THE WINNIPEG EPIDEMIC OF ENCEPHALITIS LETHARGICA

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Winnipeg

WHETHER to the internist, the neurologist, the pathologist, or the epidemiologist lethargic encephalitis is a disease of absorbing interest. The geographic distribution and general epidemic behaviour of this mysterious disease are baffling to a degree. In distinction to influenza which swept over Europe with express trains, crossing the Atlantic with fast liners, and wandering through Asia with camel caravans, epidemic encephalitis appears now here, now there, descending on the startled community like a bolt from the blue. In this it bears a close resemblance to acute poliomyelitis, a disease much given to making sudden appearances, assuming the proportions of a small epidemic, and then vanishing, only to reappear at some distant point. The explanation in both cases is probably the same, namely, that the abortive cases and carriers greatly exceed in number the typical examples of the disease, so that the infection is much more widely distributed than might be supposed.

The malady made its début in Vienna in the winter of 1916-17, where it was first described by von Economo in April, 1919, who christened it "encephalitis lethargica". The first case noted in England occurred in February, 1918, and during the following four months about two hundred and thirty cases were reported in London and the provinces. In the United States the first cases were described by Bassoe in the *Journal A. M. A.*, March 1st, 1919. During the present year localized epidemics of small proportions have occurred in New York, Chicago, and other large centres, but in no case has the disease assumed pandemic proportions.

The disease made its appearance in Winnipeg in the last week of October, and during the succeeding weeks fresh cases presented themselves almost every day. In not a single instance could any connection be traced between the different cases, and never more

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than a single case occurred in any one household. Several of the cases were sent in from isolated farms in the surrounding country.

The disease is a febrile one, involving the grey matter of the brain stem, and presenting symptoms usually so characteristic that a diagnosis can readily be made. Many cases are met with, however, in which one or more of the usual symptoms are absent, and many examples of what may be called "formes frustes" occur, in which no definite diagnosis can be made, so transient and fleeting are the symptoms, but which excite a strong suspicion that they should be grouped under the same heading.

For clinical purposes the cases may be divided into (1) those with general but no localizing symptoms; (2) those with both general and localizing symptoms. The localizing signs may appear early in the disease or not until later. The general symptoms are those of a general infection, and there may be one or more of the following:—fever, lassitude, headache, pain in the back, furred tongue, loss of appetite, constipation, conjunctivitis, and urinary changes such as the presence of albumen and blood. In a number of cases constipation was a marked feature; indeed, in one instance the first symptom noticed by the patient was the impossibility of getting the bowels opened. In others, the foul breath and thickly coated tongue furnish unmistakable evidence of a general gastro-intestinal disturbance. In one or two cases a severe degree of conjunctivitis has been present.

The importance of these indications of a general infection lies in the support which they give to the view presently to be advanced that we have been mistaken in regarding encephalitis lethargica as a purely cerebral infection with accompanying fever, etc., such as might accompany a cerebral abscess. It is rather a systemic infection with special localization in the brain, an infection which may involve the parenchymatous organs to a greater or less extent, and which perhaps in some cases may spare the brain, thus giving rise to atypical forms of the disease which could hardly be diagnosed in the present state of our knowledge. Such a conception would agree with that now held with regard to cerebrospinal meningitis, poliomyelitis, and other infections of the central nervous system.

Symptoms

The *onset* varies greatly in suddenness. Sometimes there is a distinct prodromal period, a period between the time when the patient first feels that he is not quite well and that at which characteristic features of the disease make their appearance. This period may vary from one to ten days or longer. As an example of

a long prodromal period, the case may be cited of a woman who had been suffering from a moderate degree of headache and feeling out of sorts for about three weeks. At the end of that period she developed internal strabismus due to paralysis of the sixth nerve. When seen in conjunction with Drs. Bruce Hill and Burridge, the diagnosis appeared to be one of cerebral tumour or cerebrospinal syphilis. The spinal fluid was normal. Five days later she became very lethargic and developed bilateral facial paralysis. The case was undoubtedly one of lethargic encephalitis, but the onset was so slow as to suggest cerebral tumour.

On the other hand, the onset may be so sudden that one hesitates from making a diagnosis. In two of our cases it was apoplectiform in nature, the patient falling to the ground, and in one instance becoming unconscious. As a rule, two or three days elapsed before the characteristic symptoms made their appearance, but the period varied greatly in the same mamner as did all the manifestations of this remarkable disease.

Age. The age varied between the extremes of eighteen months and seventy-two years.

Fever. Epidemic encephalitis is essentially a febrile disease, but the temperature is very variable; there may be no fever during the early stages of the disease, and in one or two of our cases the temperature went up only when the patient had become dangerously ill. It is well that this should be recognized, for the fact that the patient may have a normal temperature may readily lead to mistakes in diagnosis. The temperature as a rule varies between 100° and 102°, but towards the end of the illness hyperpyrexia may occur. The temperature cannot be taken as a certain indication as to the progress of the case. In the fatal cases, it is true, it seldom or never came down to normal. In some cases, however, in which the lethargy and paralysis cleared up in a day or two, the temperature remained above normal for a week or more. This peculiarity can be understood if we regard lethargic encephalitis as a systemic infection specially localized in the central nervous system, but involving other organs as well. This has been proved to be the case in poliomyelitis, and post-mortem evidence in some of our own cases makes it practically certain that the same is true in lethargic encephalitis.

Lethargy is so characteristic a feature that it has given the name to the disease, and yet it is not present in every case. It is possible that both the lethargy and asthenia are due, not so much to the causal virus, as to the site of election in the brain. That site of election is the mesencephalon in general and the peri-aque-

ductal region in particular, and it is a well-known fact that lesions in this part of the brain are often associated with marked degrees of somnolence. In this connection it is of interest to note that two structures come into intimate relationship with the mid-brain, the pineal body on the dorsal aspect, and the pituitary body on the ventral, the infundibulum of the latter arising from the floor of the third ventricle. Disturbances of the pituitary often give rise to conditions of lethargy, as in Fröhlich's syndrome. Those of the pineal may be associated with lethargy and adiposity, together with various forms of ophthalmoplegia.

In some of our cases lethargy associated with a rise of temperature was the only symptom. In one or two it was absent, and yet the diagnosis was not in doubt. These are probably cases in which the brunt of the attack falls upon the cerebral cortex rather than on the brain stem. One man, for instance, showed symptoms of maniacal excitement throughout the illness and at no time manifested any trace of lethargy, but the brain showed the typical lesions of the disease. The lethargy is usually associated with great drowsiness, and the patient may pass much of the day plunged in deep sleep. Curiously enough, insomnia at night is not infrequent, and there may be definite delirium. However deep the lethargy, however, it was almost always possible to arouse the patient, and remarkably clear answers to questions could be obtained. The patient would then close his eyes and relapse into his former state. One case was aroused for purposes of lumbar puncture, but when the needle had been introduced he at once sank into lethargy again.

Asthenia is usually mentioned as one of the cardinal features of the disease, but it has hardly proved so in our cases. Naturally it is often with difficulty that lethargy and asthenia can be distinguished from one another, for a lethargic patient will hardly appear to be overflowing with energy. In some of the cases described in the literature the patient is said to have been so weak that he was unable to turn in bed. Many of the present cases attained this immobility in the later stages, but this was due rather to mental lethargy than to muscular weakness.

Tremors. In several instances marked tremors were observed. In one of the first cases of the epidemic there were tremors all over the body which closely resembled the fibrillary twitchings of progressive muscular atrophy. In other cases there was what appeared to be a general trembling of the muscles which could best be appreciated when a hand was laid on the patient. One case displayed extraordinary clonic contractions of the rectus abdominis at the rate of about twenty to the minute and lasting for more than two days.

Expression. In the later stages the face assumes an appearance of gravity and placidity which resembles that of a waxen image. This may be due to two distinct causes. In many cases it is doubtless due to lack of emotional tone, but in others the cause of the immobility is bilateral weakness of the facial nerves. One case of double seventh nerve paralysis presented a face as unchangeable and inscrutable as that of the sphinx, although the patient was by no means dull emotionally. In many cases the Parkinsonian facies so characteristic of paralysis agitans and lesions of the corpus striatum and globus pallidus may be recognized.

Sensation. Disturbance of sensation is not a common symptom, but we have had four instances of what may be called severe neuralgic pains in the early stages of typical examples of the disease. In each of these cases there was severe burning pain in the fingers, hand and forearm, lasting for from one to two days, and unaccompanied by any sign of inflammation. There was no pain either on movement or pressure.

Headache is a fairly constant feature, but in many of our cases has been entirely absent.

Reflexes. When the pathology of the condition comes to be discussed it will be found that the lesions are not such as would lead one to expect any constant alteration in the reflexes, and in practice this proves to be the case. Occasionally, however, the knee jerks may be either abolished or exaggerated, and in several cases there was a positive Babinski on one or both sides. These features are due probably to involvement of the pyramidal fibres as they pass down through the internal capsule and mesencephalon.

Paralysis of extremities. In only one case was weakness of the limbs noted. This occurred in a man in whom the symptoms were almost entirely cortical, although associated with well-marked lethargy. After a series of five or six severe Jacksonian attacks in the left arm and leg he was left for several days with quite distinct weakness on that side. In some of the English cases atrophy of groups of muscles followed the disease.

Mental state. After having seen a number of cases, the observer becomes able to detect a certain mental condition which might be described as characteristic, although it is by no means present in every case. Lethargy is, of course, the most prominent feature, but it is not the lethargy of the comatose or the dope fiend. The patient appears to be plunged in a brown study, his thoughts would seem to have been laid away on the dusty shelves of forgetfulness, and he himself to have entered on a state of hibernation. And yet in many cases the intellect is wonderfully clear.

When the patient is aroused by being spoken sharply to, he may reply with an acuity which sometimes startles the physician. In many cases the condition appears to be one of paralysis of emotional tone rather than of ideation, although in the later stages all spheres of mental activity are equally involved. This possible dissociation of emotional from ideational disturbance is of interest in connection with the similar condition in the progressive lenticular degeneration of Wilson's disease, and also with the well-known dissociation in dementia præcox. Katatonia and other phenomena met with in dementia præcox have been observed in several of our cases.*

Cerebral symptoms. The common occurrence of headache has already been referred to. In some cases it was frontal, in some occipital. Vertigo and giddiness were present in a few cases. No definite examples of cerebellar ataxia, described by other writers, were observed. When it does occur it is probably due to interference with the connections of the superior cerebellar peduncle with the red nucleus in the mid-brain.

Tinnitus was present in so many of the cases early in the disease that it came to be regarded as a symptom of great diagnostic importance.

Diplopia, interference with accommodation, and disturbance of vision were amongst the commonest symptoms, and photophobia was present in one instance. A most characteristic feature was the frequently fleeting nature of these disturbances. They would be here to-day, gone to-morrow, and indeed they varied much from hour to hour. In this respect they are in marked contrast to the symptoms and lesions of poliomyelitis.

Cranial nerve disturbances. The neurologist may divide cases of lethargic encephalitis into three main groups, depending on whether the chief lesions are in the mid-brain, the pons and medulla, or the cerebral cortex. The site of election of the disease is the mesencephalon, and especially the peri-aqueductal group of nuclei which govern ocular movement. It is natural, therefore, that ophthalmoplegia, both internal and external, with the associated symptoms of diplopia, interference with accommodation, disturbances of vision, giddiness, nystagmus, and ptosis should be of frequent occurrence. These were the most characteristic features in our cases, as they have been wherever the disease has broken out. Equally characteristic, however, was the fleeting nature of the disturbances. The nerves involved were the third, probably the fourth, and in one or two cases the sixth. One case of paralysis of

*Dr. Hunter has drawn attention to the slowly fading smile seen in some cases, this being one manifestation of katatomia.

the sixth nerve when seen a few days later showed bilateral paralysis of the seventh nerve, but the sixth nerve palsy had completely disappeared. The pupillary reactions were usually sluggish, but in few cases were they completely lost.

Involvement of the lower group of cranial nerve nuclei in the lower part of the pons and the upper part of the medulla, in those, namely which were in relation to the floor of the fourth ventricle, was frequently observed. Reference has already been made to a case showing bilateral paralysis of the seventh nuclei. In another case which occurred at the beginning of the epidemic the patient presented what appeared to be a typical Bell's paralysis involving the whole of the left side of the face. There was a history of transient diplopia and tinnitus, but stress was not laid on these. It was not until the temperature rose and the patient began to pass into a state of lethargy that a suspicion was aroused as to the true nature of the condition. Slight weakness of the face on one or both sides could be detected in many cases which never developed any pronounced facial paralysis.

Disturbances of the eighth nerve (chiefly tinnitus) and the twelfth nerve have been not infrequent, but none of the other nerves in the pons and medulla have been involved. It is, of course, difficult to test such a nerve as the fifth owing to the lethargy of the patient. Optic neuritis has not been observed in the few cases examined.

Hiccough. Reference may here be made to the subject of hiccough. A few days after the first cases of lethargic encephalitis had begun to appear, a remarkable number of cases of persistent and aggravated hiccough were reported by the Winnipeg practitioners. Several doctors developed the condition, one of whom kept hiccoughing at intervals of a minute or less for five days. In most instances the attack lasted for about forty-eight hours. Over fifty cases of this severe form of hiccough have occurred in the city, and it is probable that there have been many more cases which have not been reported. A few of the cases have been accompanied by slight degrees of fever. There may be no connection between the two epidemics, but it may be noted that two of the cases of encephalitis displayed this symptom at the beginning of the illness.

Course and prognosis. It will be seen from the histories of some of the cases given later that the course of the disease varied as much as the clinical picture. Some of the cases could be described as fulminating. Thus in No. 6 the little patient was dead forty-eight hours after the appearance of the first symptoms.

Other fatal cases lasted not more than three or four days. The usual duration of the fatal cases was a little over a week. In the cases which recovered, the course was variable. The stupor in the milder cases cleared up after a few days, although a certain amount of lassitude might remain for a considerable time. In many instances the illness dragged on for a number of weeks, the patient being better one day and worse the next.

The temperature curve was of little assistance in prognosis; it certainly did not run parallel with the clinical condition of the patient. None of the cranial nerve palsies were of very great duration, although in some of the English cases they lasted for three months. On the whole the prognosis is better than the alarming appearance of the patient at the height of the illness would seem to indicate. In several cases a fatal outcome appeared certain, yet the patient recovered. In the English epidemic thirty-seven deaths occurred in one hundred and sixty-eight cases, a mortality of 22 per cent. Netter reports seven deaths in fifteen cases in the Paris outbreak, and Economo five out of eleven. In the Winnipeg epidemic, twenty-three cases out of sixty died of the disease, a mortality of 38 per cent.

Blood. Leucocyte counts were made on all of the cases which came into hospital. In a few there was a moderate degree of leucocytosis, the highest being 16,000, but in the great majority the count was quite normal, even when a considerable degree of fever was present. The differential count showed no variation from the normal.

Cerebrospinal fluid. The accounts of the condition of the spinal fluid contained in the literature vary considerably. English observers found little or no change in the greater number of cases, whereas more constant positive changes were found in the American cases. In some of our cases the fluid was normal, in others there was a moderate degree of lymphocytosis, and in two cases the increase was marked, 154 cells in the one case, 210 in the other. A probable explanation is that the condition of the fluid varies from day to day. Wegeforth and Ayer found variations in the same fluid at different times, and one of our cases showed four cells on one occasion and thirty-eight cells three days later, although by that time the condition of the patient was better rather than worse. Differential counts showed that the cells were practically all lymphocytes. The condition of the spinal fluid appears to bear no relation to the severity of the illness. Both of our cases with high counts recovered, and in most of the fatal cases the fluid was normal. The globulin was either normal or very slightly increased, even in

the cases in which the cell count was high. The Fehling-reducing power was normal. The condition of the fluid of course merely indicates whether or not the meninges are involved in the inflammatory process. An inflammation deep down in the basal ganglia or in the centre of the mesencephalon may leave the meninges untouched and produce no change in the spinal fluid.

Nature of the Disease

The cause of epidemic encephalitis, although certainly microbic in nature, is still unknown. Nevertheless it may be possible to arrive at a conception of the nature of the condition from analogy and from what may be termed circumstantial evidence. Three main views are held at the present moment: (1) that it bears a close relation to, and is indeed a complication of, influenza; (2) that it is a cerebral form of poliomyelitis; (3) that it is a disease *sui generis*.

1. *The influenza hypothesis.* The champions of this theory are able to marshal an array of facts in support of their contention which at first sight are very convincing. They use first the historical argument. Previous outbreaks of what has been termed sleeping sickness have usually followed or accompanied epidemics of influenza. The outbreak of sleeping sickness which occurred at Tübingen in 1712 was associated with an influenzal epidemic at the same time. The mysterious condition named nona, characterized by profound lethargy and drowsiness, followed immediately upon the great epidemic of influenza in 1890. Henoch described a case of polioencephalitis with paralysis of one arm in a girl coming on two weeks after an attack of influenza, and a number of similar cases were described about the same time. The recent outbreaks in Austria, France, England, and America were all associated more or less closely with the influenza epidemic. Further, many cases of influenza are marked by great lethargy and drowsiness, and some cases are said to have slept for several days.

These specious arguments fall to the ground, however, on closer inspection. Darwin's warning that analogy is a deceitful guide is as necessary now as on the day on which he uttered it. To say that the present outbreaks of epidemic encephalitis have followed the influenza epidemic has about as much value from the point of view of proof as to say that they followed the Great War. In a recent paper Heiman goes so far as to call the condition post-influenzal encephalitis, although in one of his eight cases four

months had elapsed since the attack of influenza. The prolonged sleep occasionally associated with influenza is very different from the condition of encephalitis lethargica. In none of these cases have the characteristic lesions in the brain been demonstrated. Finally, the Winnipeg experience seems to prove conclusively that no ætiological relationship exists between influenza and epidemic encephalitis. The present outbreak is typical in every respect, including the microscopic findings in the brain, but it is a year since influenza visited the city, and not one of the cases had had a recent attack. Indeed, in a majority of the cases there was no history at all of influenza.

2. *The poliomyelitis theory.* The points of resemblance between poliomyelitis and lethargic encephalitis are many and close. As the grey matter of the anterior horns of the spinal cord is traced upwards into the brain stem it becomes broken up by the decussations of the pyramid and fillet, so that many of the cranial nuclei, more especially those of the sensory and mixed nerves, come to assume a lateral position. The purely motor nuclei of the third, fourth and sixth nerves, however, maintain their median relation. Poliomyelitis is a disease which in its typical form attacks the grey matter of the anterior horns of the cord, whilst in lethargic encephalitis the brunt of the attack falls on the grey matter of the brain stem, especially the nuclei of the third, fourth, and sixth nerves. Both diseases are acute in onset, febrile in nature, motor in their manifestations, although in both there may be disturbances of sensation.

A closer scrutiny reveals points of similarity of even greater importance. Poliomyelitis can no longer be regarded as a disease involving only the spinal cord. Just as cerebrospinal fever is a systemic infection usually attacking the central nervous system, but in some cases sparing that system, so poliomyelitis must be regarded as a general infection in which other organs than the cord may be involved. As Peabody, Draper, and Dochez have shown in their masterly monograph, there is widespread involvement of the lymphoid apparatus, of the liver and other parenchymatous organs, and of the brain. The same lesions which are so characteristically found in the cord, and which are so similar to those of lethargic encephalitis, are also met with in the pons and medulla. Although not hitherto so described, there can be no doubt that lethargic encephalitis is also a systemic infection, as will be seen in the discussion of our pathological findings, with the production in most cases of characteristic lesions in the brain. The fact that

very similar changes may be found in the brain in both diseases is a fact which cannot be ignored. The essential changes are perivascular infiltration, diffuse inflammatory infiltration, hæmorrhages, and destruction of nerve cells. All these are found in both conditions, but there are certain points of difference, possibly fundamental in character, which will be discussed under the heading of pathology.

On the clinical side the resemblance between poliomyelitis and lethargic encephalitis is equally striking. Since the days of Wickman an encephalitic form of poliomyelitis has been well recognized. Peabody, Draper, and Dochez describe a number of cases of most evident inflammation of the grey matter of the brain. This may be associated with spinal paralysis, or may occur alone. Facial paralysis occurred in eight out of twelve cases of combined cord and bulb lesions, and ocular palsies were present in four cases. Nystagmus, diplopia, strabismus, and disturbances of speech were all met with. Four of Peabody's cases, moreover, displayed a marked condition of drowsiness deepening into stupor. The patients lay in a sort of coma vigil, and the face assumed a peculiar mask-like immobility. The temperature was elevated. The stupor, after lasting several days, cleared up with remarkable rapidity in the course of a few hours. In a series of four hundred cases Batten found that 12 per cent. showed evidence of encephalitis involving the medulla, pons, or mid-brain.

It must be admitted, then, that there are many striking points of similarity between poliomyelitis and lethargic encephalitis, both as regards clinical manifestations and pathological lesions. This does not mean, however, that they are necessarily one and the same disease. Diverse lesions in the brain may produce a very similar clinical picture. Both tuberculous meningitis and cerebral tumour may be the cause of lethargy and drowsiness, headache, diplopia, and cranial nerve palsies. Further, in different diseases the pathological picture may be remarkably similar. The fact that perivascular infiltration and degeneration of ganglion cells are found both in poliomyelitis and encephalitis lethargica does not prove that they are due to the same cause, for practically identical changes are found in cerebral syphilis and in trypanosomiasis, diseases of which the cause is definitely known.

If the arguments for the poliomyelitis hypothesis are strong, those against are even more formidable.

1. Epidemics of poliomyelitis occur with remarkable constancy in the summer time; the outbreaks of encephalitis have occurred during the winter months.

2. Poliomyelitis is a disease, par excellence, of children; encephalitis is much more common among adults than children.

3. The onset of paralysis in poliomyelitis is typically sudden, the effects are lasting, and there is usually muscular atrophy; in encephalitis the palsies often come on gradually, are characteristically fleeting, and there is no muscular atrophy.

4. If the two diseases are due to the same cause, it is strange that in the present epidemic no cases of spinal poliomyelitis should have occurred.

5. The virus of poliomyelitis is readily transmitted to monkeys, whereas no cases of satisfactory and undoubted transference have been reported in encephalitis.

6. Although the virus of poliomyelitis is introduced intracerebrally in monkeys, the lesions produced are always spinal, never cerebral.

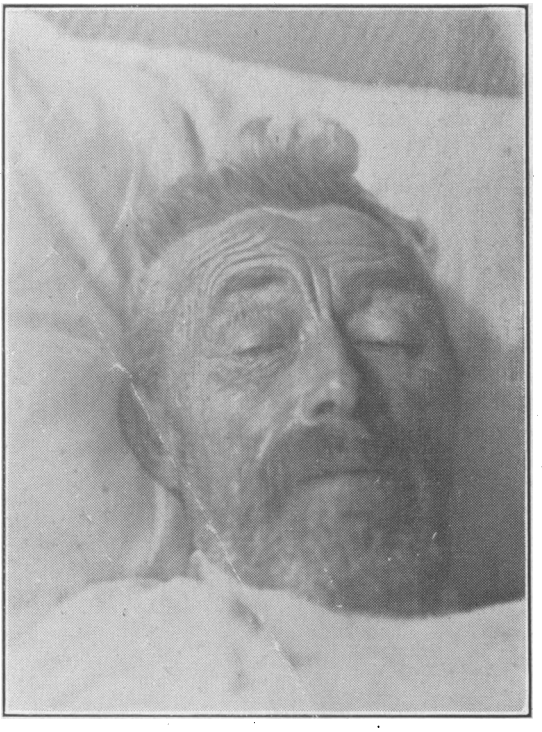
7. Although many cases of poliomyelitis may show lethargy, even coma, yet with the onset of respiratory difficulty, as Peabody has pointed out, the mental state becomes clear, and the child seems to awaken to the struggle that lies before it. Nothing like this is seen in lethargic encephalitis.

8. Leucocytosis, sometimes as high as 30,000, is met with in poliomyelitis. It is usually normal or only slightly raised in encephalitis.

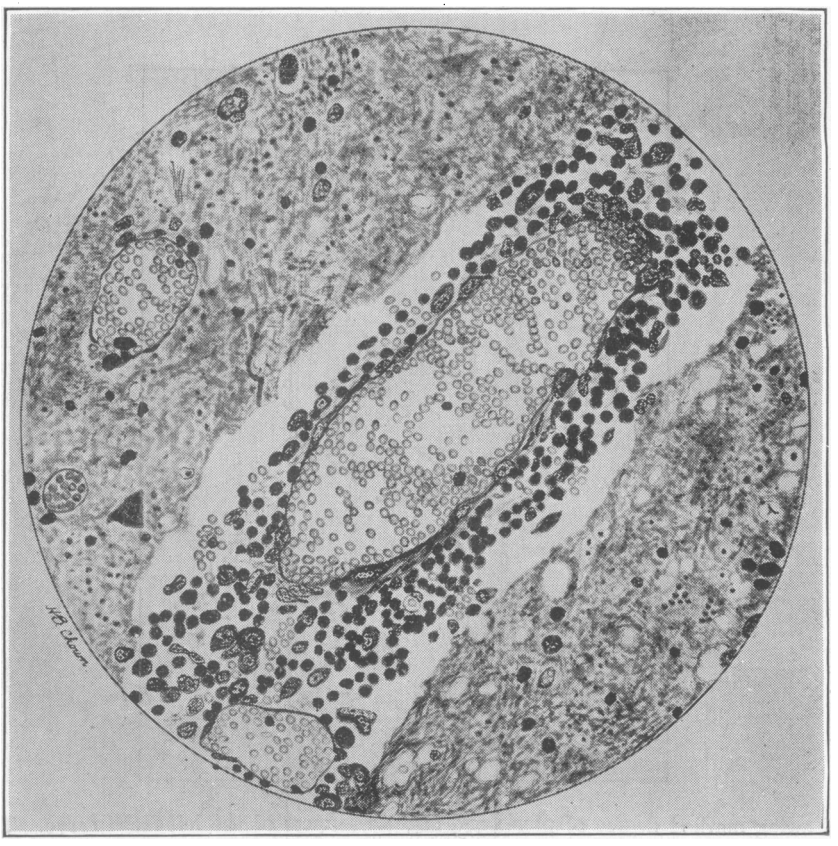
9. A lymphocytosis, sometimes marked, in the cerebrospinal fluid is the rule in the early stages of poliomyelitis; the count is normal or only slightly increased in encephalitis except in exceptional cases.

10. An attack of poliomyelitis is supposed to confer practically complete immunity, so that true second attacks, apart from relapses, are almost unknown. Batten refers to three very doubtful cases in the literature, but considers that none of them can be accepted as undoubted examples. In one of our fatal cases the patient had had a typical attack of poliomyelitis in childhood which left him with permanent weakness of one leg.

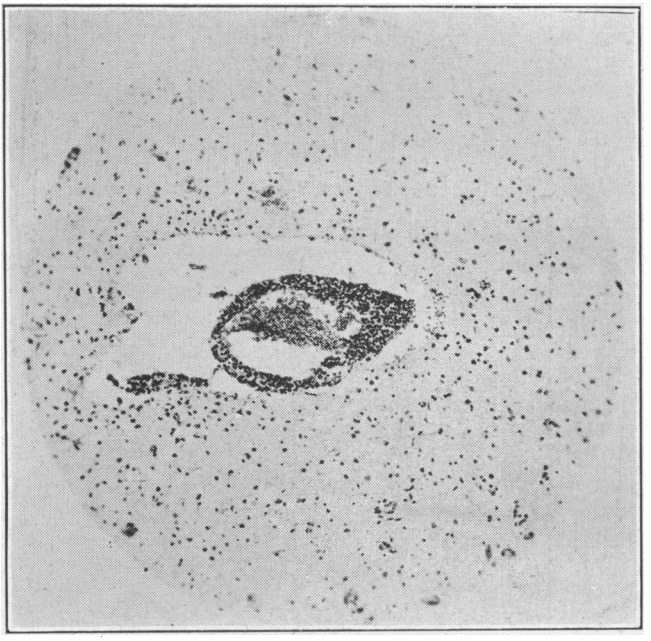
11. The ultimate decision will rest with the bacteriologist or pathologist. The bacteriological evidence, as stated above, is against the theory so far. The pathological evidence is uncertain. The evident changes in the two conditions are of course similar. Some of our work in the present epidemic, however, seems to suggest important differences.



Showing marked degree of ptosis and slight weakness of the left facial nerve. The patient is trying to look at the camera.



Vessel in mid-brain showing perivascular infiltration with small lymphocytes and larger plasma cells.



Round-celled infiltration around vessel in mid-brain.

CLINICAL CASES

It is not possible, nor indeed desirable, within the limits of this paper, to give details of all the clinical cases. They have accordingly been divided into the following groups, two or three examples of each being given: (1) mesencephalic; (2) subthalamic; (3) bulbar; (4) cortical; (5) apoplectic; (6) septicæmic; (7) maniacal. This is, of course, far from a satisfactory or scientific classification, being partly anatomical and partly based on symptoms. It is rather a series of heads under which may be described the clinical symptoms which presented themselves in the present epidemic.

Mesencephalic Type

1. *Fatal case with ocular and sensory symptoms.* F. E. C., male, aged thirty-seven, admitted to hospital on November 9th, under Dr. Hunter. For two weeks before admission he had complained of general weakness and loss of appetite, and at times felt unduly sleepy. On November 6th he felt so weak that he was unable to go to work. He suffered severe pain in the right shoulder and upper arm for which poultices had to be used, and which lasted for two days. He became very drowsy and lethargic on November 8th, and twitchings were noticed in the arms, face and lips.

On admission the patient was in a profoundly lethargic condition, taking no notice of what was going on and lying motionless in bed with closed eyes and a somewhat flushed face. When spoken to, however, he answered with clearness and accuracy. There was right-sided ptosis, inequality of the pupils, and slight weakness of the right seventh nerve. The pupils reacted but faintly to light and not at all to accommodation; the fundus was normal. Irregular tremors appeared to play over the body, now affecting the face, now the arms and legs. The knee jerks were normal, and there was no Babinski sign. The temperature was 103°, pulse 120, respirations 24. There was a leucocytosis of 16,000, and the cerebrospinal fluid was normal, apart from a slight increase in pressure.

During the next three days the lethargy deepened into coma, the ptosis became bilateral, marked cyanosis developed, and the patient died on November 12th, with a temperature of 104·5°. At no time during his stay in hospital was his temperature below 100°.

At autopsy there was marked congestion of the cerebral vessels, dilatation of capillaries in the mid-brain and the medulla,

but no gross hæmorrhages. Microscopic examination showed characteristic patches of perivascular infiltration and cellular degeneration throughout the brain stem.

2. *Severe case with typical onset.* T. R., male, aged forty-four years, admitted to hospital on November 21st, under Dr. E. W. Montgomery. The patient, a street-railway motorman, was in the best of health until November 19th, when he felt a "soreness" on the left side of the head which he was unable to localize. He felt well otherwise, and worked full hours. On the following morning he did not feel at all well, his legs were so shaky that they almost gave way under him, his head was worse, and he was relieved from duty at 4 p.m. Next day he felt better, got up at 5 a.m., and worked for two hours. His legs then became weak, and he noticed that when a car approached him there appeared to be two cars, one upon the track on which he was driving and one on the other. He went off duty chiefly because of the weakness of the legs, but by that time he was beginning to feel drowsy.

On admission the patient presented a typically febrile appearance, the face was markedly flushed, the eyes were heavy, the tongue furred, the temperature was 100·4° and the pulse 84. He was unable to shut the right eye, the pupils reacted sluggishly to light, but there were no other signs of cranial nerve palsies apart from the diplopia, which was still very pronounced. The cerebrospinal fluid was normal, and the leucocytes 7,200. During the succeeding days drowsiness alternated with periods of great restlessness, and the patient rapidly lost ground, his face acquired a pinched appearance, and although the temperature gradually returned to normal, there can be little doubt that the case will terminate fatally.

3. *Fatal case with marked insomnia.* A man, aged twenty, under the care of Dr. Chestnut, noticed a twitching of the left upper eyelid. Next day a temporary diplopia developed, lasting only twenty-four hours. About the same time he complained of what he described as a soreness in the right upper arm, and later in the left forearm and hand. There were no signs of local inflammation, nor pain on movement or pressure. Hiccough was a troublesome feature during the early stages of the illness. From the first, insomnia was marked. On several occasions there were fleeting noises in the left ear. The patient was nervous and excited, and on the second night of the illness he went to a dance. On the fifth day he began to exhibit drowsiness during the day, although wakeful at night. Distinct ptosis was noticed, and he complained

of feeling "jerky", although there were no definite twitchings of the muscles. He rapidly became very drowsy and lethargic, although restless and sleepless at night, and died in a state of coma on the eighth day of the illness.

SUB-THALAMIC TYPE

4. *Case resembling acute paralysis agitans.* Miss K., aged twenty-one years, seen with Dr. Field on November 24th. Nine days before she began to feel dull and out of sorts, complaining of a buzzing noise in the left ear. She suffered from insomnia, and during the day was alternately apathetic and restless. There were no eye symptoms nor undue drowsiness. The temperature was normal. She presented a most striking picture of Parkinson's disease, sitting leaning forward in her chair, with her head stooping forward as if she had a stiff neck, and the blank, expressionless appearance of a mask. When she walked, the gait was typical to a degree, shuffling, the back bent forwards, the arms flexed at the elbow and the hands at the wrist, the rigid gaze fixed on the ground. There were irregular tremors of the arms and legs, the knee jerks were increased, there was no paralysis of the cranial nerves, the pupils reacted well to light and accommodation. In such a case as this the lesions must almost certainly be in the same region as is involved in paralysis agitans, namely the putamen and globus pallidus.

BULBAR TYPE

5. *Mild case with mainly local symptoms.* A. M., a man aged thirty-five, seen with Dr. Victor Williams. About October 25th, he began to suffer from violent throbbing in the head and distressing dreams at night. These were succeeded by pain in the suboccipital region, vomiting, slight diplopia, and noises in the left ear. When seen on November 1st, there was complete facial paralysis on the left side and very slight lateral nystagmus. The pupils reacted normally, and there was no other sign of an oculomotor lesion. The patient was rather lethargic, but the temperature was normal. As this case occurred before the beginning of the outbreak of encephalitis, a diagnosis of ordinary facial paralysis or possibly of tumour in the cerebello-pontine angle was made. A few days later, however, the patient became extremely drowsy, and the correct diagnosis was then evident. At the end of ten days the drowsiness had completely cleared up, as had the facial paralysis, except for slight weakness in the lower part of the face.

Cortical Type

6. *Fatal case with cortical symptoms.* A girl seven years of age, admitted to hospital under Dr. Field on November 12th. She was taken ill suddenly on the morning of the previous day with headache, vomiting, ringing in the ears, failure of vision, unsteadiness in walking, and convulsions, of which she had six during the day. No diplopia nor strabismus. During the time that she was in hospital she had a series of attacks of typical Jacksonian epilepsy, in which there were severe convulsions of the right arm and leg, and the head was jerked over to the right side. Towards the end of the seizure the spasms extended to the left leg. The attacks lasted from five to ten minutes, and during them the patient was quite conscious. In the intervals she lay quietly in bed, but showed no trace of drowsiness. There was albumen in the urine, together with epithelial cells and red blood corpuscles, so that a diagnosis of uræmia was considered. She died early on the morning of November 13th. The temperature at no time was above 102°, and shortly before death it went down to 96°.

The autopsy showed marked flattening and œdema of the convolutions in the left frontal region, and the characteristic microscopic lesions of encephalitis were found in the brain stem. There was extreme congestion of the kidney, hæmorrhage into the collecting tubules, and degeneration of the convoluted tubules.

7. *Mild case with cortical symptoms.* J. H., male, aged thirty-two years, was admitted to hospital on November 13th, under Dr. Moody. On the morning of that day he noticed a noise as of whistling in both ears, and suffered from a slight headache. In the afternoon he visited a friend in the hospital, went down town feeling much better, entered a store, and then was suddenly overcome by weakness; the room appeared to go round him, and he would have fallen had it not been for the assistance of a companion. He experienced great weakness in both legs, more especially the right, and also in the right hand. He was taken back to hospital, and on admission it was noticed that there was rigidity and twitching of the right leg. An hour later he had a typical Jacksonian attack involving the right arm and leg, but not the head. There was a positive Babinski sign on the right side. He now became very drowsy, and slept for the greater part of the succeeding three days. He had five more convulsive attacks, but none after the second day. The temperature was 101° on admission, and remained

elevated for five or six days. The leucocytes were 7,600, and the cerebrospinal fluid was normal, except for a moderate increase in pressure. The patient made a good though gradual recovery. The temperature gradually returned to normal, the drowsiness departed, but there was weakness of the right arm and leg and a positive Babinski on the right side for fully a week.

Apoplectic Type

8. *Sudden onset with aphasia.* Mrs. J., aged fifty years, was admitted to hospital on November 23rd. She was perfectly well on the morning of that day. At 5 p.m. she suddenly staggered to a wall, and would have fallen but for her husband. She was laid on a couch in what was described as an unconscious condition. She was unable to speak. Spasmodic movements of the left arm and leg were noticed. On admission four hours later, she was extremely drowsy but not unconscious, the left arm and leg were stiff, the deep reflexes in those limbs were exaggerated, ankle clonus and a positive Babinski sign were present on the left side, the mouth was drawn slightly to the left. The temperature was 96°, pulse 70, respiration 26. Red blood cells were present in the urine and a large amount of albumen and hyaline casts. There was much doubt at first as to whether the case was one of ordinary apoplexy or lethargic encephalitis.

For two days she lay like a log, very drowsy, with eyes closed, uttering no word, making occasional movements with the left arm and leg. She has gradually improved and is now quite bright mentally, but is still unable to speak. She has regained the use of her limbs. The urine is now normal.

9. *Apoplectic onset with aphasia and hemiplegia.* A girl of ten years went to bed feeling perfectly well. Two hours later she awakened with a cry, and her parents found her tossing about the left arm and leg, but the right side remained motionless. She was unable to speak. When seen by Dr. E. W. Montgomery she was found to show a right-sided hemiplegia of upper neurone type with a positive Babinski and paralysis of the internal rectus on the left side. She was completely aphasic and extremely drowsy.

10. *Fatal case resembling apoplexy.* M. V., a man aged forty, after an indefinite history of headache, suddenly passed into a state of coma from which he could not be aroused. He lay on his back breathing stertorously, the right arm and leg were spastic, and there was incontinence of urine. The clinical picture was so

strongly suggestive of cerebral hæmorrhage that that diagnosis was made. He died forty-eight hours later, and at the autopsy the brain presented a remarkable appearance. The whole of the left cerebral hemisphere was studded with petechial hæmorrhages, more marked in the white than in the grey matter, and the brain substance was of a distinct pink colour. There were a few lesions of a similar nature in the right hemisphere. The basal ganglia, mid-brain, pons and medulla were all extremely congested, the change being most marked in the substantia nigra. Microscopic examination showed numerous hæmorrhages and other signs of acute encephalitis throughout the brain, marked congestion and degeneration in the kidney, and a lesser degree of congestion in the liver.

Septicæmic Type

11. Mrs. M., aged forty-two years. Ill for seven days with headache, diplopia, ptosis, strabismus, and marked drowsiness and lethargy.

Post-mortem examination by Dr. Bell showed widespread petechial hæmorrhages over the pleura, pericardium, and diaphragm, and blood-stained effusion in pleural and peritoneal cavities. The kidneys were very soft and flabby. Microscopic sections showed most remarkable changes which are described more fully under the heading of pathology. Not only was there extreme congestion of both cortex and medulla, and profound degeneration of the convoluted tubules such as might be found in corrosive sublimate poisoning, but there were focal collections of round cells in the boundary zone strongly suggesting scattered foci of infection. The pial vessels were extremely congested, and there was marked congestion of the mid-brain, notably in the substantia nigra. The microscopic appearances in the mid-brain were of the usual character.

12. G. P., aged thirty-eight years, developed headache and diplopia, and soon became very drowsy. The lethargy deepened with remarkable rapidity, although he could be aroused almost until the end. No cranial nerve palsies were noted. The illness lasted only two days, and the patient died in a state of coma. There was moderate fever throughout the illness. It is important to note that the patient had an attack of infantile paralysis when a child, which left him with a typically weak and atrophic leg.

The post-mortem examination by Dr. Bell revealed widespread hæmorrhages over the pleura, pericardium and diaphragm. The

pial vessels were very congested, and the substance of the cerebrum was much softer than normal. There was considerable congestion of the mid-brain, and the usual microscopic changes were found.

13. T. D., aged fifty years. For several days he had been ill with typical symptoms of lethargic encephalitis, and was found dead in bed. At post mortem the parietal and visceral pleura, pericardium, and diaphragm were covered with petechial hæmorrhages. The body was so decomposed, owing to having been kept for several days in a warm room, that microscopic examination of the organs was impossible.

Maniacal Type

14. A man fifty years of age, living in the country, on getting up one morning began to pray. This struck his wife as being unusual, for it was not the custom with him. He continued at his prayers all morning, and later in the day became very excited. He persisted in crawling under the bed, and had to be strapped down to the mattress. There was no trace of drowsiness or lethargy. He remained acutely maniacal for several days, and was then sent by train to the Psychopathic Hospital in Winnipeg, but died in the ambulance.

At the post mortem, hæmorrhages were found in the floor of the fourth ventricle, and microscopic examination revealed the characteristic lesions of lethargic encephalitis in the medulla, pons and mid-brain.

Pathology

Encephalitis lethargica must still be classed among the diseases of mystery. Its cause is unknown, and the pathological changes found in the brain do not throw conclusive light upon the nature of the condition. Nevertheless, quite definite microscopic changes are found, changes from which alone it is sometimes possible to make a final diagnosis in the more obscure cases. These changes cannot at present be described as being pathognomonic. This, however, is hardly to be wondered at, for the lesions in brain diseases are limited in variety, and several very different clinical entities present not dissimilar microscopic appearances.

Post-mortem examination was made in eighteen cases either by Dr. Bell or myself. Permission was obtained to remove the kidney in two private cases in which it was not possible to perform a com-

plete autopsy. The task of examining this extensive material by modern neurological methods is a matter of time, and a more detailed report of further researches on the brains and kidneys will be made in a subsequent paper. All that is at present attempted is to present the results of a preliminary and necessarily incomplete investigation.

Brain. The brain may appear perfectly normal to the naked eye, although marked changes may be found on microscopic examination. In many cases a varying degree of hyperæmia was observed in the brain-stem; being most marked as a rule in the region of the substantia nigra in the mid-brain. The substantia nigra was less clearly defined than in the normal brain, and in some cases could be distinguished with difficulty. In one case (No. 10) there were petechial hæmorrhages throughout the whole of one cerebral hemisphere, and congestion so great that the brain substance was of a distinct pink colour. Three cases showed small hæmorrhages in the floor of the fourth ventricle.

Microscopically the outstanding features have been capillary congestion and perivascular infiltration. These changes have not been found by any means uniformly throughout the brain. In the cortex, congestion has been present, but seldom any degree of perivascular change. The most pronounced changes have been in the mid-brain and medulla, and to a lesser extent in the pons and basal ganglia.

The perivascular changes are the most striking and interesting. The affected vessel is separated from the brain substance by a clear space varying in width, in some cases containing numerous red cells which have escaped from the vessel. This appearance is perhaps due to an inflammatory œdema. The vascular endothelium is unusually distinct, owing to swelling of the cells which may come to resemble fibroblasts. The wall of the vessel is infiltrated with a collar of cells which is of fairly uniform thickness around the vessel. Some of these cells are lymphocytes, but the majority in our sections are unmistakably plasma cells, with a much larger and more vesicular nucleus, often placed eccentrically, and abundant cytoplasm, the outline of the cell being often polygonal rather than round. No evidence of invasion of the surrounding brain matter by these cells could be found, so that the diffuse infiltration of other writers was not corroborated. A study of the sections gave the impression that the brunt of the attack had fallen upon the vessels, and that any changes in the nerve elements would probably be secondary. Distinct hæmorrhages were present

in some sections, but they were by no means a prominent feature, except in one or two cases where they were evident to the naked eye.

The nerve cells showed in places changes of great interest, but these are still under investigation. Varying degrees of cellular dissolution were present, from slight chromatolysis to complete disappearance of the Nissl granules and even of the cell body. In some of the cells there was an abundant yellow granular pigment, lighter in colour than that normally present in the substantia nigra, and resembling the pigment found in the senile brain. In places the body of the cell had disappeared, its position being indicated by this yellow pigment. Considering that the fatal cases were of only a few days' duration, it is indeed remarkable that such profound destruction coupled with so much pigmentation should have occurred. A detailed examination of the cranial nerve nuclei in the mid-brain, pons and medulla has not yet been made.

Some definite relation between the vascular and cellular changes would be expected, whether the cellular degeneration was secondary to the vascular changes or was the result of the action of a virus situated in the blood vessels. No such relation, however, could be found. The most inflamed vessels might be surrounded by apparently normal nerve cells, and in places where the cell bodies were mere shadows there might be no vascular change. The pathology, then, may be regarded as an acute interstitial inflammation with parenchymatous degeneration, no clear connection being established between the two conditions.

Meningeal involvement was slight and variable. In many cases none could be found, in others there was a moderate degree of infiltration around the vessels. The changes in the spinal fluid are probably directly dependent on those in the meninges.

Kidney. An observation of great importance is that other organs than the brain may show marked changes. It is rather remarkable that in the records in the literature attention appears to have been focussed on the brain so exclusively that no microscopic examination of other organs was made. This was unfortunately also true of our own earlier cases, but it was soon realized that a more general examination was necessary. It was found that striking lesions were present in the kidneys in all of eight cases examined. There were two chief types of change, extreme congestion of the vessels, most marked in the medulla but also present in the cortex, and great degeneration of the convoluted tubules. Not only were the medullary vessels distended to such a degree as to obscure the tubules, but definite hæmorrhage into the tubules

had occurred in many places. The vascularity was so great as to recall at times the edge of an infarct. The parenchymatous degeneration varied in degree, but in one case it amounted to complete necrosis of the cells lining the tubules, the picture suggesting the action of some powerful irritant on the renal cortex. The glomeruli showed considerable congestion and in some there was slight hæmorrhage into the capsular space; there was no change in the capsular epithelium. The contrast between the convoluted and collecting tubules was most marked; a convoluted tubule would show extreme disintegration whilst an adjoining collecting tubule would be apparently normal. The cells lining the ascending loop of Henle showed a similar change, although less marked in degree. The brunt of the attack, then would seem to fall on the vessels and the filtering apparatus of the kidney.

The collecting tubules, however, did not always escape so lightly as the above description might imply. Here and there in some cases the cells lining these tubules were crowded with fine yellow granules. The exact nature of these granules has not yet been determined. They were most numerous in the case showing widespread hæmorrhages throughout the cerebrum, and it is probable that they consist of blood pigment. In this case the walls of some of the collecting tubules stained so darkly with iodine as to suggest an amyloid reaction, a slighter degree of the change being also noted in the glomeruli. In one case there were abundant granules in the collecting tubules giving a fat reaction with Scharlach R in frozen sections, although the convoluted tubules which were profoundly disintegrated showed no trace of fat. This remarkable finding may have been due to the processs having been so acute in the convoluted tubules that there was no time for the fatty change to take place, whereas the slighter lesions in the collecting tubules allowed time for the reaction to occur.

In one case (No. 11) an additional lesion was noted. In the boundary zone between the cortex and medulla there were foci of round celled infiltration strongly suggesting the presence of a bacterial as opposed to a toxic irritant. These were quite localized, and it was not possible to determine whether they bore any definite relation to the vessels. The patient had been ill for seven days. At the autopsy there were widespread petechial hæmorrhages, and blood-stained serous effusion in the pleural and peritoneal cavities.

Urinary changes would be expected in view of such a condition of the kidney. Blood and albumen were present in several of the cases, one of which at autopsy showed the usual lesions in the

kidney. Some of the kidneys were obtained from outside cases, in which there was no record of the condition of the urine.

Observations on other parenchymatous organs are being made, but the results are not ready for publication.

It would appear from the above observations that there is sufficient evidence to show that lethargic encephalitis is not merely an inflammatory condition of the brain, but a general infection involving many parenchymatous tissues in which the brain is the chief sufferer. This conception falls into line with modern views regarding other infective conditions of the central nervous system. General paralysis, trypanosomiasis, cerebrospinal meningitis, and acute poliomyelitis are now regarded as general infections with special localization in the brain and cord. In view of the many points of similarity between lethargic encephzlitis and acute poliomyelitis it is of interest to note that Peabody and his co-workers found constant lesions in the liver and the lymphoid tissues, especially in Peyers patches.

All bacteriological investigations have proved negative. Cultures of the blood and the cerebrospinal fluid gave no result. Dr. Bell and Dr. Cadham emulsified portions of the brain and injected it into the brain of rabbits, but without effect. Dr. Nicholson did the same with the cerebrospinal fluid with a similar result.

Summary

1. The Winnipeg epidemic of sixty cases with twenty-three deaths corresponded closely with previous epidemics already described. The mortality of 38 per cent. was unduly high.

2. The characteristic case presenting fever, drowsiness, strabimus, ptosis, diplopia, tinnitus, some degree of facial weakness, constipation and perhaps some urinary and spinal fluid changes, is readily recognized. The fleeting nature of the disturbances is very typical. Sensory disturbances were present in a number of cases. Some of the cases were atypical, suggesting cerebral tumour, apoplexy, and other brain lesions.

3. The brain was examined in eighteen cases, and showed marked congestion, perivascular infiltration with lymphocytes and plasma cells, and occasionally hæmorrhage. Degeneration of the nerve cells was variable. The changes were most marked in the mid-brain. Marked lesions were also found in the kidneys.

4. A remarkable epidemic of hiccough occurred in this city at the same time as the outbreak of encephalitis.

In conclusion I wish to express my great indebtedness to the numerous physicians who have so generously placed their clinical material at my disposal, to Dr. Gordon Bell for providing me with much post-mortem material and for valuable assistance in solving some of the pathological problems which presented themselves, and to Miss M. van Romburgh for the devotion and care with which she has prepared the microscopic material.

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