An Address ON DISSEMINATED SCLEROSIS: WITH SPECIAL REFERENCE TO ITS INFECTIVE ORIGIN.*

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THE study of nervous diseases is always considered to be an interesting but depressing occupation, because so little can be done for the patient. This, unfortunately, applies to the majority of organic nervous diseases. Before the discovery of the important part which the *Spirochaeta pallida* plays in the production of disease of the central nervous system, the outlook, as far as therapeutic measures went, was certainly much poorer than it is to-day. Of late years much knowledge has accumulated regarding the physiology and pathology of the nervous system, but less attention has been paid to the etiology of a number of obscure diseases. Certain links in the chain connecting pernicious anaemia and subacute combined degeneration of the cord have, it is true, been filled in, especially the recognition of achlorhydria as a constant feature of this syndrome and the importance of a megalocytosis as being often the only abnormality in the blood picture during the remissions of the disease. The next gap has yet to be crossed, and it will only be achieved by the aid of bacteriology.

The symptomatology of disseminated sclerosis and its pathological basis have been described in scores of papers in this and other countries during the past twenty years, but knowledge of the underlying cause is still wanting. This can, I think, be attributed to the lack of co-operation between the neurologist and the bacteriologist. The position as regards disseminated sclerosis is much the same as that which existed in respect to syphilis prior to the discovery of the Wassermann reaction and the *Spirochaeta pallida*.

DISSEMINATED SCLEROSIS AS AN INFECTIVE DISEASE OF THE CENTRAL NERVOUS SYSTEM.

Under this heading we may consider briefly the reasons why disseminated sclerosis is considered to have an infective origin.

1. Clinical.

From the clinical aspect it is well known that so-called "influenzal" attacks may usher in the disease or accompany relapses during the course of the disease. These attacks consist of headache, general malaise, and usually slight pyrexia. It seems probable that such attacks are not "influenzal," but result from the circulation within the blood of the organism or toxin of disseminated sclerosis. Again, fever is not uncommon during the course of the disease, especially in early cases and during relapses. This question has recently been studied by Epstein¹ in 34 cases. In 22 of these fever was present at some time during their stay in hospital, but the temperature rarely exceeded 100° F. Further clinical evidence is afforded by the characteristic relapses and remissions which occur during the course of the disease in the majority of cases. Any theory which attributes the condition to developmental errors falls to the ground in the presence of the curious variations in the clinical picture. In this respect disseminated sclerosis resembles meningo-vascular syphilis, pulmonary tuberculosis, and other chronic infections. The variations in the intensity of the infective process can be best explained by supposing that a virus, or its toxin, periodically invades the central nervous system, so producing a train of symptoms which will depend on the particular part of the neuro-axis attacked.

2. Serological Evidence.

A study of the cerebro-spinal fluid in disseminated sclerosis shows that, frequently, certain changes occur in the fluid which could only result from an active infective process in the central nervous system. The usual findings in the cerebro-spinal fluid are as follows: The Wassermann reaction is always negative; there is little or no increase in the percentage of albumin or in the number of cells. The various tests with colloidal substances, such as gold and benzoïn, show a positive curve in about half the cases. The colloidal gold reaction, owing to want of standardization by the majority of workers, has not attained the important place in the diagnosis of this disease it should have. In France the colloidal gold has been supplanted largely by the colloidal benzoïn reaction, which is certainly easier and would seem to give more stabilized results.

3. Pathological Evidence.

The pathological evidence as to the infective nature of disseminated sclerosis cannot be set out in the time at my disposal. I will merely quote the opinion of J. W. Dawson,² whose work, published in 1916, forms an exhaustive treatise on this part of the subject.

"The process underlying disseminated sclerosis is a subacute disseminated encephalo-myelitis, which terminates in disseminated areas of actual and complete sclerosis." And again he writes: "It is concluded, therefore, that there is much to favour the view that disseminated sclerosis is due to a specific morbid agent which calls forth a clearly defined clinical and anatomical picture." And later he adds: "The causal agent is, therefore, probably of the nature of a soluble toxin and it is conveyed to the nervous tissues probably by the blood channel."

4. Experimental Evidence.

The experimental evidence, as is usual in such a disease as we are dealing with, is both positive and negative. Positive evidence in the hands of careful observers must outweigh the negative findings of others. Bulloch³ (now Gye) in 1913 injected into a rabbit some of the cerebro-spinal fluid from an acute case of disseminated sclerosis in a young man of 19. The injection was made in the region of the sciatic nerve. On the thirteenth day the animal showed paralysis of the hind limbs. Three days later all four limbs were paralysed and there was incontinence of urine. The animal was then killed. Intense congestion and oedema of the grey matter in the cord was found, whilst in different situations the myelin sheaths were broken up. In another experiment, using the cerebro-spinal fluid from the same patient, he was able to produce transitory paresis in the hind limbs of a rabbit, after filtering the fluid. Bulloch concluded from these experiments that he was dealing with a filterable virus. Kuhn and Steiner,⁴ in 1917, in a large series of experiments conducted on rabbits and guinea-pigs, were able to produce paresis in the limbs in two-thirds of the animals. It is interesting to note that those animals which were inoculated only with cerebro-spinal fluid were unaffected. The positive results were obtained when blood from the patients was used. Several other workers in Germany and France have obtained similar results. More recently Adams, Blacklock, and MacLuskie⁵ have worked on this subject in Glasgow. They inoculated cerebro-spinal fluid from several cases of disseminated sclerosis into sixteen rabbits. Five of the animals showed nervous symptoms, either in the form of paralysis of the legs or of typical cerebellar symptoms. On using citrated blood for inoculation, nervous symptoms appeared in five out of eleven animals. In several instances they were able to produce symptoms in rabbits after inoculation with an emulsion of the central nervous system of another rabbit which had been successfully inoculated with cerebro-spinal fluid from a patient. As I have said, other workers have carried out similar experiments with negative results, but on the whole there seems to be sufficient experimental proof of the infective nature of the disease.

THE NATURE OF THE INFECTION.

Farquhar Buzzard⁶ in 1911 suggested for the first time that the disease might be due to a spirochaete. Kuhn and Steiner, during the experiments already mentioned, demonstrated spirochaetes in the heart's blood and in the vessels

* Given before the Oxford Division of the British Medical Association.

of the liver of the animals. Siemerling⁷ observed in the brain of a man, who had died from disseminated sclerosis, living spirochaetes under dark-ground illumination. One or two others have reported similar positive results at autopsy, but none of these spirochaetes could be stained by the usual silver methods. Adams and his fellow workers found spirochaetes in various internal organs of their inoculated animals. Other evidence, positive and negative, I have not time to discuss. The spirochaetal theory of disseminated sclerosis at present rests on insufficient evidence and must be considered to be not proven. Three difficulties lie in the way: (1) the fact that spirochaetes of various sorts normally are present in most animals used for experimental purposes; (2) it has not been found possible to obtain a growth of the spirochaetes so far found by various observers; (3) if the disease be spirochaetal in origin, then the difficulties are increased by the probability that we are dealing with a class of organism that has a life cycle, and its other forms may be overlooked since we are unable to recognize them.

THE MODE OF INFECTION.

1. Endogenous Theory.

Before passing on to the more solid ground of the clinical aspect of the disease let us consider the possible methods of infection in disseminated sclerosis. Is the disease due to some endogenous cause—that is to say, is the virus present in the mouth or gastro-intestinal tract of normal individuals, and under certain conditions and in certain persons becomes pathogenic? We have numerous analogies—the pneumococcus, streptococcus, *Bacillus coli*, etc. Spirochaetes of various kinds—if a spirochaete be the cause of the disease—can be isolated from the mouths of most of us, and are present in the intestine in quite a large proportion of normal persons. It is possible that under certain conditions they may become pathogenic.

2. Exogenous Theory.

Another aspect of the disease, for knowledge of which I am indebted to Dr. D. K. Adams of Glasgow, must be considered. He has noted the relative high proportion of agricultural workers and woodworkers among the sufferers from disseminated sclerosis. He has also found that not infrequently the father of the patient follows one of these two occupations. The fact that the disease appears frequently in healthy young adults has suggested to Adams⁸ that the cause of the disease is an accidental infection. In Germany this exogenous theory of disseminated sclerosis has been studied by several observers. In a personal communication Professor Kuhn says that Steiner first advanced the theory of an external infective agent. Steiner⁹ ¹⁰ points out in a recent paper that the disease is unknown in China and Japan; it is very rare in South America, and rare in Italy. It is most common in Switzerland, and this statement is borne out by some figures in a recent paper by Bing and Reese,¹¹ who found that disseminated sclerosis in Switzerland occurs twice as frequently as does tabes dorsalis. The disease is also common in Germany, France, and Great Britain. Steiner believes that the explanation of the difference in the regional distribution of the disease may be found in the mode of life or occupation, or in the distribution of carriers of infection, possibly insects. With regard to the occupational incidence of the disease, Steiner attaches considerable importance to the work of Dreyfus¹² on this point. Dreyfus, in 1920, collected records of 1,151 cases of disseminated sclerosis which had been reported or personally observed in recent years in Germany; 672 of these were males and 479 females. He found an absolute preponderance of the disease in agricultural workers and in woodworkers. For instance, according to census figures, in Germany there were 25 carpenters per 1,000 male population. Dreyfus found the incidence of disseminated sclerosis in carpenters to be 32 per 1,000—that is, an excess of 7.8 per 1,000 over the census figures. The woodworkers of all kinds with the disease showed an excess of 18 per 1,000 over the census figures. Dreyfus adds that the number of cases investigated is relatively small, and consequently the probable error is relatively large. Steiner studied the question of occupation in 500 army pensioners,

and found that woodworkers showed a preponderance, which was also apparent in the father's occupation. Steiner mentions a striking case of two cousins who frequently spent their holidays together in the same villa, to which a garden was attached. Both the cousins contracted the disease, as did the gardener.

I have so far investigated the various points mentioned above in only 110 cases of disseminated sclerosis. This number is, of course, much too small to permit any conclusions to be drawn at the present moment, but enough positive evidence has been obtained to suggest that an accidental infection may be the cause of the disease in some cases, and that further investigation in this direction is desirable.

It seems probable that there is a latent period, which may cover several years, between the actual infection and the appearance of signs denoting involvement of the central nervous system. Therefore, in studying the history of a case, it is necessary to inquire into the circumstances of the patient's life over a long period, stretching back, in some instances, to childhood.

From the point of view of an infective agent it seems difficult to bring into line the tendency of agricultural workers and woodworkers to the disease. There is little evidence that only those working with diseased woods are attacked; on the contrary, it would seem that the highest incidence occurs in those who work with prepared wood.

Some of those who are engaged in general practice may have an opportunity of investigating this aspect of the disease, and I would suggest that a careful inquiry into the various circumstances of the patient's life prior to the onset should be made. Particular attention should be paid to the places of residence (town, country, or farm), occupation, hobbies (especially with regard to woodwork), and the father's occupation. It is possible that in this way fresh light may be shed on the problem of the causation of this common and crippling disease.

CEREBRAL FORMS.

The varying clinical pictures of disseminated sclerosis are well known. In the majority of cases its symptomatology depends on changes in the brain stem and spinal cord. These two parts of the neuro-axis may be attacked simultaneously, but quite frequently either one or the other may bear the first brunt of the disease. I shall not dwell on the common spinal cord types, but will say a word about the various symptoms which may be produced by invasion of the brain itself. I wish to make it clear, however, that the infective process, even at an early stage, is usually much more widespread than would appear from the clinical picture, and that even when this points solely to involvement of the cord, in the majority of cases the disease has already invaded the brain and in particular the margins of the ventricular cavities. Keeping this idea of the true dissemination of the disease before us, let us consider the effect of the disease on the cerebral tissues from a clinical standpoint. At an early stage three symptoms may appear, either together or independently. The first is headache, the second giddiness, and the third either diplopia or blindness. The headache is usually generalized and may be severe. It is frequently aggravated by anything which temporarily increases the intracranial tension, such as coughing, sneezing, and stooping. It is intermittent, lasting for one or several days at a time, and sometimes accompanies a clinical relapse; not infrequently it is attended by vomiting. The type of headache recalls that observed in conditions in which there is a rise in the tension of the cerebro-spinal fluid. It may either be toxic in origin or, as I am inclined to believe, is dependent on a temporary hydrocephalus. Whatever the explanation may be, this symptom is a common witness of the invasion of the cerebrum.

Hemiplegic Type.

There are a few types of cerebral disseminated sclerosis which must be mentioned. First the hemiplegic. This is somewhat rare, but probably not so rare as has been imagined. We must all have met with puzzling cases

of sudden hemiplegia in healthy young or comparatively young persons. Such attacks may be indistinguishable from an apoplectic seizure; usually there is no loss of consciousness. We examine the heart and find nothing abnormal. The urine and blood pressure are normal. We plump then for syphilis and are rebuffed by a negative Wassermann reaction. By this time our thoughts have turned to the possibility of haemorrhage into a cerebral tumour, and while we are ruminating over this, the power begins to return, and within a couple of weeks or so the hemiplegia has passed off. Such cases are often labelled "cerebral thrombosis of unknown cause." The true explanation is usually disseminated sclerosis, which has begun by attacking the region of the internal capsule. I will relate two such cases.

CASE I.

A man, aged 38, had lived on a farm since childhood. His father was a farmer. At the onset of the disease he was working as an estate carpenter. He enjoyed good health until March 20th, 1924, when he experienced a stiff feeling in the right hand which grew rapidly worse within the next few hours. The following morning he was paralysed in his right arm and leg; he was admitted to the Middlesex Hospital, where he was found to be suffering from an organic right-sided hemiplegia. The condition quickly improved and by the end of two weeks he was allowed up. A few days later, however, he had an attack in which his right arm and leg became drawn up, numb, and powerless. At the same time he had a severe headache, lost his speech, and became blind in the left eye. Diplopia was noticed about the same time. The Wassermann reaction was negative, both in the blood and in the cerebro-spinal fluid, which was normal. Unfortunately the colloidal gold reaction was not tested. I saw him for the first time within a week of this attack. The physical signs consisted of nystagmus, pallor of the temporal half of the left disc, and moderately severe right-sided hemiplegia. He again quickly improved. Within the next few months he had further slight "strokes," two affecting the right side and one the left. He was admitted under my care into the Hospital for Epilepsy and Paralysis, Maida Vale, in May, 1925. He showed a marked degree of euphoria and a tendency to involuntary laughter. Nystagmus was not present. There was about 50 per cent. loss of power in the limbs on the right side and the right plantar response was extensor in type. The power on the left side was within 10 per cent. of normal. The left plantar response was flexor in type. No sensory loss, tremor, or ataxia was apparent. The tonsils, which were septic, were removed. He was treated by typhoid vaccine and with arsenic by the mouth. He improved greatly. Subsequently he had several courses of bismuth given by intramuscular injection. During the recent strike he drove a motor bus every day for two weeks and neglected treatment. Within the last month he has had a further hemiplegic seizure.

CASE II.

A woman, aged 25, became ill first at the age of 17, six weeks after running accidentally into a signpost. She began to have severe headaches, accompanied by vomiting and followed by diplopia. About a fortnight later she noticed loss of power in the right arm, and experienced great pain in this limb. A few days afterwards she became unconscious, and remained semi-comatose for several days. She was seen by Dr. Campbell Thomson, who suspected a cerebral tumour, and ordered her removal to Maida Vale Hospital. There she was found to have moderately severe right-sided organic hemiplegia with hemianaesthesia and paresis of the left external rectus. The speech was hesitating, but there was no aphasia. The discs were normal. She improved rapidly after the first few days in hospital, and was discharged five weeks later, with no headaches and almost normal power in the right arm and leg. For some months after she was subject to headaches, especially on excitement, but these then disappeared. The paresis of the limbs entirely passed off. Since then she has remained well except for occasional attacks of pain, which she describes as a throbbing, wrenching sensation in the right arm; this pain usually lasts a few minutes. At the beginning of April, 1925, the finger-tips of the right hand suddenly became dead, and she was unable to hold a pen properly. A few days later an agonizing pain, similar to that described above, was felt in the right arm, and the hand and forearm showed involuntary movements. Within the next week or so she had three attacks of convulsions in the night, which from her mother's description appear to have been epileptiform. She was admitted to Maida Vale Hospital in June, 1925, for observation, but at that time all symptoms had disappeared. The pupils and cranial nerves were normal. There was no nystagmus, and the discs appeared normal. There was no change in her mental outlook. There was no loss of power or sensation in the right arm; no ataxia or tremor was observed. The deep reflexes in the arms were brisk and equal. The abdominal reflexes could not be obtained on the right side, and were sluggish on the left. There was no paresis or alteration in the reflexes in the lower limbs. The Wassermann reaction of the blood was negative. The cerebro-spinal fluid was normal, including the colloidal gold and the colloidal benzoin curves. She has been treated with liquor arsenicalis, stovarsol, mercury, and iodides, and has remained in fairly good health. In this case the disease seems more or less localized clinically to the region of the left internal capsule and left thalamus.

Such cases as these are often difficult to diagnose in the early stages, and may closely resemble a cerebral tumour, especially that type in which the tumour, usually a glioma, first makes known its presence by the occurrence of a haemorrhage into its substance.

Before leaving this hemiplegic type I must mention that an epileptiform seizure may be the first symptom of the disease, and sometimes is associated with hemiplegia, as in Case II. Unless, of course, other signs, such as hemiplegia, accompany the fit, such attacks are indistinguishable from ordinary epilepsy. They may at times be Jacksonian in type.

Ocular Symptoms.

Diplopia is so well recognized as a frequent early symptom of disseminated sclerosis that it need not detain us. The other important ocular symptom which may bring the patient under care is sudden blindness, usually unilateral. Headache is frequently present for the day or two preceding the failure of vision; pain is usually felt behind the eyeball. The sight fails rapidly, so that within forty-eight hours little vision remains. The central vision is chiefly affected. The pupil is dilated, and reacts somewhat sluggishly to light. On ophthalmoscopic examination the disc frequently appears normal. Should the "patch" be close up to the optic nerve head, then a moderate degree of swelling of the disc with blurring of its edges may be observed. In the great majority of these cases no septic focus, such as suppuration in the nasal sinuses, can be discovered, and it is now generally held that disseminated sclerosis is the explanation of this blindness, by virtue of a "patch" somewhere along the optic nerve. The blindness clears up more or less completely within a few weeks, but other signs of disseminated sclerosis make their appearance sooner or later. Pallor of the temporal half of one or both discs is extremely common in cases of disseminated sclerosis even when there is no history of a retrobulbar neuritis.

Why should the optic nerve be picked out in this disease? There are three possible answers to this question. (1) That the infective agent is present in the posterior ethmoidal or sphenoidal cells and gains access to the optic nerve by penetrating the very thin barrier which separates these structures. (2) The subarachnoid space is continued out along the optic nerve to within a short distance of the eyeball. Certain other cranial nerves, the fifth, seventh, and eighth, also possess this prolongation of the subarachnoid space, but in the case of the optic nerve it is wider than in the others. If the virus of disseminated sclerosis be present in the cerebro-spinal fluid, then in view of these facts it is the optic nerve, bathed by the spinal fluid throughout its course, which would be most vulnerable. (3) Lastly, the possibility of a selective action of the virus on this particular nerve has to be considered. Personally, I think that one of the first two explanations lies nearest the truth.

Alterations in the Mentality of Patients Suffering from Disseminated Sclerosis.

That mental changes may occur in some cases during the course of the disease has long been recognized. These changes have been divided into those denoting interference with the highest cortical processes resulting in varying degrees of dementia, and those characterized by alterations in mood, such as increased cheerfulness or euphoria. Under the second heading are usually grouped those cases which show pathological laughter or crying. Dementia is rare in disseminated sclerosis, and is directly dependent on the invasion of the subcortical white matter by the disease. The following case is instructive from this point of view, as well as by the rapid course of the disease.

CASE III.

A woman, aged 46 (a trained nurse), one day during December, 1924, fell suddenly and was unable to get up. It is uncertain whether she lost consciousness or not. She was admitted to the National Hospital, Queen Square, where the diagnosis was "right-sided hemiplegia? disseminated sclerosis." The cerebro-spinal fluid gave a negative Wassermann reaction, 10 cells per cubic millimetre, 0.04 per cent. albumin, and a well marked Lange gold curve. She improved slightly and was discharged three

months later. In May, 1925, she had a relapse, during which the paresis on the right side became more evident. Shortly afterwards marked tremor of the right arm made its appearance. During 1925 a great change was noticed in her mentality. She came under my care in Maida Vale Hospital in December, 1925, when the most striking point was the intense mental deterioration which had evidently taken place. She seemed to have great difficulty in understanding what was said to her, and answered questions in a slow, disjointed fashion. She had very hazy notions as to the duration of her illness, and as to how long she had been in hospital or the name of the hospital. She seemed quite unable to fix her attention on anything for more than a few seconds. She was markedly emotional, and would laugh or cry at the slightest provocation. It was impossible to ascertain whether her outlook on life was cheerful or the reverse. Her mental condition could be summed up as moderately severe dementia. There was no nystagmus, and the discs appeared normal. The speech was markedly dysarthric. There were signs of a right-sided hemiplegia, and a tremor of great range and amplitude affected the right upper limb. It was present at rest, and therefore did not conform with the usual intention tremor of disseminated sclerosis. In view of the age of the patient, the absence of papilloedema, and the negative Wassermann reaction in the cerebro-spinal fluid with other positive findings in the fluid, a diagnosis of disseminated sclerosis was made, chiefly involving the cortex. The case was too advanced for treatment to be of any avail. She gradually became worse, and died on January 19th, 1926, fourteen months after the onset of the disease. At autopsy the brain was found to be riddled with patches of disseminated sclerosis, especially the subcortical white matter and the periventricular margins.

Much more common are the alterations in mood. A recent and very instructive paper by Cottrell and Kinnier Wilson¹³ deals with this subject. In 100 unselected cases they investigated the psychological outlook on life before and after the onset of the disease. They classify their results under three headings: (1) change in mood, (2) change in bodily feeling, (3) change in emotional expression and control. A change in mood they found to be present in every case they investigated. In 63 per cent. of the cases this change was in the direction of cheerfulness or happiness, to which they apply the term "euphoria." A change in bodily feeling, which they distinguish from a change in mental outlook and to which they give the name "eútonia," was present in 84 per cent. of the cases; in the remaining cases the change was either one of physical ill-being or a combination of this with a sense of well-being. Changes in emotional expression and control were also pronounced features in their series of cases. In 90 per cent. of the cases smiling and laughing were obvious features and appeared without adequate stimuli. In only two cases were they able to demonstrate actual intellectual deterioration. Cottrell and Wilson believe that these changes occur even in the early stages of the disease and are of importance in diagnosis. In their own words,

"No single symptom of the neurological series (nystagmus, tremor, scanning speech, paræsthesiæ, spasticity, amaurosis, etc.) occurs with anything like the same frequency in an unselected century of cases of the disease, and that the cardinal symptoms are not neurological in its limited sense but belong to the emotional, affective and visceral spheres."

These observations are of great interest, and will repay close study. If a young adult whilst telling you of a weakness in an arm or a leg seems extraordinarily cheerful about the whole affair, then suspect disseminated sclerosis, and do not put off the diagnosis if none of the classical signs of the disease are present.

Cerebellar Type (so-called).

It is well recognized that the first sign of the disease may be ataxia. The usual history of such a case is as follows. A previously healthy young adult "catches a cold"; some days later he sees double, is troubled with headache, and may vomit. Later, on attempting to get out of bed, he feels giddy and unsteady on his legs; the giddiness may be marked even when the patient is in bed. On examination nystagmus and ataxia of the upper and lower limbs, usually more marked on one side, are evident. There may be no signs of interference with the pyramidal tracts. Such is the picture of so-called "acute cerebellar ataxia." These symptoms clear up wholly or partially, but eventually relapses occur. The following case conforms to this type.

CASE IV.

A girl, aged 14, was admitted into Maida Vale Hospital in May, 1926, under the care of Dr. Anthony Feiling, to whom I am indebted for the notes.

Previously a healthy girl, she "caught a cold" on December 3rd, 1925, and was confined to bed for three weeks. During this time she vomited and complained of severe occipital headache. She saw double on more than one occasion. On getting out of bed at the end of the three weeks it was noticed that she could not walk properly owing to unsteadiness. There was no weakness in her arms and she could sew and knit. After a week or so she was able to get about, but was very unsteady in her gait. Examination in hospital showed no alteration in mentality; the pupils were equal and reacted normally; the discs were normal and vision was full in each eye. There was a horizontal nystagmus on looking to the left. Marked inco-ordination in both the upper and lower limbs was present, especially on the left side. There was no loss of power or any evidence of involvement of the pyramidal tracts except absence of the abdominal reflexes. The Wassermann reaction of the blood was negative; the cerebro-spinal fluid was not examined. There was no history of otitis media, and examination of her ears was entirely negative. Within the course of the next few weeks she improved so that, on discharge, her gait was nearly normal. The fundi remained normal. This girl was sent in with a diagnosis of "P. cerebellar tumour," but the disappearance of the headaches with improvement clinically leaves little doubt that it was a case of disseminated sclerosis.

Vertigo is also a common symptom during the course of disseminated sclerosis, and may be accompanied by headache, the patient labelling such attacks "bilious turns."

TREATMENT.

The treatment of a disease such as disseminated sclerosis, because of our lack of knowledge of its cause, must of necessity be unsatisfactory. Even if the exogenous theory prove to be correct, the problem, so far as treatment is concerned, becomes endogenous. The infective agent after entering the body must find a home. The real problem is to detect its hiding place, from which it or its toxins emerge at intervals to raid the nervous system. Suitable lairs might exist in the mouth, intestines, or liver. Early diagnosis of the disease should naturally be aimed at; it would be considerably facilitated if we had at our disposal a complement fixation test comparable with the Wassermann reaction in syphilis. Until we gain some knowledge as to the causative organism a suitable antigen will only be found as a result of guesswork. The first step in treatment, having explained the nature of the disease to the patient or a near relative, is to investigate the case from a general point of view, especially with regard to septic foci. We are told in the treatment of infective arthritis, for instance, to search for and treat septic foci; this we do, and sometimes we are rewarded by immediate improvement. We may attribute the arthritis to this hidden focus—for instance, an apical abscess—but there is no proof that I am aware of that infective arthritis is actually caused by the organism, probably a streptococcus, isolated from that tooth. And yet removal of the sepsis, probably by once again turning the balance in favour of the patient's resistance, permits of clinical improvement. And so, I think, we should regard disseminated sclerosis—namely, as a subacute or chronic infective disease. The mouth should be put in order, and if any doubt exists as to the state of the teeth, then an x-ray picture must be taken. I recently had under my care a nurse suffering from this disease, expressed clinically in recurrent attacks of retrobulbar neuritis which had eventually resulted in rather a high grade of optic atrophy. The teeth appeared excellent, but an x-ray picture showed apical abscesses in three. These teeth were removed, and the vision in the left eye, previously 6/36, improved to 6/12 within two weeks after the extractions. The right eye remained as before. True, this might be a natural remission of the disease, but as her vision had been very poor for some months it was at least a very happy coincidence. Septic teeth should not be removed wholesale, as on two occasions I have seen a definite exacerbation in the clinical picture result within forty-eight hours. In cases associated with or commencing by blindness, the condition of the nasal sinuses should be investigated.

Careful attention should be paid to the bowels, as constipation is a common symptom, even in the early stages of the disease. In some cases it becomes marked just prior to a relapse.

Medicinal Treatment.

Arsenic has long been recognized as the most useful drug, and the upholders of the spirochaetal theory lay emphasis on this fact. Where possible, early cases should receive precisely the same treatment as that used in neurosyphilis; the dose of intravenous novarsenobillon should, however, never exceed 0.6 gram. Failing intravenous injection, intramuscular preparations of arsenic or bismuth should be given. When such methods are for any reasons impracticable, Fowler's solution should be administered by the mouth, and may be used as a variant to the intravenous and intramuscular methods.

Pyrexial Treatment.

Protein therapy has been tried during the past few years in the treatment of this disease, and some encouraging results have been reported. A mild degree of protein shock may be produced by an injection of milk. It is preferable, however, to obtain a definite rise of temperature, and it has been found that the intravenous injection of typhoid vaccine produced this result. It is usual to commence with a small dose—for instance, 25 million—and gradually increase the amount so that by the end of six or eight injections the patient is receiving 200 millions. Within a few hours of the injection a rigor occurs, and the temperature rapidly rises to 102° or more. During this period there is, of course, general malaise and usually a temporary exacerbation of the symptoms, especially diplopia and spasticity. The injections should be given every fifth day or so, and it is best to give a small dose of novarsenobillon on the day following the injection. This form of treatment should be repeated from time to time. Malaria has also been tried; reports from Vienna are not encouraging in this respect, but Dreyfus and Hanau,¹⁴ in a recent paper, express the opinion that it is more satisfactory than typhoid vaccine treatment. Dr. F. Golla informs me that relapsing fever has replaced malaria at the Maudsley Hospital in the treatment of general paralysis of the insane, and that the results are just as satisfactory as with malaria, and the risk of a fatal termination is considerably less. Relapsing fever might therefore prove more suitable than either malaria or typhoid vaccine as a pyrexial agent in disseminated sclerosis.

It is not easy to say whether any of these various forms of pyrexial treatment are of any real value; the natural mutability of the disease and the comparatively short time that this form of treatment has been on trial have both to be remembered. In a well established case which is more or less stationary I feel sure that no such treatment is of the least use. On the other hand, in a moderately severe case of relatively short duration, in which the disease is obviously active, pyrexial treatment does sometimes appear to bring about a remission. In early cases the chances of arresting the disease, even though temporarily, are greater, and remissions occurring within a short time of the treatment are not uncommon. It may be argued that such remissions are independent of the treatment, and would have taken place in any case. That may be so, but at least such remissions, whatever their cause, do not contraindicate this line of treatment.

In conclusion, it is evident that little advance has been made in the treatment of disseminated sclerosis, and no real progress in this direction can be looked for until we know more of its etiology. The exogenous theory of this disease, though it may seem at first glance to be wild and speculative, is one that may repay further study.

REFERENCES.

- ¹ Epstein, H. A.: *Monats. f. Psych.*, 1925, lix, 70.
- ² Dawson, J. W.: *Trans. Roy. Soc. Edin.*, 1916, i, 517.
- ³ Bulloch, W. E.: *Lancet*, 1913, ii, 1185.
- ⁴ Kuhn, P., and Steiner, G.: *Med. Klin.*, 1917, xxxviii, 1007.
- ⁵ Adams, D. K., et alia: *Quart. Journ. Med.*, 1923-24, xvii, 129.
- ⁶ Buzzard, E. F.: *Lancet*, 1911, i, 98.
- ⁷ Siemerling: *Berl. klin. Woch.*, 1918, ii, 273.
- ⁸ Adams, D. K.: *Glasgow Med. Journ.*, 1923, c, 294.
- ⁹ Steiner, G.: *Ergebniss. d. Inner. Med. u. Kinderheilkund.*, 1922, xxi, 251.
- ¹⁰ Steiner, G.: *Jahresber. f. ärztlich Fortbild.*, 1926, xvii, pt. 5, 1.
- ¹¹ Bing, R., and Reese, H.: *Schweiz. med. Woch.*, 1926, lvi, 30.
- ¹² Dreyfus, H.: *Zeit. f. d. ges. Neurol. u. Psych.*, 1921, lxxiii, 479.
- ¹³ Cottrell, S. S., and Wilson, S. A. K.: *Journ. of Neurol. and Psychopath.*, 1926, vii, No. 26, 1.
- ¹⁴ Dreyfus, G. L., and Hanau, R.: *Deut. med. Woch.*, 1926, 391.

THE PATHOGENESIS OF RESPIRATORY ANOMALIES AFTER EPIDEMIC ENCEPHALITIS.

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AMONG the many mental and physical after-effects of epidemic encephalitis the respiratory disorders are now recognized as occupying a very definite place. Knowledge of this aspect of the disease has gradually accrued by the publication of numerous isolated case reports.

GROUPING OF CASES.

In an earlier paper¹ we pointed out that encephalitic respiratory disorders may occur both in the acute stage and also as "sequelae." The symptoms on analysis may be resolved into three main groups: (1) disorders of the respiratory rate, (2) disorders of the respiratory rhythm, and (3) respiratory "tics." Combinations of these groups often occur, and any of these manifestations may be constant, though more usually they are intermittent.

Respiratory Rate.

The disorders of the respiratory rate comprise acceleration (tachypnoea) and depression (bradypnoea). There is usually no alteration in the pulse rate, no cyanosis, and no thoracic distress in these varieties. In some instances the disorder supervenes only when the patient is supine, in others only when the patient stands upright. In other cases, again, the acceleration in respiration rate only comes on during sleep. The onset is frequently determined by emotional disturbances, such as those occasioned by fright, shyness, or excitement; the attack can often be checked temporarily by a strong effort of will on the patient's part. Again, the attack can frequently be cut short by speaking sharply to the patient or by ordering him to hold his breath, breathe through his nose, or perform some complicated act which will necessitate the patient's close attention. Consciousness is usually retained throughout an attack, but on rare occasions may be lost.

In some instances the lungs become over-oxygenated during the tachypnoeic spells; carbonic acid is washed out of the circulation and the acid-base balance is altered in the direction of a temporary alkalosis. Such a metabolic change results in tetany, of which some half-dozen cases following post-encephalitic tachypnoea are on record.

Bradypnoea is a much rarer manifestation, but may be met with during both the acute and chronic stages. The respiratory rate may fall as low as 6 per minute, and, in order to maintain full oxygenation of the blood, each breath is usually of greater amplitude than normal.

Respiratory Rhythm.

Disorders of the respiratory rhythm comprise those in which there is an irregular spacing in the normal cycle of inspiration: expiration. Such an arrhythmia may be regular or irregular in its metre; it may be paroxysmal or continuous in appearance. The arrhythmia may be apparent during the waking state only, or, conversely, only when sleeping. In other instances it may occur whether the patient is awake or asleep.

Sighing.—This is perhaps the commonest example of a respiratory dysrhythmia, and is often so slight in degree as to escape casual observation. It is especially common in association with Parkinsonism. From time to time the patient takes a deep inspiration followed by a prolonged expiration. A short period of compensatory apnoea usually follows. These sighs occur without any apparent reason at intervals throughout the day or night, often without the patient's knowledge.

Apnoeic Pauses.—Occasionally a patient can be observed to hold his breath in the middle of normal respiration without any preparatory acceleration of rate or depth and without any previous sighing. More commonly the apnoeic pause is ushered in by a series of deep gasping respirations,