post Office 1 Painters 1 Road Repairs 1 Docks 2 Bricklayers 2		
<u>CHEMICALS, DYES, etc.</u>	Chemical Manuf. ^r 1 Chemist 2 (Chem. make up for bleachers 1 (Dyers & Cleaners (charge hand 1 (Foreman, Mineral Water Factory 1	Chemist 2	

Industry	Males Employed		Females of no occupation associated with these classified industries, wives, etc.,	
<u>DOMESTIC AND NURSING</u>				
Domestic	8	Hospital Nurse	1	Office Caretaker 2
		Children's "	2	
		(Domestic Service)	8	
		Cook	2	
		Lady's Maid	1	
		" Companion	1	
		Housekeeper 1 M., 1 F.	2	
		(Caretaker, School)	2	
Warehouse-women	3	(Warehouse-women:		
		1. Brass founders	1	
		2. Potter's and Biscuits	1	
		3. Yarn finisher	1	
Window Cleaners	2	Window cleaner	2	
		Waitress	1	
<u>CLOTHING</u>				
Cotton		Draper	5	Cotton Twister 2
		Dressmaker	6	Warp Twister 1
		Cotton spinner	2	Machinist 2
		" reeler	1	Tailor 1
		" weaver	2	Cotton Salesman 2
		" winder	2	Cotton Looker 1
		" warper	1	(Cotton Mill
				(Manager 1

Industry	Males Employed	Females of no occupation associated with these classified industries, wives, etc.,	
<u>CLOTHING, continued.</u>			
<u>Cotton:</u>	(Cotton Cloth (looker 1 (Loom overlooker 1 Mule piecer 1 (" Parceller, (cotton goods (warehouse 2 (Grinder, cotton (mill 1	Weaver 1 Textile Agent 1	
<u>Silk:</u>		Weaver	1
<u>Hats:</u>	Milliner 1	Hatter	1
<u>Wool:</u>			
(Worsted em- (ployers	6	Hosier 1 (Outfitter's (Assistant 1 Cloth Merchant 1 Wool Merchant 2 (Worsted Mill (Manager 2 (Wool dealer's (Manager 1	(Woollen Manu- (facturer 1 (Grey cloth mer- (chant 1 Shirt cutter 1 (Worsted ware- (houseman 1
(Worsted (workers	4	Worsted Twister 2 " River 1 Cardroom hand 1 Hosiery factory warehouseman 1	

Industry	Males Employed		Females of no occupation associated with these classified industries, wives, etc.,	
<u>GLOVES</u>	Glove cutter	1		
<u>SHOES AND BOOTS</u>				
Shoemakers	2	2	Shoemakers	5
Shoe finishers	2	2	Shoe finishers	1
Shoe clicker	1	1	Shoe Machinist	2
	(Boot & Shoe Merchant)	1	(Shoe shop Manager)	1
	(Boot Dealer's Manager)	1	(Foreman, slip-per warehouse)	1
	Shoe clicker	1		
<u>CARTERS, DRIVERS, CARMEN, etc.</u>				
	Drivers	3	Lorry Driver	2
	Carmen & Carters	7	Carter	2
	(Porter (Boot makers)	1	Bus conductor	1
	Tram controller	1	Tramway manager	1
			Tram driver	2
<u>TIMBER</u>				
	(Firewood dealer)	1	Timber merchant's foreman	1
	(Wood panel roller grainer)	1		
	(Wood sawyer (colliery (above)	1		

Industry	Males Employed		Females of no occupation Associated with these classified industries, wives, etc.	
<u>HOUSING</u>				
(Carpenters & Joiners)	9	Joiners 9 " Shipyard 1 (" Basket makers 1 Coach builder 2 (Cooper, victual-ling yard 1	Carpenters 4 Coach trimmer 1 Sawyer 1	
<u>Furniture</u>			Furniture dealers 2 " remover 1 Cabinet Maker 1 Upholsterer 1	
<u>Decoration:</u>	7	Painters 6 Decorator 1 Scenic Artist 1	(Painter or Decorator 6 Paper hanger 1	
<u>Building:</u>		Builder 2 (" Merchant's foreman 1 Brick layer 3 " setter 1 " maker 1 Stone mason 2 Tile worker 1 (Potter's thimble maker 1	Builder 1 Bricklayers 2 Plasterer 2 Masons 3 Quarryman 2 (Potter's mould Maker 1	
<u>Stone:</u>				
<u>Pottery:</u>				

Industry		Males Employed		Females of no occupation associated with these classified industries wives, etc.,	
<u>PRINTING AND BOOKS</u>					
		(Letter Press (printer	1	Printer's Manager	1
		(Printer, book (binder	1	Book seller	1
		(Pattern book (Maker	1	Journalist	1
		(Printing Ma- (chine minder	1		
		(Paper Bag (Manufacturer	1		
		Librarian	1		
		Compositor	1		
		Die stampers	1		
		(Printer's Ware- (houseman	1		
<u>PROFESSIONS</u>					
		Ministers	2	Clerk in Orders	1
		Solicitors	2	Solicitor	1
				Physician	1
<u>CLERKS AND TEACHERS</u>					
Male Clerks	11	Bankers	3	Assurance Agent	1
		Clerks) both) sexes	15	Banker	1
		Typists)	2	Bank Messenger	1
		School master	2		
		" Mistress	8		

Industry	Males Employed		Females of no occupation associated with these classified industries, wives, etc.,		
<u>GOVERNMENT AND MUNICIPAL</u>					
		Registrar Post master Police (Sanitary Inspector)	1 2 2 1	Police Postman " Overseer (Town Hall Attendant)	1 1 1 1
<u>ARMY</u>					
		Pensioners (Other Ex. Service)	11 2	Various ranks	4
<u>ENGINEERS</u>					
Plumbers	3	Mechanical (Engineer Driver, Agricultural) Engine turner (Engineer fitter Marine) (Engine man colliery) Plumbers (lass ^t) Gas pipe welder Motor Mechanic (Hydraulic Engineer) (Engineer's gill setter) Civil Engineer Stoker "	3 1 1 1 1 1 1 1 1 1 1 1	Gas Fitter Engineer " 's fitter (Steam crane driver) Plumber (Hydraulic packer Docks)	1 8 1 1 1 1 1 1 1

Industry	Males Employed		Females of no occupation associated with these classified industries, wives, etc.,	
<u>ENGINEERS, continued.</u>				
<u>RAILWAYS</u>	(Telephone linesman 1 (Machinist, cable worker 1 (Draughtsman, Engineer's 1 11 (Signalman 2 (Shunter 1 (Goods porter 1 (Ticker collector 1 (Porter 1 (Guard 1 (Platelayer 1 (Engine drivers 3		Shunter 1 Guard 1 Porters 4 Signalmen 2 Railway constable 1	
<u>SHIPS</u> Total	3 (Steamship's greaser 1 (Sailor, merchant service 1 (Master mariner 1 (Customs & Excise officer 1 Royal Marines 1 (Fishing rod tackle maker 1 Stevedore 1 Commander R.N. 1		Dock foreman 1 Barge captain 2 Naval pensioners 3 Shipowner 1 Steamship Steward 1 Ship's fireman 1 Shipping merchant 1 Customs watcher 1	

Industry	Males Employed	Females of no occupation associated with these classified industries, wives, etc.,
<u>IRON AND STEEL</u>		
Moulders	3	
	Iron moulder	Steel erector
	3	1
	Iron master	Iron merchant
	1	1
	(Steel Rolling Mill Manager) (Steel Building Erector)	Boiler smith
	2	Riveter
	Tinman	Blacksmith
	1	3
	1	Plate worker
	Whitesmith	1
	Blacksmith	(Steel manufacturer)
	1	1
	" (colliers)	Furnace minder
	1	1
	" (striker)	Galvaniser
	1	1
	" (stoker - docks)	Wire drawer
	1	1
	(Tin plate store-keeper)	Iron drilller
	1	3
	Iron turner	Turner
	1	1
	Saw sharpener	
	1	
	File cutter	
	1	
	Grinder (steel)	
	2	
	Smelter	
	1	
	(Boilerman (Furnace):-	
	(Steel blast furnace boiler cleaner)	
	1	
	(Sheet metal worker (Carpet Wks)	
	1	

Industry	Males Employed	Females of no occupation associated with these classified industries, wives, etc.,	
<u>COAL</u> (Miners below Ground)	20 (Hewers 8 (Miners 2 (Stall men 2 (Shifters 3 (Rigger 1 (Banksman 1 (Sipper 1 (Labourer (below) 2 Depot Manager 3 Coke worker 1 Hauler (above) 1 Colliery mason 1	Coal miner Mine overman	13 1

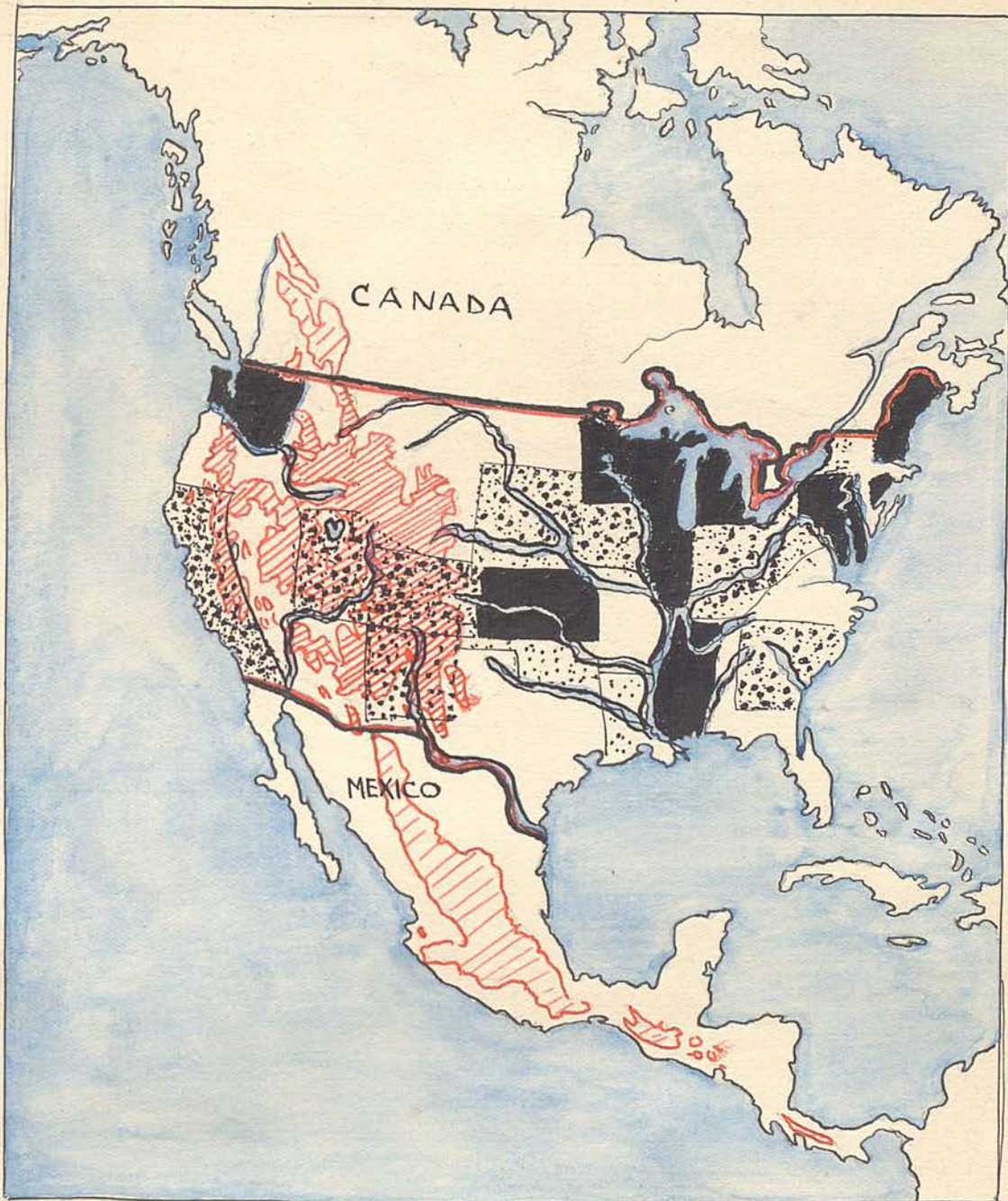
<u>FOOD AND DRINK, AND SHOPS</u> MISCELLANEOUS	Grocer 4 (Licensed Vic-tualler 4 General dealer 2 (Store-keeper (Co-op. 1 Stores Assistant 1 Baker 2 (Confestioneer's (Packer 1 (Confectioner's (Assistant 1	Grocer (Licensed vic-tualler (General shop-keeper Cellarman Wine Merchant Baker	6 2 2 1 1 6
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Industry	Males Employed	Females of no occupation associated with these classified industries, wives, etc.,
<u>FOOD, DRINK AND SHOPS, continued.</u>		
	Fishmonger 1 Slaughterman 1 Butcher 1 Fruit salesman 1 Tobacconist 1 Hardware 1	Milk retailer 1 Fishmonger 1 (Slaughterman, (daughter, aged (15 1 Greengrocer 1 Brewer 1 Oil & Colour man 1 (Hardware and (carpets 1
<u>JEWELLERS</u>		
	Watchmaker 1	Silversmith 1 Jeweller 1
<u>COMMERCIAL TRAVELLERS</u>		
	Commercial 1 Brewers 1 Provision 1	Commercial 4
<u>MISCELLANEOUS</u>		
	(Music Hall (Artiste 1 Frame washer 1 (Elec. Light (Factory hand 1 Fireman, works 1 Hairdresser 1 Mattress maker 1	(West African (Merchant 1 Auctioneer 1 Hairdresser 1 Cleaner in mills 1 Surveyor 1

Industry	Males Employed		Females of no occupation associated with these classified industries, wives, etc.,
<u>MISCELLANEOUS, (continued)</u>	(Company Director)	1	
<u>NO OCCUPATION</u>	Men	4	
	Women	15.	

Map of
Adapted for
incidence of
related

Map A



Map of United States of America.

Adapted from "Multiple Sclerosis" (Assn. Res. Nerv. & Ment. Dis. 1921)

incidence of **Disseminated Sclerosis** (black)

related to Waterways and Lakes (blue)

Mountains in red.

MAP B

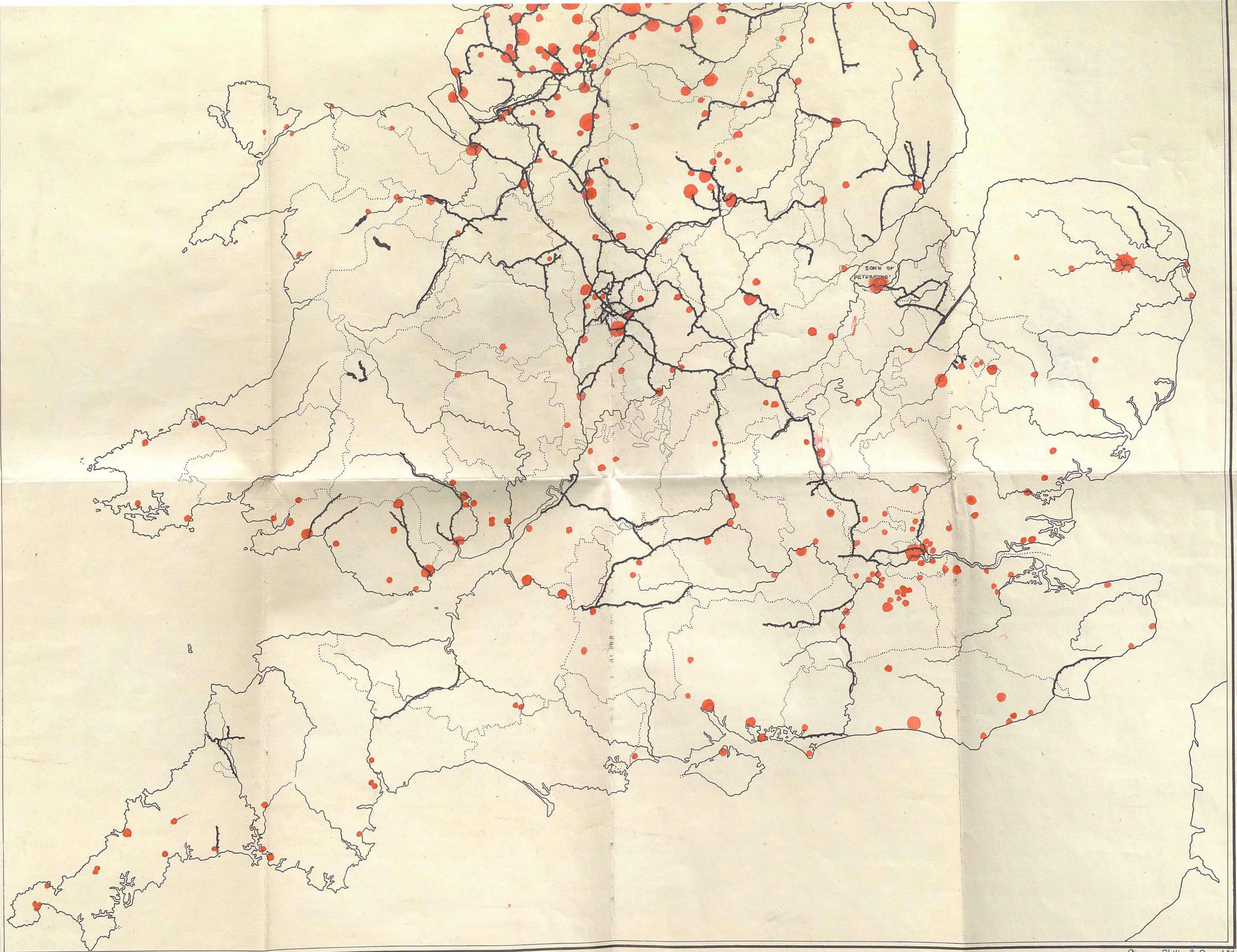
ENGLAND AND WALES SHOWING DEATHS FROM DISSEMINATED SCLEROSIS in relation to larger waterways: 1925.

Many large towns are on canals: this has to be taken into account. Special features are ① Crop of cases in Norwich ② Occurrence of many scattered cases in Cornwall ③ Crop of cases in Surrey (Croydon, Mitcham etc) on the slow-flowing Thames Tributary, the Wandle Small and medium rivers not shown

The number of cases in Lancashire is counteracted to some extent by thick population (Death rate there 26.90 Average=17.7)

One case - - - - - ●
Two cases - - - - - ●
Three or more - - - - - ●









PHILIPS'
NEW LARGE PRINT MAP
OF THE
COUNTY OF LONDON

SCALE:— TWO INCHES TO ONE MILE

In this map, each black spot represents a death from Disseminated Sclerosis in 1925. The placing of some of these round the basins of Regent's Canal (4-1&16-1) is striking when the duration of the disease is thought of (For obvious reasons no attempt has been made to locate the exact section in the street, nor the house, which was at the time of death the home address of the patient, in every case shown)





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