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Subject: LETHARGIC ENCEPHALITIS. A CLINICAL STUDY OF ELEVEN CASES WITH SIX AUTOPSIES.

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LETHARGIC ENCEPHALITIS.A STUDY OF ELEVEN CASES WITH SIX AUTOPSIES.

Introduction. In the Lancet for April 20th 1918 there appeared two short papers one by Harris[1] of London entitled "Acute Infective Ophthalmoplegia or Botulism" and the other by Hall[2] of Sheffield entitled "Note on an Epidemic of Toxic Ophthalmop legia associated with Acute Asthenia and other Nervous Manifestations". Both these papers described small epidemic s of an obscure cerebral condition characterised chiefly by ocular paralysis and more or less marked drowsiness, accompanied as a rule by pyrexia and asthenia. Within the next few weeks it became evident that the same obscure disease had appeared in various towns throughout the country, and in all, several hundreds of cases were reported from one source or another during the next six months. A small number of cases occurred in Glasgow at that time,some of which were published by Picken[3] in the Lancet while others were described by Findlay[4] in the Glasgow Medical Journal. Harris's original suggestion that the disease was Botulism, a Toxic condition due to the action of the Bacillus Botulinus was apparently based on the fact that most of his patients had partaken of sausage or some other form of tinned food shortly before turning ill. The only other evidence he produced was the discovery in the urine and stools of one of his patients of anorganism morphologically resembling the Bacillus Botulinus. It soon became evident, however, that the new disease was not Botulism and it was suggested by Crookshank[5] that it was in all probability a rare form of Heine-Medin Disease the best known form of which is Acute Poliomyelitis.

Meanwhile it had been discovered that the new disease had appeared in France about the same time as in England where it had been described first by Netter[6] who was convinced

that it was not a form of Acute Poliomyelitis but a separate disease to which he applied the name L'Encéphalite Léthargique Epidémique a name under which Economo[7] had described the same disease in Vienna during the winter 1916-1917. It appeared, then, that the disease was much more widespread than was at first apparent, and since that time it has appeared in various parts of the world, notably in America, where various small outbreaks have been described by various writers. In this country, too, the disease has remained alive in sporadic form, the epidemic of 1918 falling offin the summer, but attaining proportions again in the early months of 1919 and again in 1920, although in neither of these years reaching the prevalence that it had in 1918. In France too there has been a renewed prevalence of the disease at the end of 1919 and the beginning of 1920 not only in Paris but in some of the other large towns notably Lille. Cases, too, have been reported recently from Roumania and from Egypt. The disease has not been described in Australia but it is interesting to note that a somewhat similar disease, characterised more by convulsive seizures than by lethargy, attained epidemic proportions in that continent in 1917 and again in 1918, attacking principally children but also adults and having an extremely high mortality rate. The pathological lesions found were similar in type to those found in encephalitis but their distribution was different the cord being very widely involved in the Australian epidemic while in lethargic encephalitis it is hardly involved at all.

Following on the discovery that the "new disease", as it was popularly termed, had appeared in other countries besides Britain, came the information that it had appeared at other times too, in the past, so that its claim tobe new could not be substantiated. Crookshank[8] was able to show that it had appeared in different countries in Europe over and over again during the past 450 years, very often as a new and mysterious disease described under many different names some of which

strangely enough, suggested as its cause food poisoning, for example, Kriebelkrankheit (or ergot disease) and Raphania (or radish seed poisoning) while in 1820 it was attributed to sausage poisoning just as it was in 1918. In Italy the disease was known in the sixteenth century as Mal Mazucco and in the last decade of the nineteenth century it was rife in Northern Italy and Hungary as Nona. In England a convulsive form of encephalitis was described by Willis in the seventeenth century as "a fever chiefly infestuous to the brain and nervous stock" while a few years later in 1673 a lethargic type was described by Sydenham as a "comatose fever". Netter[9] quotes Albrecht of Hildesheim as describing the disease in 1695 with its chief symptoms of lethargy, fever, and ocular palsies. In 1712 it appeared in epidemic form at Tübingen and was described by Kammermeister under the name of Schlafkrankheit or sleeping sickness -- the newspaper name for it to-day,

The cases which form the subject of this Thesis occurred, ten of them in Glasgow and one in a neighbouring town, between April 1919 and January 1920, and were under my care in Ruchill Fever Hospital. The first three cases were admitted in April, May and August respectively, while the remaining eight were admitted between October 23rd and January 2nd, a period of just over ten weeks. The first taree were obviously sporadic cases; the remaining eight might be regarded as possibly a small epidemic outbreak although they were very widely scattered over the city and it was impossible to establish any definite connection between different cases.

Case 1. N. W. an unmarried woman of 32 years, while not robust, was in fairly good health until 11.4.19 when she was seized with a very severe headache. The headache persisted and on the following day was accompanied by sickness and vomiting which occurred from time to time during the following eight days. On 20.4.19 she lost power in all her limbs, and became drowsy and stupid. The drowsiness persisted passing at times into semi-consciousness from which patient could be

roused with a little difficulty until she was admitted to Hospital on 25.4.19 with the diagnosis of Cerebro-Spinal Fever.

On admission she was semi-conscious and very cyanosed. Temperature was 98.2°F, pule 88, and respirations 28. When seen about an hour later her colour was much better and she was conscious and able to answer questions. Her mental condition seemed rather dull and her answers came very slowly and not too intelligently. The voice was husky and articulation difficult, speech apparently requiring very great muscular effort. There was also considerable difficulty in swallowing so that saliva tended to collect in the throat and dribble from the mouth. There was no ophthalmoplegia and no facial palsy nor any palsy of any of the other cranial nerves. There was paresis of all four limbs amounting to practically complete flaccid paralysis of both legs while the arms could be moved very slightly. There was no impairment of sensation to be determined anywhere. Superficial and deep reflexes could be elicited but were not active. Plantar reflexes were flexor in type. There was no retraction of the head and no stiffness of the cervical muscles.

Cardio-Vascular system --- The heart's sounds were pure and of good quality. The pulse was of high tension and the arteries sclerosed.

No pulmonary lesion could be detected. The urine was free from albumen and sugar. The Wasserman Reaction was negative. The tongue was coated and the bowels constipated. Control of the bladder was retained.

Lumbar Puncture yielded a clear fluid under slightly increased pressure. The fluid did not form a fibrin-web on standing and the cell content was only slightly increased. The centrifuged sediment was negative bacteriologically to microscopical and Cultural examination.

Patient was inclined to be noisy and delirious at nights

when she complained much of headaches while during the day she was quiet and drowsy. Her condition remained unchanged for two days after admission T. varying between 98°F. and 98.8°. On the evening of the third day, however, the Temperature rose suddenly to 104°F. breathing became difficult and the colour very cyanosed and death took place a few hours later, the Temperature just before death being 104.8°F.

Post-mortem examination was done 12 hours later. On opening the skull the Dura appeared congested. There was some congestion also of the pia-arachnoid and the surface of the brain was wet and soft. On section the whole brain substance showed some congestion but this was most marked in the medulla and pons where minute haemorrhages were visible. There was no sign of meningitis. The right side of the heart was distended with blood and venous engorgement of the abdominal and thoracic organs was found.

Microscopical examination of the pons and medulla showed very definite lesions. Many of the small vessels were seen to be surrounded with deeply staining collars of small round cells. These were mostly small lymphocytes but a few plasma cells were present too. The collars varied greatly in thickness, some consisting of several layers while in other cases only a single layer might be seen. There was in addition to this perivascular infiltration, a diffuse infiltration of the substance of the pons and medulla, the cells mostly concerned being small lymphocytes, although plasma cells were present also and proliferated neuroglial cells. Considerable congestion of the vessels was seen and one fairly large haemorrhage in the medulla, red cells being diffused over a considerable area round the ruptured vessel. Changes were seen in some of the nerve cells consisting of disappearance of the Nissl granules with a tendency towards excentricity of the nucleus. Small round cells were seen in a few cases lying close to ganglion cells but no actual neuronophagia was seen. Large vacuolated spaces were seen in the medulla the

significance of which was not determined. It is possible that they may be the result of acute localised oedema such as has been described by Blanton[10] in acute poliomyelitis.

Case 2. J. M. male, aged 25 years, complained of severe headache on 9.5.19 which was slightly better next morning but in the evening he felt sick and vomited. The sickness continued till the following night when he became delirious and noisy. He remained more or less in this condition for the next two days and was sent to hospital on 13.5.19 as a case of Cerebro-Spinal Fever.

Temperature on admission was 98.6°F., pulse 72 and respirations 24. Patient was quite conscious and complained of severe frontal headache. He complained also of double vision but no obvious ocular palsy could be determined. The pupils were equal and reacted normally. No facial paralysis was present nor was there any other cranial nerve palsy. There was no paralysis of the limbs. Reflexes were active and normal. There was a slight degree of retraction of the head and some stiffness of the cervical muscles. A very indefinite Kernig's sign was obtained.

Cardio-vascular system --- the heart appeared healthy, the sounds were pure and of good quality. The pulse was strong and regular, the blood pressure was distinctly raised. Lungs --- nothing of note. Digestive system --- tongue was coated but moist: the bowels were constipated.

The urine contained no albumen or sugar.

Lumbar puncture done on admission showed the cerebro-spinal fluid to be under greatly increased pressure and to contain a considerable amount of blood. Microscopical examination of the centrifuged sediment showed abundant red blood cells but very few white cells. Cultures were negative. The Wassermann

Reaction was negative both in the blood and in the cerebro-spinal fluid.

A few hours after admission the Temperature rose suddenly to 103.4°F. and patient became quite unconscious in which condition he remained several hours, passing his urine involuntarily. Early next morning he had a severe epileptiform seizure involving all the limbs and accompanied by great cyanosis and stertorous breathing. Bleeding to the amount of ten ounzes was done and seemed to give immediate relief after which patient became quite quiet. In the morning he was conscious again and able to answer questions and it was noticed that a fairly well marked facial paralysis was present on the right side but no limb paralysis. The cerebro-spinal fluid was again found to be deeply bloodstained and under a considerable pressure.

During the next fortnight there was little change in patient's condition, periods of semi-consciousness lasting for several hours alternating with periods of consciousness during which he was able to speak and take his food. Speech was slow and slurred and very monotonous. The diplopia still persisted but without any obvious ocular paralysis. The facial paralysis became no more marked nor did any other cranial nerve become involved. The optic discs showed slight engorgement but this passed off. The mental condition was quite abnormal so that although patient was able to speak and answer questions intelligently he did not seem to recognise his friends at all and his memory was very bad. He had no further convulsive seizures. Lumbar puncture done as late as 12 days after admission still gave a deeply bloodstained fluid under a considerable pressure. The temperature remained elevated

for five days after admission at about the level of 100°F. and then fell to normal remaining normal during the remainder of the illness. During patient's third week in hospital he became much brighter mentally and the periods of semi-consciousness gradually ceased altogether being succeeded by a tendency towards restlessness and slight delirium at nights. The facial paresis was still present at this time as was also the diplopia. The improvement begun then was continuous, and patient was dismissed from hospital two months after admission. At that time he was quite fit physically, the diplopia had gone but slight facial paresis was still present on the right side. His mental condition was, however, by no means normal. His memory seemed to be extremely bad so that he would forget events almost immediately after they had happened. He had lost all confidence in himself too, so that he was afraid togo out alone. When seen again three months later, there was very little change in his condition but he was about to start work again as a storeman in a warehouse. He was able to continue at work for over four months in spite of the fact that his memory was very bad and his mental condition not quite normal. After that time he developed cardiac symptoms and went to the country for a change. While there he became acutely ill and was removed to Glasgow Royal Infirmary on 17.3.20 where he died next morning of Ulcerative Endocarditis. Unfortunately no history of his encephalitis seems to have been given to the physician under whose care he was, so that, although a post-mortem examination was made, no detailed examination of the brain was carried out and so a valuable opportunity of investigating the repair processes in encephalitis missed.

Case 3. C. B. female, aged 20 years, a clerkess, was said to have fallen and hurt the front of her head on July 1st, 1919.

She did not make any great complaint about this and seemed to be quite well until August 1st when she complained of feeling tired and done out. She was able to continue at work, however, for 12 days although she complained frequently of slight headache and a feeling of sleepiness. On August 13th she fell asleep on the car going to work and had to be roused by the conductor. Two days later she had diplopia and some unsteadiness in her gait. She was taken to see an eye surgeon who said she was suffering from lethargic encephalitis. During the following week she became gradually more lethargic and on August 23rd she had great difficulty in swallowing and her speech was thick and slurred. She was now very drowsy all the time but could be roused to answer questions. Lumbar puncture was done that day and yielded a clear fluid which was said to show nothing abnormal. She was admitted to hospital on August 25th.

On admission temperature was 98.6°F. pulse 88, and respirations 20. Patient was a well nourished, healthy looking girl, and lay most of the time in the dorsal decubitus in a helpless semi-conscious condition. At times, however, she became very restless and attempted to get out of bed. The eyes were almost closed and the face absolutely devoid of expression. She could be roused to answer questions put to her which she did intelligently, but speech was very slow and deliberate, with considerable slurring and a definite nasal tone. She complained of frontal headache but not of any other pain. Double facial palsy was present, more complete on the left side than on the right. Practically complete double ptosis was present too, and when the eyelids were raised there was a right external strabismus. The pupils were slightly dilated and responded sluggishly to light. The optic discs appeared normal. There was very great difficulty in swallowing, fluids being returned by the nose or retained in the back of the throat. Examination of the limbs showed some

loss of power in the left arm but none in any of the other limbs. The muscles of the legs were slightly rigid. No hyperaesthesia or anaesthesia could be determined. Abdominal reflexes were active, knee-jerks were exaggerated on both sides and quite definite patellar and ankle-clonus could be elicited. Plantar reflexes were extensor in type. Bladder and bowel control were unimpaired. The bowels were very constipated. The urine was free from albumen and sugar. The cardiac action was very weak and the pulse of poor quality so that patient was put on to strychnine hypodermically immediately on admission.

During the 10 days following admission little change took place in patient's condition except that the difficulty in swallowing gradually passed off and the quality of the pulse improved considerably. After this, however, the lethargy became gradually less marked and the mental condition much clearer although it was by no means normal yet. At the same time the facial paralysis and the ptosis began to pass off, but the strabismus was still present although not constantly and the weakness of the left arm persisted. Five weeks after admission patient was very much better. The various palsies had by this time passed off completely including the paresis of the arm. During her convalescence she had very definite cerebellar symptoms. When sitting up in bed she had the greatest difficulty for some time in maintaining her balance and very great difficulty in trying to feed herself. On getting up, too she had well marked ataxia which was not affected by closure of the eyes and was accompanied by increased superficial and deep reflexes and extensor plantar reflexes. The mental condition was still unsatisfactory, patient being almost as emotional and wilful as a child and very difficult to manage.

Little further improvement took place in the mental condition which was still distinctly abnormal when patient was dismissed from hospital fourteen weeks after admission.

Knee-jerks were still very active and patellar and ankle-clonus could be elicited while plantar reflexes were still extensor. The physical condition was quite satisfactory. Enquiry four months later showed that patient's general condition remained very satisfactory but that no improvement in her mental condition had taken place.

Case 4. K. M. male, aged 22 years, was in good health until October 16th 1919 when he complained of headache. He went to a picture house that evening but complained of seeing everything very dimly and had to be led home feeling very weak and unsteady. Next day he had a very severe headache and remained in bed. On the following day when he got up he felt very weak and looked ill so that he was sent back to bed. On October 20th he had severe headache, slight retraction of the head and some tremor of the left arm. Next day the tremor was present in both arms, the headache and retraction were more marked, and he was inclined to be drowsy. On October 22nd his eyes were closed and he was very drowsy, but could be roused to answer questions, and the tremor had gone. On the following day the drowsiness was so marked that it was with great difficulty he could be roused at all. He was removed to hospital that day.

On admission temperature was 102,2°F. pulse 128 and respirations 28. Patient who was a well-nourished, well-developed man was quite unconscious and could not be roused at all. There was no definite retraction of the head but some stiffness of the posterior cervical muscles. The face was mask-like and expressionless and both eyes almost completely closed. The conjunctivae were congested and discharging slightly. The pupils were unequally dilated and responded very sluggishly to light. The optic discs appeared normal. On account of the deeply comatose condition it was impossible

to determine whether any cranial nerve palsies were present. Superficial and deep reflexes were very feebly present. No limb palsy could be determined.

No cardiac or pulmonary lesion could be detected. The pulse was rapid but of good quality. The tongue was thickly coated and dry. The bowels were very constipated. Urine was passed involuntarily.

Lumbar puncture yielded a clear fluid under greatly increased pressure which contained a greatly increased number of cells, the majority of which were polymorphonuclears. No organisms were found on microscopical examination and cultures made were negative.

Patient did not regain consciousness but became more and more deeply comatose until the second morning after admission when he died on the 10th day of illness.

Post-mortem Examination. The brain membranes were much congested and the sinuses full of blood. The brain substance itself was very oedematous and the convolutions showed considerable flattening. On section great congestion was seen, affecting both the white and the grey matter but especially the grey. The congestion was well marked in the large basal nuclei and in the pons and medulla but no haemorrhages could be seen.

On microscopical examination very marked congestion of the whole brain tissue was seen. This was well seen in the cerebrum affecting both white and grey matter; a slight suggestion of perivascular infiltration was seen in the case of some of the small vessels passing into the cortex from the pia-arachnoid. Beyond this there was no sign of round cell infiltration of the cerebrum. In the cerebellum similar capillary congestion was well marked in some parts but in others the vessels seemed quite normal and there was neither perivascular

nor interstitial infiltration seen. The cells of Purkinje however, showed complete absence of Nissl granules, a finely granular protoplasm, an indefinite badly-staining nucleus, and a well-stained nucleolus.

In the large basal nuclei congestion was a very marked feature, but no naemorrhages were seen. Interstitial round cell infiltration was well marked but there was very little evidence of perivascular infiltration. In many of the ganglion cells, the Nissl granules seemed to have disappeared and the nucleus taken up an excentric position, and in some instances round cells were seen in close apposition to ganglion cells although no neuronophagia was observed. The majority of nerve cells however, showed well marked Nissl granules and appeared to be quite healthy.

In the pons, medulla and upper part of the cord, the changes seen consisted of well marked capillary congestion, well marked interstitial infiltration, slight but definite perivascular infiltration of the small venules, and slight chromatolytic change in some of the ganglion cells. Very slight meningitis was seen.

The marked feature of the whole brain tissue in this case was the intense capillary congestion affecting practically every part of it, not accompanied at all by haemorrhage and only slightly by perivascular and interstitial infiltration.

Case, 5. A. D. male, aged 36 years complained of pain in his eyes on October 22nd 1919 and of severe headache and shivering. He went to bed on the following day but the headache persisted and was accompanied by great restlessness and slight delirium. The restlessness alternated with periods of drowsiness and continued until October 26th when he became wildly delirious

shouting loudly and getting out of bed. In the evening he became very quiet and fell into a stuporose condition in which he remained until admitted to hospital on the following day.

On admission temperature was 98°F. pulse 112, and respirations 32. Patient who was a strong, well nourished man, lay helplessly in the dorsal decubitus with eyes closed and face quite expressionless. He seemed to be quite unconscious but when spoken to persistently he could be roused to answer questions put to him. Speech was slow and monotonous. Double ptosis was present but no squint. When the lids were raised the pupils were seen to be dilated but responded sluggishly to light. Double facial palsy was present apparently complete on the right side but not quite complete on the left. No other cranial nerve palsy could be determined. There was no head retraction and no stiffness of the posterior cervical muscles. Kernig's sign was not present. Superficial reflexes were present but not active. Urine was passed involuntarily. The bowels were constipated. The mouth was dry and dirty and the tongue coated. The heart and lungs appeared healthy; the pulse though rapid was of good quality.

Lumbar puncture gave a cerebro-spinal fluid under greatly increased pressure but quite clear and showing an excess of lymphocytes. No organisms were seen on microscopical examination and cultures were negative.

No improvement took place in patient's condition. The stupor increased gradually and death took place on the following day, the 7th day of illness. During the 24 hours he was in hospital the temperature did not rise above 99°F.

Post-mortem examination was done 24 hours after death.

The dura mater was adherent to the calvarium and the cerebral sinuses were full of blood. There was well marked congestion of all the brain membranes and engorgement of the surface vessels of the brain. No meningitis was seen. On section wide spread congestion of the brain substance was found and in the large basal nuclei minute haemorrhages could be seen with the aid of a hand lens. On microscopical examination the following findings were made. There was intense congestion of both cerebral hemispheres involving both grey and white matter but especially the former. Even the minutest capillaries were seen to be packed with red cells and in a number of cases rupture of the capillary wall must have taken place for red cells were seen lying free in the tissues. The most careful search failed to detect anything more than the very faintest sign of perivascular infiltration only a few venules showing a few round cells lying in their adventitia. There was no interstitial infiltration and no change in the pyramidal cells of the cortex. The pia-arachnoid vessels were congested but no meningitis was seen.

The cerebellum showed some congestion but no haemorrhage and no perivascular or interstitial infiltration. The vessels in the pia-arachnoid were congested but there was no meningitis. The cells of Purkinje showed the same changes as in the previous case.

The lesions in the large basal nuclei were very definite. These consisted of intense congestion of the vessels with well marked perivascular and interstitial infiltration and abundant minute haemorrhages. The perivascular infiltration varied much in degree, some venules having a collar of cells many layers deep while others showed only a single layer. The cells forming the collars seemed to be mostly lymphocytes but plasma cells were seen also. The haemorrhages varied in size according to the size of the ruptured vessel and very often the ruptured vessel with its collar of lymphocytes could be seenin the centre of the haemorrhage. Many of the ganglion cells showed

absence of Nissl granules and excentricity of the nucleus. In some cases one or more round cells could be seen in close apposition to a chromatolysed ganglion cell and in the Optic Thalamus distinct if slight evidences of neuronophagia were seen.

The pons, medulla, and upper part of the cord showed very marked congestion but no perivascular or interstitial infiltration and no haemorrhages. Some of the ganglion cells showed loss of Nissl granules but most appeared healthy.

Case 6. H. E. male, aged 24 years.

About 15th October 1919, patient complained of weakness and slight pains in his legs. He was able to continue at work, however, until October 26th when he had a severe headache and a feeling of sickness and shivering. The headache and sick feeling persisted for several days and patient began to be restless and slightly delirious. On October 30th he was very drowsy and lay with his eyes closed most of the time. The drowsiness increased gradually until his admission to hospital on November 4th when he was in a condition of deep stupor.

On admission temperature was 99.4°F. pulse 88, and respirations 28. Patient lay helplessly on his back with the eyes closed and the face mask-like and devoid of expression. The colour was rather cyanosed and the skin damp with perspiration. He appeared to be quite unconscious but could be roused with difficulty to respond to simple questions. He was apparently unable to open his eyes but when the lids were raised the pupils were seen to be widely dilated and responded very sluggishly to light. The conjunctivae were congested and discharging slightly. There was no strabismus. The face was devoid of expression but it was impossible to

say whether double facial palsy was present or not, nor could any other cranial nerve palsy be determined. There was no retraction of the head and no Kernig's sign. Superficial and deep reflexes were present but not active.

The mouth was dry and dirty and the tongue coated and dry. The bowels were constipated. The bladder was very much distended and had to be emptied by catheter. The urine contained a small amount of albumen but no blood or sugar.

Heart and Lungs showed nothing abnormal. The pulse was of rather poor quality and the colour poor.

Cerebro-Spinal fluid was under increased pressure but was quite clear. The cell content showed an excess of small lymphocytes. No organisms were seen on microscopical examination and cultures were negative.

A few hours after admission patient was sick and vomited a quantity of altered blood. The stupor became gradually deeper and he died 12 hours after admission,on the 10th day of illness.

Post-mortem examination was performed within 24 hours after death. The brain membranes were slightly congested and on section the brain itself showed some congestion. The general condition of the abdominal organs was one of acute congestion. The spleen was considerably enlarged but quite firm. The stomach contained several ounzes of altered blood apparently the result of oozing from the mucous lining which was acutely congested although no actual haemorrhagic points could be seen. Petechial haemorrhages were found in the heart wall.

The microscopical lesions in the brain were well marked. The cerebral cortex and the cerebellum showed no changes except that in the latter the cells of Purkinje had the same appearance as seen in the two previous cases. In the large

basal nuclei well marked interstitial infiltration was seen and parenchymatous changes were also observed, many of the ganglion cells staining badly and showing absence of Nissl granules, while others appeared to be quite healthy. No perivascular infiltration was seen and no haemorrhages.

The pons and medulla showed no congestion and no haemorrhage but very well marked perivascular and interstitial infiltration. The connection between the perivascular infiltration and the small round cell elements in the interstitial infiltration was well seen in sections of the medulla. The preponderance of the proliferating neuroglial cells in the interstitial infiltration was very well marked in this case. Corresponding changes to those seen in the large basal nuclei were seen in many of the nerve cells but it was very noticeable that many nerve cells were apparently quite healthy although lying in the midst of fairly dense interstitial infiltration. No neuronophagia was seen

Sections of the kidney, spleen, and liver showed intense congestion, especially marked in the kidney.

Case 7. M. S. female, aged 34 years.

Patient was in good health until October 26th, 1919 when she had a slight gastric attack lasting for about three days. On October 30th she had severe occipital headache and next morning when she got up she felt very weak and giddy so that she had to go back to bed. On the following day she felt worse and was very sleepy. The drowsiness became more marked and on November 3rd she was removed to a Nursing Home. At that time she had retention of urine and loss of feeling in the left hand and arm. The temperature was 99.6°F. but it rose the same evening to 101.4°F. There was little change in her condition during the next two days and she was removed to hospital on November 5th,

Temperature on admission was 100°F., pulse 92 and respirations 24. Patient was a rather poorly nourished woman and lay quietly in bed in a semi-conscious condition from which she could be roused without any difficulty to answer questions, falling back however into the semi-conscious condition immediately she ceased to be spoken to. Speech was slurred and slow and slightly nasal in tone. The face was devoid of expression and definite facial palsy was present on the left side. There was double ptosis, marked on the left side but slight on the right. The pupils were slightly dilated but responded to light and in accommodation. Patient complained of diplopia and there was paresis of the left external rectus muscle with convergent strabismus. The strabismus was not constant but only appeared when the eyes had been kept open for a minute or two. At times a coarse nystagmus was seen affecting especially the left eye. The optic discs were normal. There was slight difficulty in swallowing and a tendency to regurgitation of fluids by the nose. Beyond this no other cranial nerves seemed to be affected. There was no definite paralysis of any of the limbs but the hand grip on the left side was not so strong as on the right. Patient complained too, of a tingling sensation in the left hand and arm but beyond this no anaesthesia or hyperaesthesia could be determined. Abdominal reflexes were present and active. The knee-jerk was active on the right side but only faintly present on the left. Plantar reflex was active and flexor on the right side but absent on the left. The bladder was much distended and had to be emptied by catheter. The urine contained neither albumen nor sugar. The bowels were very constipated. Heart and lungs showed nothing abnormal. Cerebro-spinal fluid was under increased pressure but perfectly clear. A slight lymphocytosis was present but no organisms could be seen microscopically and cultures were negative.

A blood examination done some days after admission gave a white cell count of 8200. A differential count gave the following figures -- Polymorphonuclears 68%, Large Mononuclears 8%, Small Lymphocytes 24%.

The Wassermann Reaction was negative.

Patient ran a mildly febrile temperature for a fortnight after admission.the temperature swinging between normal and 100.4°F. after which it remained normal or subnormal. During that time she remained in a lethargic condition which was never so deep as to cause any difficulty in rousing her to speak or eat. Lethargy during the day tended to alternate with delirium at night which at times was rather noisy. No increase in the severity of the paralysis took place but a gradual lessening so that at the end of three weeks the palatal and pharyngeal paralysis had gone completely and the strabismus was no longer seen although patient still complained of diplopia. Nystagmus too, was not seen after the second week. Slight ptosis was still present and slight left facial paresis. The weakness in the left arm was still present, although not so markedly as on admission,and the tingling sensation still persisted. The lethargy passed off completely during the third week and the mental condition became quite bright.

In spite of the fairly rapid clearing up of the various palsies convalescence was very slow,due to the general muscular weakness which was a marked feature of this case,and patient was not discharged from hospital till 3 months after admission. By that time recovery seemed to be complete except for occasional diplopia coming on when the eyes became tired with reading,slight numbness in the little and ring fingers of the left hand,and very slight facial paresis with some lack of facial expression. Superficial and deep reflexes were active

and normal and the mental condition seemed perfectly good.

Case 8. N. R. female, aged 21 years.

Patient was a strong, healthy-looking girl and had a good health history except for epileptiform seizures, from which she was said to have suffered during the year previous to the onset of her illness. She had never been known to injure herself in any way during one of these seizures.

She complained of headache on December 1st 1919 and was in bed for several days. On December 6th she had a very severe headache and felt very sick. Next day she was very drowsy and on the following day the drowsiness was so great that she lay all day as if asleep and could hardly be roused to take food. Any attempts she did make to take food were not very successful as she was apparently unable to swallow. She was admitted to hospital on December 9th.

On admission temperature was 100°F., pulse 124, and respirations 28. Patient was in a condition of deep stupor from which it was impossible to rouse her. She lay helplessly on her back with both eyes closed and the face quite expressionless. When the lids were raised the pupils were found to be dilated and they responded very slightly and sluggishly to light. She was unable to swallow and so was fed by a nasal tube. From her stuporose condition it was impossible to determine which, if any, of the cranial nerves were affected. Abdominal reflexes were present. Knee-jerks were present but not active. Plantar reflexes were flexor in type. There was no retraction of the head and no post-cervical stiffness. Kernig's sign was negative. Well marked flexibilitas cerea was present in the arms and to a less extent in the legs.

The mouth was dry and dirty, the tongue coated and dry. Bowels were constipated. The urine was passed involuntarily.

Heart and lungs showed nothing abnormal. The pulse was rapid but of fairly good quality.

Cerebro-Spinal fluid was under increased pressure but quite clear. The cell content was much increased, 50 cells being present per cu. mm. practically all small lymphocytes. The protein content was also increased. No organisms were found on microscopical examination and cultures were negative.

Blood examination showed a Leucocytosis of 14,600 and a differential count gave the figures -- Polymorphonuclears 66%, Large Mononuclears 6% and Small Lymphocytes 28%.

The Wassermann reaction was negative.

Patient became gradually more stuporose after admission sinking into a deep coma from which it was impossible to rouse her. On the evening after admission temperature was 104,2°F. and the pulse 136. Next day temperature was 105.4° and in the evening 105.8°. Respiration became very much embarrassed and patient died on the following morning on the 7th day of illness.

Post-mortem examination was done 12 hours after death. The dura mater and pia-arachnoid were very much congested and the cerebral sinuses were full of dark blood. On section the brain seemed slightly congested but no haemorrhages or other lesions could be detected with the naked eye.

On microscopical examination the only lesions found in the cerebral cortex were fairly definite interstitial infiltration and slight but distinct perivascular infiltration. No changes were seen in the nerve cells. The pia-arachnoid vessels were congested but no meningitis was present.

In the cerebellum the only changes seen were congestion of the meningeal vessels and chromatolysis of the cells of Purkinje.

The large basal nuclei showed no lesions at all.

The pons showed very marked interstitial and quite distinct perivascular infiltration. The vessels were not congested and no haemorrhages were seen. Perivascular infiltration was best seen in the case of the vessels in the floor of the Fourth Ventricle. The changes in the ganglion cells were very marked. The cells had lost all sign of Nissl granules and appeared very washed out, the protoplasm staining quite uniformly except for the nucleus.

The medulla and upper part of the cord showed well marked interstitial round cell infiltration but only slight perivascular infiltration. The changes in the nerve cells in the medulla were the same as those seen in the pons.

The most noticeable feature in the histological appearance of this brain was undoubtedly the interstitial round cell infiltration which was present all over except in the cerebellum and in the basal nuclei and was not accompanied by a correspondingly well marked degree of perivascular infiltration or by any marked congestion of the vessels. Nor was it possible to show any definite relation of the infiltrating round cells to the vascular system. The other marked feature was the appearance of the nerve cells which seemed to have suffered acute toxic change.

Case 9. D. M. Male, aged 56 years.

Patient was in good health until December 9th, 1919, when he complained of slight headache and of feeling tired and unfit for his work. He felt sleepy during the day but was restless and unable to sleep at night. Next day he went to see his doctor who told him that his temperature was slightly elevated and sent him home to bed where he remained for the next ten days. During that time the temperature was slightly febrile, ranging as a rule between 99° and 100°F. but on one occasion reaching 101.6°. He was very drowsy for the

most part, but at times was very restless wanting to get out of bed, and go to work. The pupils were,as a rule,contracted and the response to light was very slight. At times he appeared to have some paresis of the right external rectus but this was not constant. There was no facial palsy and no sign of involvment of any of the other cranial nerves beyond slight difficulty in swallowing. Superficial reflexes were active and normal. Knee-jerks were elicited with difficulty owing to slight muscular rigidity of the legs. The drowsiness became gradually more pronounced until he was admitted to hospital on December 20th.

On admission temperature was 100.2°F. pulse 132 and respirations 26. Patient lay in bed on his back in a semi-conscious condition from which he could be easily roused to answer questions. The answers were perfectly rational but were slow in coming and speech was deliberate and slurred. At times however, he spoke very quickly and in a rambling incoherent fasion. The facies was mask-like and quite devoid of expression, but there was at the same time no definite facial palsy. There was double ptosis but not complete and patient could open his eyes partially with an effort. The pupils were slightly dilated but were equal and responded feebly to light. Patient complained of diplopia but the movements of the eyes were good and no actual paralysis could be determined. The optic discs showed slight congestion of the vessels. There was no evidence of involvment of any of the other cranial nerves except some difficulty in swallowing and some difficulty in putting out the tongue. There was no paralysis of any of the limbs. There was no head retraction or stiffness of the cervical muscles and Kernig's sign was not present. Superficial and deep reflexes were present but not active. There was considerable rigidity of the muscles of the legs and to a less

degree of the arms. Flexibilitas cerea was well marked in the arms. Retention of urine was present so that the catheter was used constantly. The urine was free from albumen and blood. The heart and lungs appeared healthy. The pulse was rapid but of good quality. The tongue was coated and dry and the mouth dirty with mucus tending to collect in the throat. The bowels were constipated.

The cerebro-spinal fluid was under greatly increased pressure but was quite clear. The cell content was increased to 50 cells per cu. mm. mostly small lymphocytes and the protein content was also increased.

Examination of the blood showed a Leucocytosis of 32,000. The Polymorphonuclears were 86%, the Large Mononuclears 6%, and Small Lymphocytes 8%.

The Wassermann Reaction was negative.

Patient made no progress after admission. The lethargy gradually increased but in spite of it he was at times inclined to be very restless and constantly trying to get out of bed. No increase in the cranial palsies took place but respiration became gradually more difficult. On December 23rd he had an intraspinal injection of 20 c.c. of convalescent serum taken from Case 7, but with no apparent benefit and death took place from respiratory failure on the following day, the 17th day of illness. During patient's stay in hospital the temperature was for the most part over 100°F. and at times as high as 102.6°. On the day before death it fell to 99° and did not thereafter rise higher than 99.6°. The pulse was rapid all the time, about 130, and respirations rose from 26 on admission to 50 just before death.

Post-mortem examination was done 36 hours after death. The brain membranes were very congested and at the base of the brain the pia-arachnoid seemed to be rather opaque. The brain

substance was firm and on section there was seen marked congestion of the whole brain. No haemorrhages could be seen with the naked eye but the small vessels in the brain stem seemed to be dilated and full of blood.

On microscopical examination the cerebral cortex showed no change beyond some congestion of the vessels.

The cerebellum showed no changes except in the cells of Purkinje which were the same as in the other cases although not quite so pale and colourless, and the nucleus not quite so indefinite.

In the basal nuclei a considerable degree of congestion was seen and some interstitial infiltration but no haemorrhages and no perivascular infiltration. The ganglion cells stained poorly.

In the pons well marked perivascular infiltration was present, seen best just under the floor of the Fourth Ventricle, on either side of the median raphé and in the neighbourhood of the Aqueduct of Sylvius. There was also well marked interstitial infiltration. Many of the ganglion cells showed evidence of chromatolysis and excentric nuclei but others showed healthy Nissl granules and a normal nucleus. No evidences of neuronophagia were seen.

In the medulla and upper part of the cord there was slight perivascular and interstitial infiltration and changes in some of the nerve cells, just as in the pons. Most of the nerve cells, however, appeared to be healthy.

Case 10. R. H. male, aged 25 years.

Patient was in good health until December 2nd, 1919, when he felt out of sorts and complained of cold and shivering. About a week later his eyes became inflamed and after being treated by his own doctor for a few days he was sent to the Ophthalmic Institute for treatment. The inflammation subsided but on December 19th, he had a right sided facial palsy and was

unable to close the right eye completely. Next day his head began to shake and on the following day he was slightly delirious. On December 22nd the eyes began to twitch and on that day and the following one he had several noisy delirious attacks during which he had to be restrained in bed. He was admitted to hospital on December 23rd.

Temperature on admission was 98.4°F., pulse was 130, and respirations 36. Patient was quite conscious and was able to talk intelligently. Speech was very monotonous and slow and slurred. He complained of diplopia but there was no obvious squint. A very coarse lateral nystagmus was present from time to time. There was a slight degree of ptosis on both sides. The pupils were unequal, the left more dilated than the right, but they reacted quite well to light and to a less extent in accommodation. Optic discs were healthy. Facial paresis was present on the right side but not very markedly. From time to time there was a very coarse tremor of the posterior cervical muscles causing a violent antero-posterior shaking of the head which could, however, be controlled voluntarily by patient. There was also a coarse tremor of both hands, but especially of the right. Abdominal reflexes were active, knee-jerks exaggerated, and plantar reflexes flexor. Slight ankle-clonus could be elicited on the right side. No anaesthesia or hyperaesthesia could be determined and there was no bladder disturbance. The bowels were constipated, the tongue coated, and the mouth dry and dirty. The heart and lungs appeared to be healthy; the pulse was very rapid, about 136 per minute, and the arterial tension high. The urine was free from albumen, blood and sugar.

The cerebro-spinal fluid was under greatly increased pressure but quite clear. The cell content was raised. 60 cells being present per cu.mm. practically all small lymphocytes.

The protein content was also increased. No organisms were seen on microscopical examination, and cultures were negative.

The blood showed a Leucocytosis of 14,400, and a differential white count gave the figures, Polymorphonuclears 73%, Large Mononuclears 7%, and Small Lymphocytes 20%.

The Wassermann Reaction was negative.

For three weeks after admission the condition became gradually worse. The tremor of the head and arms became much more marked and in the arms it took on very definitely the character of an intention tremor. The nystagmus, too, was very troublesome. The right facial palsy became more severe, and a less marked left facial palsy developed too. Ptosis became more marked and great inequality in the pupils was constant, the right being very widely dilated and not responding to light at all. Pharyngeal paralysis developed too, so that patient had great difficulty in swallowing. Superficial and deep reflexes became more active and ankle-clonus could be elicited easily on both sides. A tendency towards lethargy was first noted five days after admission and increased slowly until patient became quite stuporose but even then he could be roused to answer questions although speech was slow and slurred. Incontinence of urine developed five days after admission and persisted for about ten days.

On the sixth day after admission patient was put onto 5 grains of urotropine, 4 hourly, and two days later he had profuse haematuria, the urine containing abundant small blood clots. The urotropine was at once stopped, but the haematuria did not clear up for several days afterwards.

On 30th December, eight days after admission, patient was given 15 c.c. of convalescent serum from Case 7 intrathecally, but with no apparent benefit, the lethargy

being, if anything, more marked on the following day. The dose was repeated on January 1st but still without any apparent benefit and no further serum was given.

During these three weeks, while patient was becoming gradually worse, the temperature was mildly febrile, swinging between 99.6° and 97°F. for the first ten days, and afterwards remaining almost stationary at 99°. The pulse during the same period ranged between 84 and 126 but was mostly about 100°.

After this patient began to improve slowly, the lethargy becoming gradually less marked, while the cranial palsies began to pass off, and control of the bladder was regained. The face, however, retained its mask-like appearance, the tremor was only slightly diminished and reflexes remained very active for several weeks.

On February 14th, two months after the actual onset of illness, the lethargy had completely gone, and patient appeared quite bright. Speech, however, was still monotonous and slow. The facial palsy had passed off completely although the face still lacked expression. The ptosis had gone, but nystagmus was still present although not constantly. The intention tremor was still very marked in the hands, and the mental condition was not quite normal.

Patient was seen again on March 13th, by which time all signs of cranial nerve palsies had disappeared completely along with the tremor in the hands. The mental condition, however, had become very much worse so that patient was at times wildly demented and had to be restrained forcibly in bed. The physical condition was quite satisfactory.

Case 11. J. H. male, aged 46 years.

Patient complained of a "cold" on December 12th, 1919, but this passed off after a few days and he was apparently quite well until December 27th, when he had a headache and

some abdominal pain. Spasmodic twitching of the muscles of the anterior wall of the abdomen on the left side commenced the same day and continued until admission to hospital. The bowels were constipated and no movement took place after December 29th. Patient was slightly fevered at this time and unable to sleep. He had a slight headache and a dry, dirty tongue, and was sent to hospital on January 2nd as a case of Enteric Fever.

Temperature on admission was 101.6° pulse 104, and respirations 32. Patient was a very stout, well nourished man. The abdomen was much distended and the liver and splenic dulness obliterated. There was no localised pain or tenderness and no localised rigidity of the muscles. Satisfactory examination of the abdomen, however, was made impossible by a spasmodic contraction of the anterior abdominal muscles on the left side which occurred every few seconds and was said by the patient to have been present for 7 days previous to admission. The spasms were so severe and apparently so painful as to make patient "catch his breath" and occurring, as they usually did, every 20 or 30 seconds, they caused him constant trouble and prevented him from getting any proper rest. The mouth was dirty and the tongue dry and coated. The bowels were apparently very constipated. There was no sign of a "rose-spot" eruption. The mental condition was very interesting. Patient appeared to be in a condition of low muttering delirium closely resembling the typhoid state, but he had not the appearance of being nearly so ill as his typhoid condition would warrant. The pulse rate was not higher than 104 and the temperature was about 101°. He rambled incoherently and made restless movements, but immediately he was spoken to he could pull himself together mentally, and answer questions quite intelligently, and it was this which first suggested

the diagnosis of lethargic encephalitis. A blood culture was negative and a Widal Reaction a few days later, gave a doubtful result. A second one was negative.

Heart -- cardiac sounds were rather soft, the pulse was of poor quality. Lungs -- a few bronchitic rales could be heard throughout both lungs. The urine was free from albumen and sugar.

For some days after admission no change took place in the general condition. Patient complained once of seeing things double, but no ocular palsy could be made out. The face was slightly expressionless but there was no facial or other cranial nerve palsy. Reflexes were present and active and no anaesthesia or hyperaesthesia could be determined.

Lumbar puncture was done four days after admission and yielded a perfectly clear fluid under greatly increased pressure. The cell content was very much increased, 230 cells per cu.mm. being present, practically all small lymphocytes. The protein content was slightly increased. Cultures were negative and no organisms could be seen in the centrifuged deposit. Blood examination showed a Leucocytosis of 12,800. A differential count gave the figures, Polymorphonuclears 64%, Large Mononclears 8%, Small Lymphocytes 28%.

The Wassermann Reaction was negative.

After About a week in hospital the spasmodic contraction of the abdominal muscles became gradually less marked and in ten days it disappeared altogether. About the same time patient developed a left facial palsy, the only cranial palsy which appeared. His mental condition was still the same as on admission and the restlessness of the day tended to develop into noisy delirium at night, so that it became necessary to administer a nightly hypnotic of 10 minims of Battley's Solution. This had a very soothing effect and enabled patient to get much needed rest. The constant incoherent muttering

became gradually less and after about a month in hospital the mental condition was almost normal again.

A fortnight later the mental condition seemed still slightly abnormal but there was absolute freedom from restlessness and insomnia . The only palsy present was the left facial which was still quite evident. The temperature was not yet completely settled tending to reach 99°F. in the evenings and respirations were still between 30 and 40.

Patient was dismissed from hospital on March 20th by which time the facial palsy had gone completely and patient was quite well except for very slight mental facileness.

The diagnosis of lethargic encephalitis was made in this case first on the mental condition, which while not absolutely typical of the disease, yet strongly suggested it. It was confirmed by the characters of the cerebro-spinal fluid and by the appearance of facial palsy.

A CLINICAL ACCOUNT OF THE DISEASE.

From the clinical point of view three types have been distinguished by Macnalty[11] (1) with general disturbance of the functions of thecentral nervous system, but without localisation; (2) with various localisations, and (3) mild or abortive. The third type is very rare and not re presented in my series of cases. As for types (1) and (2) it is impossible to allocate my cases definitely in these two classes, because in all of them the general disturbance of the central nervous system was present along with localising symptoms. These latter were present in varying degree in the different cases, but in none were they absent completely, and the same is the case with the symptoms of the general disturbance of the central nervous system, so that I am unable to classify my cases more definitely than to say that in some the general symptoms predominated over the more localised, while in others the opposite was the case. To me even the division of symptoms into local and general seems rather unsatisfactory, as in all probability such general symptoms as lethargy and delirium are the results of definite localisation of the inflammatory process in certain areas of the brain. As regards the severity of the disease it was quite obvious in my cases that where such symptoms as lethargy and asthenia predominated over the more definitely localised symptoms, the outlook was very much more serious than when these conditions were reversed.

Incubation Period. No information could be gained from my cases as to the length of the incubation period, as there was no evidence of one case being infected from another. A number of cases have been published by different writers where more than one case occurred in the same house, and in these cases the incubation period has varied from a few days to over a fortnight. In a disease like this, however, where it is impossible to say absolutely in such cases that one case

has been infected from another, and not both from a common source it is impossible to fix absolutely the length of the incubation period.

Prodromal Period. In 7 of my cases it was possible to find fairly distinct evidence of a prodromal period, varying in length from 4 to 15 days, characterised usually by such general symptoms as headache, shivering, tiredness, sleepiness, sickness and vomiting, general malaise, and conjunctivitis. This last symptom was found in only one case, but gastric symptoms, so common in the prodromal period of Acute Poliomyelitis, were a prominent feature of two cases. In 4 cases the onset appeared to have been quite sudden without any prodromal period. It is possible however, that there may have been prodromal symptoms so slight as not to attract attention.

Onset. After the prodroma l period the declared symptoms seem to have manifested themselves in most cases very markedly. A very common feature was severe headache, which was noted 7 times. Drowsiness was noted 3 times, vertigo 3 times, diplopia twice, facial palsy, delirium and loss of power in the limbs once each, as initial symptoms. Others were shivering, vomiting, tremor and muscular twitchings. The headache was often severe and persisted for several days, but as a rule it passed off within a few days, as did also such symptoms as vomiting and shivering, and in most cases the cardinal symptoms of the disease, as described by some of the original writers on the subject, became very definite. These were lethargy, asthenia, pyrexia, and cranial nerve palsies.

Lethargy. This was the most prominent symptom in my cases taken as a whole. It was present in one form or another in all my 11 cases and a very marked feature of nine of them. It usually appeared early in the disease sometimes as one of the initial symptoms, and was manifested at first as an irresistible desire for sleep. One patient fell asleep in the car

when going to business. The drowsiness gradually deepened as the disease progressed, into a lethargic state, in which the patient seemed to take no interest in his surroundings at all. But even when, to all appearances, he was sound asleep, he could usually be roused without any difficulty to answer questions, and to take his food, and it was remarkable how quickly a patient could grasp what was said to him, so as to answer quite intelligently, even though the answer might be long in coming, and spoken slowly. From this it seemed to me that in a number of cases at least, the lethargy was not nearly so deep as one would take it to be from the unconscious appearance of the patient, and that muscular asthenia accounted to a certain extent for the relaxed helpless appearance. The fact that considerable mental acuity, even in apparent deep lethargy, might be present along with incontinence or retention of urine, does not seem to me to negative this idea, as I have observed that a lethargic patient could sometimes be induced to use the slipper when it was given to him, even when he was reported to be constantly incontinent. Later on in the disease, as the lethargy deepened into stupor, and then into coma, it became impossible to rouse patients at all, and then the asthenia element was of no account. In fatal cases, as a rule, the lethargy developed before death, into absolute coma so that no response could be got from the patient for many hours or even a few days before death. It has been remarked by Bassoe[12] that sometimes there is not nearly so much real sleep, as is indicated by the sleepy expression of the patient, and that some patients actually suffer from insomnia. This was certainly the case with one of my patients in whose case a tendency towards lethargy was accompanied by a low muttering delirium which tended to became noisy at nights. He was put on to small doses of opium with very satisfactory results.

Delirium. may be present along with the lethargy, especially early in the disease. It is usually nocturnal, alternating with stupor during the day. This was so in several of my cases. It may be very mild or at times very noisy. Sometimes it is accompanied by muscular tremor and according to Hall and Sainton[13] may suggest Delirium Tremens.

Asthenia. Muscular Asthenia was present very definitely in 8 of my cases, and in 5 of these it was a very marked feature. It was very largely responsible for the characteristic helpless attitude of the patient and his very expressionless facies. The patient usually lay on his back in a relaxed helpless-looking condition, apparently unable to make any voluntary movement, and with a mask-like face devoid of expression, suggesting as has been observed by Hall and others myasthenia gravis or paralysis agitans. That the helplessness was due to asthenia and not to actual paralysis might be shown by inducing the patient to move his limbs, and that the mask-like face was not always due to facial paralysis, although it very often was, might be shown similarly by getting the patient to show his teeth or try to whistle. The muscular immobility was particularly marked in three cases where the condition of flexibilitas cerea was present too, affecting the arms especially, which if placed passively in any posture would remain unmoved for several minutes at a time. The three cases in which this was seen were very severe, two ending fatally and the third only recovering after a very tedious illness.

Muscular Rigidity, was seen in 5 of my cases, usually late in the disease, but was not a prominent feature of any case.

Changes in Speech were noted in practically every case. Speech was slow and slurred, very monotonous and in several cases slightly nasal. This monotonous speech usually persisted well into the convalescent stage. In two cases speech was at times rapid and incoherent, but still very monotonous. In one case

patient appeared to have great difficulty in speaking at all, phonation requiring very considerable muscular effort.

Tremor was noted as very prominent in two cases, in one affecting both arms and in the other both arms and the head. In the latter case the tremor was very definitely of the intention variety, and was present for about 7 weeks.

Muscular Twitching was seen in two cases, in one affecting the facial muscles and in the other the abdominal muscles on the left side. In the latter case the twitching passed off in about a fortnight, while in the former it persisted for many weeks.

Nystagmus was a marked feature of two cases. In both it was of the lateral variety, and the movements were very coarse.

Reflexes. Superficial and deep reflexes as a rule were present and normally active. In three cases they were noted as present but not active. In three cases they were very active and the knee-jerks exaggerated. In one case double ankle-clonus was elicited and in another both ankle and patellar clonus. In one case Babinski's Sign was positive. In another the plantar reflex was normal on one side and absent on the other. Retention of urine was present in three cases and incontinence in 5 cases.

Cranial Nerve Palsies. These form one of the cardinal symptoms of the disease and were present in one form or another in all my cases. In two cases where the patient was so deeply comatose on admission that it was impossible to determine which cranial nerves were affected, the cranial nerve palsies were respresented in the one case by a history of early diplopia and in the other by a history of early ptosis. In two other cases where the lethargy was very deep on admission it was very difficult to determine whether the double ptosis which was present was due to paralysis or to asthenia.

While in theory the cranial nerve lesion in encephalitis

may be supra-nuclear, nuclear or infra-nuclear, the nuclear variety is by far the commonest of the three and was the one present in all my cases. This is what one might expect from the distribution of the lesions usually found post-mortem. The paralyses may be early or late in their appearance but are usually gradual in their onset and in their disappearance. They may be single or multiple, unilateral or bilateral. Where they are bilateral it is seldom that the lesion is symmetrical or that the paralyses appear at the same time. As a rule, facial palsy is well marked on one side before it appears on the other and it may begin to clear up on one side sometime before any change is noticed on the other.

The nerves most commonly affected in my cases were the 3rd and the 7th. In addition to these, affections of the 6th 9th, 10th and 12th nerves were noted but no lesions pointing definitely to any of the other cranial nerves were observed. Ophthalmoplegia. This was one of the cardinal symptoms of the disease as first described and was the commonest symptom of cranial nerve palsy seen in my series. It was noted in all in 8 cases. In 2 more cases the comatose condition of the patient during the time he was under observation was so deep that it was impossible to determine whether any ocular palsy was present or not, so that in only one case in eleven could it be definitely said that no symptoms of ocular palsy were present. In the 8 cases of ophthalmoplegia the symptoms varied widely. In three diplopia was the only symptom noted, no strabismus being seen at all. In three cases there was well marked strabismus, the muscles affected being the internal rectus in one case and the external rectus in the other two. Affection of the intrinsic muscles of the eye was more commonly seen, being present in all of the 8 cases at one time or another in varying degree, represented by widely dilated pupils either quite immobile or only sluggishly responsive to light and hardly at all in accommodation. Ptosis was present in 5 cases

in every case bilateral, but varying greatly in degree. It was usually an early symptom and tended to pass off quickly. In the two cases in which the 5th nerve was affected ptosis was present too,

Facial Palsy. This was definitely present in 6 cases in three of which it was bilateral and in three only present on one side. While in most cases it was an early symptom in some it was rather late in appearing and in one case did not appear until the 5th week of illness. Where it was bilateral it was always unequal in degree on the two sides and appeared on one side usually some days before the other. In some cases it cleared up fairly quickly but in others it persisted for many weeks and even months.

Affection of the 9th Nerve. Difficulty in swallowing was noted in 6 cases. As a rule it was a very transient symptom never lasting for more than a few days.

Affection of the 10th Nerve. In several cases the speech was slightly nasal and in one case there was a very definite palatal paralysis on one side. In one there was considerable difficulty in phonation.

Affection of the 12th Nerve. This was seen in one case where the patient was unable to protrude his tongue at all. The lesion was apparently bilateral.

Limb Paralyses. In 3 cases paralysis affecting the limbs was noted. In one all four limbs were affected, loss of power being practically complete in the legs but not quite complete in the arms. The muscles were quite flaccid and superficial and deep reflexes were feebly active. In 2 cases there was weakness of one arm not amounting to actual paralysis. In one case the loss of power was accompanied by a tingling sensation in the same arm. The two cases with the weakness in the arms became perfectly well after some weeks, the case with all four limbs affected, died.

Ataxia was present as an early symptom in two cases, while

in a third it appeared after the acute manifestations had passed off and convalescence begun. In this case it was very persistent lasting for several weeks and appeared to be definitely cerebellar in type.

Meningeal Symptoms. These were not very well marked in spite of the increased pressure found in the cerebro-spinal fluid and the practically constant lymphocytosis. Vomiting was noted in 7 cases but only in two cases was there definite retraction of the head with stiffness of the posterior cervical muscles at the time of admission to hospital. In a few of the other cases there seemed to have been some head retraction early in the illness but no sign of this was present when they came under observation.

Mental Condition. Mental symptoms may be present during the acute stage of the illness but are usually most marked during convalescence and may persist for months afterwards. In my cases they were represented by loss of memory, slight silliness, lack of confidence in oneself and a tendency to talk nonsence. In one case during the convalescent period patient became wildly demented and had to be forcibly restrained. One patient became very unreliable so that her friends complained of her wilfulness and propensity to lying after her dismissal from hospital. Previous to her illness she was said to have always been quite docile and perfectly truthful.

Pyrexia. A febrile temperature was one of the three cardinal symptoms of this disease as described first by Netter and it was present at one time or another in all my cases. In one case which was admitted to hospit al only in the third week of the disease the temperature was already normal on admission and remained normal afterwards but it was quite clear from the history that the early stage of the disease had been accompanied by fever. In the other cases the severity of the febrile reaction varied very widely. Three cases were admitted

moribund, dying within 48 hours, one on the 7th and the other two on the 10th day of illness. In one the temperature on admission was 98°F. rising to 99° the same evening but fell before death next morning, to 97.2°. In another the temperature on admission was 99.4° and death occurred a few hours later. In the third the febrile reaction was well marked, temperature on admission being 100.2° and rising to 102.2° before death which took place 36 hours later. Case 8 was admitted comatose on the 4th day of illness with a temperature of 100°. During the next three days as the coma increased the temperature rose gradually, registering 105.8° just before death on the 7th day of illness. Case 1 was a mildly febrile case, the temperature never rising above 100° until the night before death when it rose suddenly to 104° and when death took place next morning the temperature was 104.8°. As opposed to this gradual or sudden rise of temperature to very high registers before death, we may instance case 9 where the temperature was febrile from the commencement of illness, running between 98.6° and 100° before patient was admitted to hospital and rising after admission to 102.6° on the 14th day of illness to fall gradually again to 99.4° just before death on the 17th day. Of the four remaining cases, Cases 7 and 9 ran mildly febrile temperatures for about four weeks with a daily range between 98° and 100.4°, after which they fell to normal and remained normal thereafter. In Case 2 the temperature on the 5th day was 103.4° and it remained elevated above 100° till the 10th day when it fell to normal and remained at that level during the remainder of a very tedious illness characterised by deep lethargy prolonged over several weeks. Case 11 ran a febrile temperature for three weeks before admission which suggested the diagnosis of Enteric Fever with which he was sent to hospital and for the next three weeks it ranged between normal and 100° after which it began to fall very gradually so that even at the end of six weeks in hospital the temperature

still tended to reach 99° in the evenings. I have since seen another case with the same type of temperature chart where the gradual lysis by which the temperature fell from 100° to normal extended over a period of almost three weeks. It is evident that the elevation of temperature is a fairly constant symptom of lethargic encephalitis but there is apparently no fixed type of temperature chart. Cases described as afebrile are most likely those in which the patient has come under detailed observation late in the disease when the pyrexia has subsided. In none of my cases was there any recrudescence of fever after the temperature had originally fallen to normal.

Pulse. In all my cases the pulse rate was raised. In about half the cases it was only moderately raised, to about 90 per minute. Two of these cases died, the pulse rate in one rising to 128 before death while in the other it remained at 88. In the other half of the cases the pulse rate was well over 100, in the majority from 120 to 140 according to the temperature during the pyrexial stage. In two cases the tension was noted as very high. In most of the other cases the pulse was rather soft and the force of the beats diminished.

Respirations were in all cases increased in frequency even when there was no pyrexia. In one case which was afebrile on admission the respiration rate was 22; in all the other cases it was above 24 during the active stage of the illness, and when there was marked pyrexia the rate was sometimes as high as 44 or 50 without any definite pulmonary complications to account for it. In one case the rate was above 30 for 6 weeks on end without any physical signs in the chest to account for this rate. In no case was Cheyne-Stokes breathing observed, even as a terminal feature of the disease.

Gastro Intestinal System. The tongue was usually dry and thickly coated and the mouth very dirty. In some cases there was considerable difficulty in swallowing and mucus

tended to collect in the throat. In one case there was excessive salivation so that saliva dribbled form the mouth. In every case constipation was a very marked and it was often rather difficult to overcome. Vomiting, except in the prodromal period was hardly seen at all. In one case, however there was vomiting of blood and post-mortem the stomach was found to contain a considerable quantity of altered blood, the result of oozing from a very congested gastric mucous membrane.

Urine. The urine in several cases contained a small quantity of albumen. In one case there was profuse haematuria for a few days which might possibly have been due to the fact that patient had been taking urotropine for two days previously. Profuse haematuria however, has been described in two cases by Combemale and Duhot[14] where no drugs at all were being employed so that in my case it is possible that the bleeding may have been quite independent of the urotropine.

Eruptions. In one case facial herpes was noted and in another large bullae appeared on the buttocks in the second week of illness. A third case had a fairly severe crop of boils during her illness. Beyond these no eruptions of any kind were seen. French writers (Chauffard and Bernard,[15] Sainton and others) are very insistent on the liability to bed-sores in this disease but I saw no sign of these in my cases. Eruptions have been noted as occurring in the disease by several writers notably Macnalty and Buzzard and Greenfield[16] the last named writer describing both Morbilliform and scarlatiniform rashes in well marked cases.

Duration of Illness. In fatal cases death usually takes place within the first three weeks of illness. In my cases it occurred twice on the 7th day of illness, twice on the 10th, once on the 17th, and once on the 19th day. Macnalty records

one case in a child of 1 year and 9 months where death occurred on th e second day and another where death took place on the third day. Death may take place, however, after many weeks' illness. McCaw, Perdraw and Stebbing[17] had a death on the 42nd day, Buzzard[18] on e on the 43rd day, and Macnalty records a death on the 49th day of illness.

In non-fatal cases duration of illness is equally varied. Mild "abortive" cases have been described in which recovery was complete within two or three weeks. In the great majority of cases however, recovery is very gradual and tedious, partly on account of the great muscular weakness, which so often results and partly because the various cranial nerve palsies occasionally tend to persist for a very long time. In addition to this mental changes are often well marked for many months after the stupor has passed off completely. In 4 of my "recovered" cases mental symptoms are still present at the time of writing (one of these cases has since died) and in the 5th some sensory disturbance is still present. Kinnier Wilson[19] reported sluggish pupils and occasional diplopia in one of his cases three months after the onset of illness, Netter reported defect of accommodation persisting equally long and Findlay reported a case in which facial palsy, ptosis and squint persisted 5 months after the onset of illness.

In 93 non-fatal cases collected by Macnalty, recovery took place by the end of one month, in 23 cases, by the end of two months in 22 cases, by the end of three months in 10 cases, while in the remaining 38 cases the duration of illness was protracted beyond the space of three months.

EPIDEMIOLOGY.

Infectious Nature of the Disease. On its first appearance in 1918 very few cases of lethargic encephalitis were reported where more than one case occurred in the same household, and no evidence was forthcoming as to any connection between different cases occurring in the outbreak. It was recognised to be an infectious disease because of its comparatively wide-spread occurrence and because of its close resemblance in many ways to acute poliomyelitis a proved infectious disease. In the outbreaks since then however, both in this country and in France multiple cases occurring in the same household have been more common, reports of such cases having been made by Netter[20] and Macnalty[21]. In one outbreak reported by the latter, 12 caseswith 5 deaths occurred in a Home for Girls with only 21 inmates. Since 1918, too, the disease has been successfully conveyed to monkeys and rabbits, reproducing lesions similar to those found in man. At least two apparently distinct organisms have been described as the causal factor, one by Wiesner[22] in 1917, and the other by Loewe and Strauss[23] although it is possible that these may be different forms of the same organism. Further proof however, is required before either can be accepted as the real cause. The demonstration of the virus of the disease in the nasopharynx of casesof lethargic encephalitis as also in the nasopharynx of animals successfully inoculated intra-cranially with brain-emulsion from a fatal case by Loewe, Hirshfeld and Strauss[24] may be taken as direct proof of the infectious nature of the disease and also as suggesting the most likely route of infection. It would seem to prove that in this disease, just as in acute poliomyelitis and cerebro-spinal fever, the source of infection lies in the nasopharynx of the infectious person, and infection takes place by the inhalation by the healthy subject of droplets of mucus containing the virus, coughed or sneezed out by the infectious person. It suggests, too, that infection may take place

either directly from a person suffering from the disease or apparently recovered from it, but still harbouring the virus in his throat, or that it may be conveyed by a third party in the shape of a "carrier". The fact that multiple cases have been so comparatively uncommon would seem to indicate that the infectivity of the disease is slight. This may be due to the possible presence of neutralizing substances in the nasopharynx of the ordinary healthy subject which destroy the virus, similar to the substances found in the case of acute poliomyelitis by Amoss and Taylor[25]. The occurrence of sporadic cases of the disease, on this theory would be explained, just as it has been demonstrated in the case of cerebro-spinal fever, as due either to an individual harbouring the virus in his throat for some time with impunity and then becoming susceptible through some breakdown in his natural resistance, or to a non-immune person becoming infected with a strain of the organism which has attained the degree of pathogenic action described as specific. So too, just as in the past, sporadic cases of acute poliomyelitis and of cerebro-spinal fever have occurred constantly between epidemics of these diseases, we are justified in expecting that the sporadic cases of lethargic encephalitis occurring at present may be the forerunners of epidemics of this disease in the future.

In my small series of cases careful enquiry was made to try to discover any possible connection between any of the cases, but only in one instance did even the slightest sign of possibility of connection present itself. Case 2, after discharge from hospital and about ten weeks spent at home, obtained employment in a large store. About a month afterwards Case 8 turned ill. She had a sister with whom she slept, employed as a clerk in this store and coming in contact daily with Case 2. The connection appears very meagre and it is at least very doubtful whether the one case had anything to do with the other.

On the theory that in lethargic encephalitis there might be

cases of the disease occurring in such a mild form as not to be recognised and yet capable of helping in the spread of the disease, just like some of the so-called abortive cases of acute poliomyelitis, careful inquiry was made in connection with my cases as to the occurrence of mild febrile attacks with nervous symptoms among the friends of the patients, but in no case with any real success. The medical attendant of one case said he had attended a mild case of meningitis on the same stair-head as Case 6, about 10 days before Case 6 turned ill, but the meningitis passed off quickly and the patient became quite well very soon. It is possible that this may have been a mild or abortive case but the evidence is so slight as to be of no value.

Age Incidence. To judge from my small series of cases lethargic encephalitis is a disease of adult life, the ages in my eleven cases varying from 20 to 56 years. Six were from 20 to 30, three from 30 to 40, one between 40 and 50 and one between 50 and 60. While the disease has been reported in a child of a few days and in another of 1 year and 9 months the majority of cases recorded have been in adults. Of 54 cases recorded by Netter 77% were over 15 years of age. Of 126 cases studied by James[11] 39.6% were under, and 60.4% over 20 years. Of 127 cases, however, reported by Crookshank[26] 44.8% were under 10 years and 55.2% over 10 years. Of 242 cases occurring in England in the first quarter of 1919 50% were under and 50% over 20 years.

Sex. 4 of my cases were females and 7 males. This agrees roughly with the proportion in most series. Thus in James's 126 cases 68 were males, and 58 females, while in Crookshank's 127 cases, 77 were males, and 50 females. In the latest series published, however, of 242 cases, the proportions are reversed, 116 cases being males, and 126 females. The usual proportion of male to female in epidemics of acute poliomyelitis is roughly 3 to 2.

Seasonal Incidence. All my 11 cases occurred between April 1919 and January 1920. The first three occurred in April, May and August respectively, while the remaining 8 occurred in a period of about 10 weeks between October 23rd 1919, and January 2nd 1920. This is in keeping with the usual seasonal incidence of the disease, the greatest prevalence in all the outbreaks described so far being in the winter or spring months. In the 1918 outbreak in this country, the largest number of cases occurred in March, April and May the epidemic reaching its highest point in April. The same was the case with the 1918 outbreak in France, while in 1917 the outbreak in Vienna was rather earlier. In 1919 the majority of cases in this country occurred in the first quarter of the year, the epidemic curve reaching it s summit in the first week of February. In the first quarter of the year 242 cases were reported, in the second quarter 109 cases, and in the third quarter 64 cases (Howell)[27]. This winter the disease seems to be prevalent again in France, a number of cases having been reported in Paris, Lille and other towns during the months of December and January. It would seem then, that the disease is more prevalent in the colder months of the year than in the summer as opposed to acute poliomyelitis which is usually most prevalent in the summer months.

Local Distribution. In its local distribution lethargic encephalitis seems to be a disease of the town rather than the country. Of 283 cases reported in England in the first few months of 1919 Reece[21] reports that 250 occurred in urban districts and 33 in rural, the proportion of urban cases to rural being, in terms of population 9.4 to 4.9.

Mortality. The death rate in lethargic encephalitis has varied considerably in different series of cases. In my 11 cases, 6 died, a mortality of 54.5%. Economo had the same number of deaths in his 11 cases, Netter had 7 deaths in 15,

a mortality of 46.6%. Crookshank recorded 26 deaths in 127 cases, a mortality of 20.4%. Kinnier Wilson had two deaths in 13, a mortality of 15.3%, while Hall[26] had 16 cases without a death. Of 242 cases reported in England in the first quarter of 1919, 112 died, a mortality of 46.2%, but the highest mortality recorded in this country was at Stoke-on-Trent in 1918 when 5 cases died out of 8, a mortality of 62.5%. In the American records we find the same differences in the death rates. Tucker[28] had 3 deaths in 12, Bassoe 4 in 11, Wedgeforth and Ayer[29] 5 in 9, Pothier[30] 1 in 8, and Woods[31] 0 in 7.

The type in which the mortality is highest seems to be that in which the general symptoms predominate over the localising symptoms, i.e. in which localised palsies if present at all are insignificant compared with the predominating lethargy. This at least was the case in my series with the exception of Case 1. and it agrees with the record of Macnalty's cases. In 168 cases collected by him, 37 deaths occurred. 10 of these occurred among 29 cases without localising signs while 27 occurred among 139 cases with localising signs. Many of these, of course had well marked lethargy and asthenia in addition to localised palsies but the palsies were the predominating feature in the clinical picture. In fatal cases the worst sign seems to be a gradual deepening of the lethargy into stupor and then into coma from which the patient cannot be roused. This occurred in 5 of my 6 fatal cases. In the 6th death took place from respiratory paralysis at a time when the lethargic condition had never been very severe. Respiratory paralysis is the commonest cause of death recorded by all writers on the subject but cases have been described in which death was due to respiratory complications such as acute bronchitis and bronchial pneumonia.

CLINICAL PATHOLOGY.

Blood Picture. Clinical examination of the blood was done in 5 cases and in all of them a leucocytosis was found ranging between 8,200 and 32,000 per cu,mm. the lower number being found in Case 7 which recovered, and the blood count being done late in the course of the illness. In the other cases the blood count was done comparatively early, usually within 10 days of the onset of illness, and in none was the white count less than 12,000. The highest count was 32,000 and this was obtained in Case 9 on the day before death took place. Differential white counts showed the Polymorphonuclears to vary from 64% to 86%, the Large Mononuclears from 6% to 8%, and the Small Lymphocytes from 8% to 28%. Early in the disease the small lymphocyte count seemed to be low, while later, it tended to rise, although in one case which ended fatally on the 7th day, the small lymphocytes numbered 28% on the day of death.

These results differ from those recorded in this country in 1918. In 10 cases Vaidya[32] found the blood counts practically normal, 18 counts giving an average of 7,600 white cells per cu.mm. The average percentage of polymorphonuclears he found to be 66, while in a few counts it was decidedly increased. Kinnier Wilson described a case with a leucocytosis of 33,600. In the American outbreaks most observers have found a leucocytosis. Bassoe describes a case with a leucocytosis of 12,200. Tucker found an almost constant leucocytosis of from 8,000 to 14,000. Wegeforth and Ayer give counts of from 6,000 to 16,000, Barker Cross and Irwin[33] of from 6,200 to 22,850, and Neal[34] records a case with a leucocytosis of 26,500.

Vaidya thought that the low white count which he described was of value in differentiating the disease from acute poliomyelitis where the more or less constant leucocytosis of from 15,000 to 25,000 obtains, but it now appears that so far as the blood picture is concerned the difference between

the two conditions is not sufficiently great to attach any diagnostic importance to. It is interesting to note that in acute poliomyelitis the blood picture at first described showed a leucopenia and it was only later that the correct description of a leucocytosis was given.

Characters of the Cerebro-Spinal Fluid. In all my cases without exception the cerebro-spinal fluid escaped under pressure when lumbar puncture was done. In some the pressure was only slightly increased, but in the majority the fluid was under greatly increased pressure such as one expects to find in acute meningeal conditions. In every case the fluid was clear except in one, where on each occasion that lumbar puncture was done the fluid contained a considerable quantity of blood. It was obvious that this blood was not due to puncture of a vessel in inserting the needle, an accident that happens at times in doing lumbar puncture, but was the result of bleeding somewhere in the brain or spinal cord. This patient had a severe epileptiform seizure a few hours after admission, and was more or less stuporose for several weeks, so that it is likely that frequent haemorrhages of varying degree occurred somewhere in the brain substance where the blood obtained access to the cerebro-spinal fluid. Similar cases have been described by Buzzard and Box[35], the patient in Buzzard's case having an attack of vomiting with some aphasia and hemianopia before blood was found in the cerebro-spinal fluid, while in Box's description vomiting, twitchings and epileptiform convulsions preceded the appearance of blood in the fluid. These cases may be confused with cerebral haemorrhage of the ordinary type, but differ from it mostly in the age incidence and in the absence of signs of cardio-vascular degeneration or chronic renal disease.

In all cases the cerebro-spinal fluid was centrifuged and the sediment examined. In one case the amount of blood present prevented any estimate of the white cell content being made. In all the other cases the cell content was found to be increased

to a varying degree the prevailing cell in practically all cases being the small lymphocyte which was often almost the only cell seen, a few large endothelial cells being sometimes present too. In one case, although lymphocytes were present, the majority of the cells found were polymorphonuclears. In this case the observation was made on the 8th day of illness, and death took place on the 10th day, the predominating lesions found post-mortem being acute congestion of the whole brain substance, well marked interstitial infiltration and slight basal meningitis. Kinnier Wilson records a similar case with a marked leucocytosis of the cerebro-spinal fluid in which 95% of the cells seen were polymorphonuclears.

In four cases the cells in the fluid were counted, the results being, Case 8, 50 per cu.mm., Case 9, 50 per cu.mm., Case 10, 60 per cu.mm. and Case 11 230 per cu.mm. The number of cases is too small and the observations too few to draw any conclusions from, but if the cells had been counted in the rest of the cases the numbers found (to judge by the centrifuged sediment) would have been in at least 6 of the 7 cases much increased above the few cells found per cu.mm. in normal spinal fluid. The actual numbers found threw no light on the severity of the condition. Thus cases 8 and 9 with 50 cells each died, while cases 10 and 11 with 60 and 230 cells respectively, recovered. The last count of 230 is interesting as showing that a very high cell count is not necessarily a very bad prognostic sign, this case being on the whole the mildest of the series. In acute poliomyelitis on the other hand, Draper[36] maintains that a high cell count early in the disease i.e. within 36 hours, of the onset of meningeal symptoms, is of serious prognostic import, while after that it is only of diagnostic value. As all of my cases were ill for several days at least before admission to hospital, the cell counts were done comparatively late in the disease so that the results might be expected to have little prognostic value. It is interesting to note that in most

of the early descriptions of the disease in 1918 the changes in the cell content were said to be very slight. In Netter's cases the lymphocytes were from 1 to 7 per cu.mm. Macnalty found a lymphocytosis in 12 cases out of 39. Vaidya found a slight excess of lymphocytes in a few of his cases but never more than 20 cells per cu.mm. Box[26] found an excess of lymphocytes in 6 cases out of 14, while Crookshank found an excess in 25 cases and a marked excess in 6 cases out of 43. In more recent American descriptions a lymphocytosis has been found in most cases. Although Bassoe in 11 cases found a cell content usually below 10 and never above 26 per cu.mm., Pothier in 6 cases found the cells to vary from 20 to 85 and Wegeforth and Ayer in 9 cases recorded cell counts of from 5 to 150 per cu.mm. Barker, Cross and Irwin in a recent article, recorded cell counts of from 2 to 97 per cu.mm. and in some recently published French cases Achard[37] describes a marked lymphocytosis in two cases with cell counts of 80 and 100 respectively. Thus the marked difference which was stated to exist between the cerbro-spinal fluid of this disease and that of acute poliomyelitis has very largely disappeared with an increased number of observations, although in no case has the cell count been recorded as approaching at all to the very high figures obtained in severe cases of acute poliomyelitis. It may be noted that there is one type of poliomyelitis in which Draper always found a surprisingly low cell count, usually below 100 per cu,mm. This type of patient was usually drowsy or even comatose, and as a rule showed a transient facial paralysis. The differences in the cell counts found by different observers may be due partly to the varying severity of the disease and partly to the fact the the counts may have been done at different stages in the illness the count tending to be high early in the disease and sink gradually to normal. It should be noted however, that my highest cell count was obtained in the third week of illness.

Chemically the only change found in the cerebro-spinal fluid

was a slight increase in the protein content which was noted in most of the cases. This is in agreement with most other observations recorded. In every case the fluid was able to reduce Fehling's Solution although very slowly.

Bacteriological examination both by culture and by microscope was in every case negative. In 7 cases of the 11 the Wassermann Reaction was done with the cerebro-spinal fluid and in every case it was negative.

The condition of the cerebro-spinal fluid in lethargic encephalitis may be summed up as follows. The fluid as a rule is perfectly clear and under increased pressure: it contains an excess of lymphocytes, the cell count varying from a few cells per cu.mm. to several hundreds. The protein content is slightly increased but the sugar content unchanged. The fluid is sterile to ordinary culture methods. Exceptionally it contains a varying amount of blood.

PATHOLOGY.

From the account given of the individual post-mortem examination of the 6 fatal cases, it will be seen that while all 6 cases were more or less alike, individual differences existed between them all. In every case there was congestion of the brain membranes, the pia-arachnoid usually appearing pinker than is normal. Some congestion, too, was present in practically every case throughout the brain substance and in two cases it was certainly the outstanding feature. In one case quite marked oedema of the brain tissue was noted, in all the others the consistence of the brain seemed normal. In one case minute haemorrhages could be seen in the large basal nuclei with the naked eye aided by a hand lens. In other cases what appeared to the naked eye to be haemorrhages turned out to be dilated vessels full of blood.

While in most cases changes of one kind or another could be found on microscopical examination, in practically every part of the brain, in every case certain regions were especially involved in the inflammatory condition, the chief seat of the mischief being the large basal nuclei and the brain stem . In Case 1 the only portions of the brain examined microscopically were the pons and medulla both of which showed marked changes. In only one of the other 5 cases did the basal nuclei show no change. In 4 they showed very marked lesions, while in all 6 cases definite lesions were found in the pons and medulla. Changes corresponding to those found in the medulla were seen in some cases in the cervical region of the cord but not very markedly. Congestion of the meningeal vessels was seen in several cases but only in one case was actual meningitis noted and then it was very slight.

The cerebral cortex was examined in 5 cases and in 4 showed some change. In two cases there was very marked congestion of the cerebrum, both white and grey matter, while in the other two cases the congestion was not so marked. In two cases slight

perivascular infiltration was seen in the cerebral cortex and in one of these slight interstitial infiltration was noted too.

The cerebellum was examined in 5 cases. In one it showed intense and in another marked congestion. The other abnormality noted was seen in all 5 cases and affected the cells of Purkinje. These were destitute of Nissl granules, but finely granular in appearance showing a pale indefinite nucleus with a well-stained nucleolus. These appear to me to be the changes noted by Marinesco[11] in this disease, called by him "lesions primitives" and explained as an expression of cellular exhaustion.

The most important lesions appeared to me to be perivascular and interstitial infiltration. Both of these were found in every case although in very varying degree and in one case or another in every part of the brain as well as in the upper part of the cord. The perivascular infiltration was found usually in the mesencephalon, pons and medulla, and as a rule was best seen under the floor of the fourth ventricle in the neighbourhood of the various cranial nerve nuclei. While usually bilateral in distribution it was not necessarily symmetrical. It was very well marked in one case in the large basal nuclei. The interstitial infiltration very often accompanied the perivascular infiltration and could usually be fairly definitely connected with the vascular system. In some cases however, it was well marked where the perivascular collars were hardly to be seen at all and at times it was difficult to connect it definitely with the blood supply. The cells involved in the perivascular infiltration were almost altogether mononuclear, mostly small lymphocytes although some plasma cells were also seen and some larger mononuclear granular cells too. Polynuclears as a rule were seldom seen. In the interstitial infiltration the small round cells, the same as those seen in the perivascular infiltration, played a prominent part but proliferating neuroglial cells played a part too, and in many cases these latter were in the majority. The vessels involved

in the perivascular infiltration were mostly the small venules although arterioles were occas ionally seen too, with small white cells closely surrounding them.

Vascular congestion was a marked feature in two cases, in one of which it was almost the only change seen, perivascular and interstitial infiltration being almost altogether absent, and chromatolytic changes in the nerve cells very slight. In the other the congestion was very intense but was accompanied by well marked cell changes, perivascular and interstitial infiltration, and abundant minute haemorrhages.

Haemorrhages were seen in two cases. In one there was one fairly large haemorrhage in the medulla, red cells infiltrating a comparatively large area of tissue. In the other very abundant minute haemorrhages were present in the basal nuclei. These varied in size apparently, according to the size of the ruptured vessel. In many places the ruptured vessel with its white-cell collar could be seen lying in the centre of the haemorrhage but in others no break in continuity of the vessel wall could be seen. In no case was there evidence of a large confluent haemorrhage such as has been described by Kinnier Wilson in one of his cases.

Nerve cell changes were noticeable in most of the cases but did not occupy a prominent place in the histological picture. In many cases the ganglion cells appeared perfectly healthy, even when surrounded by fairly dense interstitial infiltration, or close to vessels with well marked white-cell sheaths. In other cases, however chromatolytic change was seen, with disappearance of the Nissl granules and a tendency towards an excentric position of the nucleus. In some cases the protoplasm seemed to be disintegrating. Round cells and large glial cells were seen lying close to many of these ganglion cells and in one section through the optic thalamus actual though slight neuronophagia was observed. In no case at all were the changes in the nerve cells found at all

corresponding in severity to the intensity of the inflammatory condition of the surrounding tissues.

In several cases anotner lesion was found. This was proliferation of the columnar epithelial cells lining the central canal of the spinal cord so that the canal appeared quite full of proliferated cells and the continuity of the epithelial wall had gone, the canal being represented by a mass of apparently actively proliferating cells which were infiltrating widely into the tissues around. This was seen in several cases but in one case the central canal was quite normal in appearance. In anotner the canal was quite patent but the lining epithelium was apparently proliferating actively, the proliferated cells spreading into the tissues around. What the significance of these appearances is, is difficult to say, there being no very obvious reason why there should be any irritation in the central canal in a disease in which the meningeal reaction is so comparatively slight. It is of interest to note that Hoche (according to Romer[38] and Wickman[39]) has suggested that in acute poliomyelitis the central canal serves as a channel for the virus of that disease but this view has received very little support.

PATHOGENESIS. A study of the pathological lesions found in the disease shows a very close similarity to those found in acute poliomyelitis and suggests that the pathogenesis of the two diseases is similar. This is further suggested by the demonstration by Loewe, Hirshfeld and Strauss of the virus of the disease in the nasopharynx of human cases and also of animals inoculated intracranially with virus from a human case. If this is so, the virus makes its way by way of the lymphatics from the nasopharynx to the base of the brain and spreads in the brain substance along the perivascular lymph-spaces, giving rise to the perivascular exudates. Why the disease should localise itself in the brain and not in the cord as does poliomyelitis no one has yet explained.

It has been said by some observers (Greenfield and Buzzard) that Lethargic encephalitis is a haematogenous infection while poliomyelitis is lymphogenous. This view is based apparently on the fact that in the former disease the brunt of the attack in the brain is borne by the blood vessels, which are often very much congested, and haemorrhages are frequently found, while in the latter the chief lesion is destruction of the nerve cells. Further evidence in favour of the general character of the infection and the possibility of its spread by the blood stream may be deduced from the acute congestion found in the abdominal and thoracic organs in two of my fatal cases, from the occurrence of haematemesis in one of these and from the occurrence of haematuria in two French cases reported. Recently a case died in Ruchill Hospital in which evidence of acute congestion was found post-mortem, in the abdominal and thoracic organs, with petechial haemorrhages into the wall of the intestine and of the heart and under the visceral pleura of both lungs. Wilson[40] too, has stated that the filter-passing organism which he describes as the cause of lethargic encephalitis, is present in the blood during the febrile stage of the disease but this has not so far, been confirmed.

Against this view we note that the lesions found in the two diseases are essentially the same and differ only in degree so that it is unlikely that their modes of transmission in the tissues should be different. One would also expect if lethargic encephalitis were a blood borne infection to find the inflammatory changes most marked round the capillaries of the brain tissue but this is not so, the vessels chiefly affected being the small veins just as it is in poliomyelitis. The damage to the blood vessels resulting in rupture and haemorrhage in that disease is said by Draper to be due, not to any action of the virus in the blood but to the pressure of the surrounding cellular infiltration and the same explanation would seem to hold good in encephalitis

the abundant minute haemorrhages seen in one of my cases being easily traced in most cases to venules involved in perivascular infiltration.

ETIOLOGY.

In all my cases careful microscopical examination of the cerebro-spinal fluid and, in the fatal cases, of the brain tissues was made with a view to determining the presence of pathogenic organisms. Cultures, too, were made in practically all cases from the cerebro-spinal fluid and in fatal cases from the brain tissues. The results however, both of the microscopical and the cultural examination were uniformly negative.

The means at my disposal did not allow me to do any inoculation experiments with a view to elucidating the etiology of the disease. A great deal of work however, has been done by other observers in this line and the results obtained are of great interest and value. Wiesner in 1917 successfully inoculated a monkey with virus from a fatal case of lethargic encephalitis and recovered from the central nervous tissues of the monkey a diplo-coccus for which he claimed specific properties, on the ground that when injected into monkeys it produced a haemorrhagic encephalitis. McIntosh[11] in this country in 1918 inoculated monkeys with material from fatal cases but without result and concluded from this that the virus was not the same as that of acute poliomyelitis with which he had obtained successful results before, working under exactly the same conditions. In November 1919 however, he was successful in conveying the disease to a monkey by intra-cerebral inoculation of material from a fatal case producing lesions similar to those found in human cases. In 1918 Marinesco found a diplo-coccus in sections of the brain stem examined microscopically but was unable to obtain cultures. In 1919 Bradford, Bashford and Wilson conveyed the disease successfully to monkeys and were able to recover from the blood, spinal fluid, and brain tissues both of human cases and of infected

monkeys a small filter-passing organism which could be cultured anaerobically by the Noguchi method. This however has not been confirmed. More recently in America, Loewe, Hirshfeld and Strauss have been able to produce the disease in monkeys by intra-cerebral injection not only of an emulsion of brain tissue from fatal cases but also of a filtrate of the nasopharyngeal mucous washings of a fatal case. Two of these same workers have been able to grow an organism from a filtrate of nasopharyngeal washings and from an emulsion of brain tissue from fatal human cases by the Noguchi method. This organism in its morphology, cultural and staining properties, appears to them to resemble closely the globoid bodies described by Flexner and Noguchi as the causal organism of acute poliomyelitis. In this connection it is of interest that the diplo-coccus described in the Vienna cases of lethargic encephalitis by Wiesner has been said by Crookshank[41], with exactly what authority he does not state, to be identical with the pleomorphic coccus described in acute poliomyelitis by Rosenow and Wheeler[42] for which they claim etiologic properties in that disease, and which is also said by these and several other observers to be the aerobically grown form of Flexner and Noguchi's anaerobic globoid bodies.

So far none of the discoveries of causal organisms in encephalitis have been confirmed by other workers so that it is impossible to decide whetner the actual organism responsible for the disease has been discovered or not.

Predisposing Causes. I was much struck by the fact that practically all my patients were strong, healthy persons with a good health record , the only exception being Case 1, who gave a history of chronic gastric disturbance lasting over several years although she had been comparatively well for some months previous to the onset of encephalitis. Among the others the reasons assigned for the disease were various. One gave a history of a fall on the head a month before she turned ill.

Another was out of work for 2 months before turning ill and had become much depressed by his repeated failures to find employment. A third had been very much upset by the death of his wife some months before, followed by great business worries. Three were demobilised soldiers and one a demobilised sailor and although they seemed quite fit physically their friends were unanimous in every case in ascribing the illness to the nervous strain of the war. One patient had been subject to epileptic fits for about a year previous to her illness. In three cases no predisposing circumstances at all could be elicited. In no case at all was there a history of influenza.

Relationship of Lethargic Encephalitis to Influenza.

Attention has been drawn by various writers to the close connection that has been noticed to exist between the incidence in time of lethargic encephalitis and influenza. Thus it was just before the onset of the 1918 summer epidemic of influenza that lethargic encephalitis was first observed in this country and the majority of cases reported in that year occurred in March, April and May while the summer epidemic of influenza reached its height at the beginning of July. In 1919 lethargic encephalitis was most prevalent in the first three months of the year reaching its maximum number of cases in the first week of February about a fortnight before the spring epidemic of influenza reached its height. Further, influenza was present in Vienna in 1917 when Economo described the outbreak of encephalitis there and in Paris in 1918 when Netter drew attention to encephalitis there. In the present year Achard has drawn attention to the recrudescence of encephalitis and influenza at the same time in Paris. That the connection between the two diseases is something more than the mere fact that they both tend to be more prevalent in the cold than in the warm months is held by many writers, notably Hamer[43] and Crookshank in this country, Chartier[44] in France and Jelliffe[45]

in America. Crookshank has been able to show that lethargic encephalitis is no new disease but one which has appeared over and over again in the different countries of Europe during the past 450 years and that practically every appearance recorded has coincided with a prevalence of influenza in the same place. From this he deduces that epidemic encephalitis may "represent an intensive specialised reaction that has perhaps the same epidemiological relation to pandemic influenza, as have the prevalences and epidemics of septic pneumonia and of gastro-intestinal disturbance described before and after that affection." Hamer has pointed out that examination of the recorded outbreaks of influenza in this country shows that when the epidemic has prevailed in spring and summer, cases of nervous type have predominated. While Chartier questioned in December 1918 whether lethargic encephalitis is really "an autonomous affection and not merely a symptomatic variety of a general infection like influenza." It is well known that lethargy may occur in patients suffering from influenza but whether this is actually encephalitis is quite another question. In a recent paper however Crofton[46] has described the successful treatment by means of bacillus influenzae vaccine of several cases presenting symptoms suggestive of lethargic encephalitis.

I have been unable to trace any connection between my cases and influenza. Influenza was epidemic in Glasgow in February and March 1919 but died off then and has not appeared in epidemic form since. My first case occurred in April 1919. In no single case of my 11 had the patient suffered recently from influenza although all of them must have been in contact with it during one or other of the three epidemics of 1918-1919. Among American writers there is a difference of opinion as to the connection of the disease with influenza. Bassoe was unable to find a history of preceding influenza in any of his 11 cases Woods found such a history in three cases in 7, Barker, Cross and Irwin in 5 cases in 8, Neal in 25 cases in 38 and Tucker in all of

his 13 cases. Bassoe suggested, however that encephalitis may be due to a virus which in order to become active must have been in contact at one time or another with that of influenza. One likely form of connection between the two diseases may be that the person who has had influenza recently or who has been exposed to it without having had a clinical attack of the disease is likely to have had his natural resistance to such a disease as lethargic encephalitis lowered.

RELATIONSHIP OF LETHARGIC ENCEPHALITIS TO ACUTE POLIOMYELITIS.

In discussing the relationship between these two diseases it is necessary to refer briefly to the "mysterious disease" which occurred in epidemic form in different parts of Australia in 1917 and 1918 and which has been described by different writers under different names such as "Acute Encephalitis of Unknown Origin" (Mathewson and Latham[47]) "a Clinically Aberrant Form of Acute Poliomyelitis")(Breinl[48]) and "Acute Encephalo-myelitis" (Cleland and Campbell[49]). The disease was most prevalent in children, more than 50% of all cases occurring in children under 10 and had a very high mortality rate, anything from 60% to 80%. It was characterised by its sudden onset, after an incubation period of 5 to 12 days with vomiting, fever, headache and convulsions as a rule, followed by lethargy and confusion passing into varying degrees of unconsciousness. Cranial nerve palsies were hardly seen at all and limb palsies were very uncommon. Death took place usually in fatal cases in from 4 to 6 days but might occur earlier. In recovery cases the acute symptoms passed off in 10 or 12 days and convalscence was rapid although mental symptoms persisted in many cases. The lesions found were of the same nature as those seen in acute poliomyelitis, congestion and haemorrhage, perivascular and interstitial infiltration, and varying degrees of destruction of nerve cells. Their distribution was throughout both brain and cord, all parts of the brain being

affected, but especially the cerebral cortex, the basal nuclei, the dentate nucleus of the cerebellum, and the dorsal region of the pons and medulla. In practically all of their 16 post-mortems, Cleland and Campbell found the changes in the brain to be dominant, greater and never less than those found in the spinal cord, a finding quite in agreement with the clinical manifestations of the disease. Other writers, however found the lesions fairly equally distributed between brain and cord. Inoculation of various animals including monkeys with a brain emulsion from fatal cases reproduced the disease with similar lesions to those found in the human case and a similar distribution. It was noted that the epidemics did not synchronise with, and could not be connected with any epidemic of acute poliomyelitis or cerebro-spinal fever or influenza. No organism was described as the etiological factor in the disease.

It is obvious that the description of this disease does not conform to that of any recorded outbreak of acute poliomyelitis and it is also obvious that it is not a description of lethargic encephalitis as that disease has occurred in Europe and America. It seems to occupy a position between these two diseases.

A comparison of the pathological lesions found in lethargic encephalitis with those found in acute poliomyelitis shows that they are essentially the same and differ only in degree, certain elements in the histological picture being much more marked in the one disease than in the other. Perivascular infiltration is a much more prominent feature in lethargic encephalitis than in acute poliomyelitis but the reverse is the case with interstitial infiltration which is usually very dense in the latter disease. Nerve cell changes too, are much better marked in acute poliomyelitis than in encephalitis, constituting perhaps, the most important feature of the former disease while in the latter they are a very secondary feature, the absolute destruction of the nerve cell by neuronophagia in poliomyelitis being represented in encephalitis

by comparatively slight chromatolysis of the cell and occasional slight suggestion of neuronophagia. Marked differences however are seen between the two diseases in the distribution of the lesions. In acute poliomyelitis the inflammatory process is most marked in the cord and affection of the brain in most cases is slight, while in lethargic encephalitis the brain stem is the part chiefly affected, any changes found in the cord being of little account. While affection of the brain in most cases of acute poliomyelitis is unimportant in comparison with the affection of the cord, lesions have been found by Wickman in the medulla in every fatal case of poliomyelitis examined in which death was not due to an intercurrent malady. These lesions resemble those found in the cord but are said by both Wickman and Draper to differ in degree. "The lesions tend to be disseminated and no preponderating localisation in the motor areas, such as is seen in the spinal cord, occurs. The vessels most infiltrated are those present immediately beneath the fourth ventricle and the focal interstitial lesions tend to be smaller than those in the cord. In general the alterations of the ganglion cells are slight and are mainly chromatolytic. Where interstitial changes are absent the ganglion cells always appear normal. Usually the more evident the infiltration, the more do the ganglion cells suffer but it is remarkable how exceptionally well preserved the ganglion cells may be in the midst of a densely infiltrated zone." This description, taken almost verbatim from Wickman, of the lesions found in the medulla in acute poliomyelitis could be taken as an almost exact description of the changes found in the medulla in many of my cases of lethargic encephalitis. It is possible then, that the differences in degree of the lesions in acute poliomyelitis and lethargic encephalitis are in part at least due to their differences in anatomical distribution.

In practically all the large epidemics of acute poliomyelitis which have been recorded and in many of the small ones a number

of cases have occurred in which the symptoms differed from those of the ordinary spinal type of the disease and could be referred to affection of some part of the brain, mostly the medulla and pons. This bulbar or pontine type of poliomyelitis is usually characterised by various cranial nerve palsies, the nerves mostly affected being the facial, the abducens, the motoroculi and the hypoglossal, although others may be affected too (Wickman). Sometimes a varying degree of stupor may be present but these cases seem to differ from the ordinary case of lethargic encephalitis, rapid recovery being the rule (Draper). It should be remembered however, that many cases of lethargic encephalitis are very mild and recover fairly quickly.

If little evidence is to be found in the pathological lesions of the individuality of the two diseases still less is to be got from the clinical pathology. In both there is a well marked leucocytosis to be found, as a rule, and in both there is, as a rule, a well marked lymphocytosis in the cerebro-spinal fluid. It is true that the spinal fluid cell counts recorded in lethargic encephalitis are far from reaching the high numbers found in acute poliomyelitis but it must be remembered that the high figures in the latter disease are found in its early stages and so far no epidemic of the former disease has attained such proportions as would insure cases being recognised early enough for correspondingly early counts to be made. It has been noted by Draper that low cell counts are obtained in the group of cases of poliomyelitis which show cranial nerve palsies with accompanying stupor.

The differences between the two conditions are more marked when we come to study the mortality, age incidence, seasonal incidence, and symptomatology of both.

Mortality. Comparison of the mortality rate of the two conditions is difficult because it has varied so much in both. In lethargic encephalitis it has been as high as 62.5% in one small series of cases while in another larger series no deaths

took place at all. In 126 cases investigated by James in 1918 the mortality rate was 20%, while in 242 cases reported by Reece in 1919 it was 46.2%. In acute poliomyelitis the mortaltiy has varied widely in different epidemics and according as cases without paralysis are included or not. In German epidemics it has varied according to Römer between 10% and 22% when only cases with paralysis were considered. In Sweden , Wickman found it to vary between 10% and 42% on the same basis while in New York in 1916 when many"abortive" cases were included the mortality rate was as high as 27%. It is of interest that the mortality rate in adults is much higher than in children. Wickman found the mortality rate in children under 11 years to be 11.9% while in patients between 12 and 32 it was 27.6%. On the whole the death rate in lethargic encephalitis appears to be higher than in acute poliomyelitis. It must be remembered however that lethargic encephalitis is still not a very widely-known condition, so that it is probable that many mild cases are not recognised and consequently the recorded death rate may be really much higher than the actual death rate.

Age Incidence. Acute poliomyelitis is essentially a disease of childhood although adults may be attacked too. In the Hesse-Nassau epidemic of 1909 96% of all persons attacked were under 10 years of age, 90% under 5 years and more than 75% under 3 years (Römer). In 5496 American cases reported by Draper 96.4% were under 10 years. Of 227 cases of lethargic encephalitis reported by Crookshank in 1918 44.8% were under 10 years and of 54 cases reported by Netter only 23% were under 15 years. Of 242 cases reported by Reece in 1919 50% were under 20 years. The difference in age incidence between the two conditions seems quite definite.

Seasonal Incidence. Acute poliomyelitis is said to be a disease of the warm weather, most of the large epidemics having occurred in summer their greatest prevalence being reached in July

or August. In lethargic encephalitis all the outbreaks so far reprted have begun earlier in the year during the winter or spring. The epidemic of 1918 occurred chiefly in March, April and May the maximum prevalence being reached in April. The same was the case in France, while in Vienna in 1917 the outbreak was even earlier. In 1919, too, the greatest prevalence of the disease in England was in the first quarter of the year. It must be remembered however, that epidemics of acute poliomyelitis have occurred during the winter months in Sweden (Wickman) and America (Draper) while in Römer'S Hesse-Nassau outbreak the maximum prevalence was in October. Two great stress then should not be laid on differences of seasonal incidence.

Symptomatology. The differences in symptomatology between the two conditions are largely the result of the difference in localisation of the inflammatory process. Thus cerebral symptoms are marked in lethargic encephalitis and slight or absent in acute poliomyelitis. Cranial nerve palsies are a marked feature of the former disease and so is stupor or some form of lethargy, while limb palsies are rare. On the other hand limb palsies are the prominent feature of acute poliomyelitis, cranial nerve palsies and stupor or lethargy being seldom met with. Differences however, in the onset of the palsies are marked. The flaccid paralysis of acute poliomyelitis usually appears suddenly and is at its maximum on its first appearance. The cranial palsies of lethargic encephalitis are gradual in their onset, and are progressive after they have appeared. The palsies in encephalitis are very often bilateral the one side being affected after the other, while in poliomyelitis bilateral lesions are infrequent and it is rare for one palsy to follow another. In poliomyelitis residual paralyses are of frequent occurrence, while in encephalitis the vast majority of paralyses tend to clear up within a few months. The onset of acute poliomyelitis is usually abrupt, often with convulsions, after a short prodromal period of a few days. In lethargic encephalitis

the onset is usually gradual after a prodromal period which may be as long as three weeks, and convulsions are exceptional. The clinical pictures of the two diseases are fairly distinct but may not be so well marked when the ~~there~~ rare cerebral cases of poliomyelitis are met with.

Inoculation Experiments. Monkeys inoculated intra-cranially with virus from acute poliomyelitis usually develop poliomyelitis. Monkeys inoculated intra-cranially with virus from lethargic encephalitis develop encephalitis. This seems strong evidence that the diseases are distinct but encephalitis does sometimes follow the intra-cranial inoculation of poliomyelitis virus into monkeys, and Römer in his book shows photographs of good examples of facial, oculomotor, and hypoglossal palsies in such cases. These cases are the exception however, rather than the rule and not nearly so common as they should be, if encephalitis were merely a variety of poliomyelitis.

Further evidence against the identity of the two conditions is found by many writers in the fact that no connection has been found between cases of acute poliomyelitis and lethargic encephalitis occurring in the same locality, and that with the appearance of the latter disease during the past two years, there has been no corresponding increase of the former, such as one might expect if the two were the same disease. It must be remembered, however, that in very few instances has any connection been demonstrated even between individual cases of lethargic encephalitis, and also that if the prevailing type of poliomyelitis during the past two years has been the encephalitic there is no necessity that the spinal cases should be increased in number too.

Lastly it seems to be remarkable that while Loewe and Strauss have discovered in lethargic encephalitis an organism for which they claim etiologic properties and which resembles in its morphology, culture, and growth, the globoid bodies described by Flexner and Noguchi in acute poliomyelitis, another worker, Wiesner, has claimed etiologic properties for a coccus described by him which is said

to be the same as the pleomorphic coccus for which Rosenow and Wheeler claim etiologic properties in acute poliomyelitis.

A perusal of the literature of letnargic encephalitis shows that the majority of writers who have considered the relationship between this disease and acute poliomyelitis have been in favour of regarding it as an autonomous infection, quite distinct from poliomyelitis. In my opinion, however, the evidence against this view is almost as strong as that for it, and it seems to me that the question is yet far from having been decided, no absolute proof being yet forthcoming on one side or the other. If we are to decide that the two conditions are distinct diseases, because of the different distribution of the pathological lesions, the differences in symptomatology resulting largely from these distributions, the different age incidences and mortality rates, what are we to say about the Australian outbreak? There the lesions were divided fairly equally between brain and cord, the symptoms were mostly those of brain affection, the age incidence was that of acute poliomyelitis, and the mortality rate much nigher even than that of lethargic encephalitis. Is this an autonomous infection, too, or are all three varieties of the same Heine-Medin disease? Our present knowledge does not seem to me to be full enough to answer this question accurately. Further experimental work is required and especially immunological experiments. If it could be demonstrated that immune serum from acute poliomyelitis protected against experimental inoculation with the virus of lethargic encephalitis and immune serum from lethargic encephalitis against inoculation with poliomyelitis virus, fairly definite proof would be had of the identity of the two conditions, while failure to protect would be evidence against their identity. It has been suggested by Macnalty and others that the relationship between the two conditions may correspond to that between enteric and paratyphoid fever the viruses being quite distinct but closely related to one another.

If the two conditions are distinct diseases we must conclude

that the standard descriptions of acute poliomyelitis have been rather loose and have included certain encephalitic cases which were really cases of lethargic encephalitis. If they are the same disease we have witnessed during the past three years a remarkable change in the biological properties of a disease, but this change is no greater then that which has during the past 30 years transformed the comparatively uncommon sporadic infantile paralysis into the wide-spread epidemic acute poliomyelitis. Change in the biological properties of a disease is by no means uncommon and changes have occurred even in lethargic encephalitis during the two years it has been known in this country and in France, particularly in its infectivity, multiple cases occurring in the same household much more commonly to-day than two years ago. What Sydenham[50] wrote almost 250 years ago, seems to be true still to-day. "Nothing in my opinion, strikes the mind that contemplates the whole and open domain of medicine, with greater wonder, than the well-known varied and inconsistent character of those diseases which we call epidemic. It is not so much that they reflect and depend upon different conditions of climate in one and the same year, as that they represent different and dissimilar constitutions of different and dissimilar years."

DIAGNOSIS.

In some cases the clinical picture may be so clear and the symptoms of the disease so well marked that diagnosis of lethargic encephalitis may present no difficulty even to one who has not previously seen the disease. In the majority of cases however, the clinical picture is not clear nor are the symptoms as definite as they might be and diagnosis may be a matter of considerable difficulty, so that the patient may have to be kept under observation for several days before a definite diagnosis can be arrived at. The difficulty depends largely on the time of the illness at which the patient is seen.

In the prodromal period a catarrhal condition like conjunctivitis might suggest the possibility of the disease to one on the lookout for it during an epidemic . Other suggestive symptoms would be headache, shivering, general malaise, gastric disturbance and drowsiness, but all these symptoms might occur in several other mildly febrile conditions.

In the acute illness diagnosis is easier. Headache , pyrexia drowsiness, or stupor from which patient can be roused, dilirium, asthenia, an expressionless face, speech changes, constipation, are all fairly typical of the disease. Where localising symptoms are present, diplopia, ptosis, ocular muscle palsies, facial palsy, dysphagia, are all strongly suggestive of lethargic encephalitis. When the palsies are bilateral, ingravescent in onset and transient in appearance the suggestion is strengthened. The finding of a definite leucocytosis in the blood and a lymphocytosis in a clear cerebro-spinal fluid escaping under pressure, would help to confirm the diagnosis as would also a negative Wasserman/n Reaction in the spinal fluid.

When the patient comes under observation later in the disease in a condition of deep coma, in which it may be impossible to determine the presence of cranial palsies, dependence may have to be place/d on the history of the illness, the results of lumbar

puncture and the absence of such signs or symptoms as choked disc, albuminuria or glycosuria which might throw light on the comatose condition.

Differential Diagnosis. The differential diagnosis between lethargic encephalitis and acute poliomyelitis has been considered already in discussing the relationship of these two conditions. The following are some of the commoner diseases with which lethargic encephalitis may be confused, with brief notes on the points of difference.

Tuberculous Meningitis. There may be a tubercular history or diathesis. Tubercles may be seen in the choroid. Convulsions are common. The cerebro-spinal fluid is clear and usually under pressure but forms a web on standing in which tubercle bacilli may be found.

Cerebro-spinal Fever. Marked meningeal symptoms are usually present. The meningococcus can usually be found in the cerebro-spinal fluid.

Septic Meningitis. There is often a history of old middle-ear disease or of injury to the head, or there may be a septic condition elsewhere. The causal organism is usually easily demonstrated in the cerebro-spinal fluid.

Cerebral Syphilis. There is usually a history of syphilis. Optic neuritis may be present. The cerebro-spinal fluid shows a well marked lymphocytosis and the Wassermann Reaction in the fluid is positive. Response to anti-syphilitic treatment is definite. It is possible of course, for lethargic encephalitis to occur in a person with a positive Wassermann Reaction in the spinal fluid, and a case in which this occurred was reported by Lortat-Jacob and Hallez[51].

Cerebral Haemorrhage. This may be confused with the epileptiform onset type of encephalitis, but a history of syphilis or of chronic renal disease would help to clear up the diagnosis.

Cerebral Tumour. There is usually a history of persistent headache with vomiting and convulsive seizures. Choked disc is a common symptom.

Cerebral Thrombosis. Convulsions are not uncommon and paralysis is gradual in its onset. There is usually a history of vascular degeneration or of syphilis or an inflammatory lesion may be present elsewhere.

Uraemia. There is a history of renal disease. Oedema may be present and albumen and tube-casts found in the urine.

Diabetic Coma. There is a history of diabetes mellitus and sugar may be found in the urine.

Enteric Fever. The spleen is usually enlarged and rose-spots may be found. Early in the disease the bacillus typhosus may be recovered from the blood, and later, the Widal Reaction is positive.

Diphtheritic Paralysis. There is usually a history of recent diphtheria and the diphtheria bacillus may be still present in the throat. Cranial nerve palsies in diphtheria are not at all likely to be accompanied by lethargy.

Botulism. The chief symptoms of this disease are said to be dilated pupils, dryness of the mouth and throat, with burning thirst and obstinate constipation. Stupor, so common in lethargic encephalitis, is not one of them. There are usually multiple cases in the same household, who have been exposed to a common source of food poisoning.

Hysteria. There is usually a history of previous attacks. The onset is sudden, and the objective symptoms well marked. Epileptiform seizures are frequent. Recovery is usually abrupt. Many cases of encephalitis present functional symptoms.

Myasthenia Gravis and Paralysis Agitans may both be suggested by the expressionless facies in lethargic encephalitis but these are both chronic conditions and the history of the illness would be sufficient to dismiss them.

Lastly, lethargic conditions may occur in influenza, which it may be very difficult to differentiate from lethargic encephalitis. Cranial nerve involvements are not so common in influenza as in encephalitis and the lethargic state is not likely to be of such long duration. It must be remembered, however, that the view has been upheld by some observers that lethargic encephalitis and influenza are etiologically closely connected.

PROGNOSIS.

With a mortality rate which is exceptionally very low, but as a rule anything from 15% to 50%, the prognosis cannot be said to be good. As regards survival, the majority of cases have a favourable issue although in my small series 6 out of 11 ended fatally. To judge from my cases, as from most other cases published, a bad prognostic sign is the predominance of the general lethargic condition over localised palsies. Cases in which localised palsies are well marked as a rule do well, while those in which lethargy is the predominant symptom, as a rule, end fatally. Gradual deepening of the lethargy into stupor and then coma, is a very bad sign.

As to absolute recovery in non-fatal cases the prognosis is much more difficult. Very few cases seem to return to their normal condition within, atleast, a few months. In none of my 5 recovered cases can recovery be said to be complete at the time of writing. In one case dismissed from hospital 8 months ago, the mental condition was not yet normal when he died of ulcerative endocarditis a few weeks ago. In another dismissed four months ago the mental condition is still so unsatisfactory that patient can hardly be allowed out by herself. The third case is quite normal mentally, but has still some sensory disturbance in one hand, five months after the onset of illness. The 4th case, four months after the onset of illness, suffers from

violent attacks of dementia, during which he has to be forcibly restrained, while between the attacks he is quite silly. The 5th recovery is still said to talk nonsense at times, three and a half months after the onset of illness. In all these cases the cranial palsies have cleared up completely, as a rule within about three months of the onset of illness. Kinnier Wilson, Netter, Findlay, Jelliffe, and others have noted the persistence of cranial palsy and mental changes for many months after apparent recovery, otherwise. The mental changes may be merely slight silliness, memory defects, or anxiety states and, according to Jelliffe, may be mistaken for hysteria, while they are really the direct results of focalised lesions in the first and second frontal lobes.

The amount of evidence at present available is quite insufficient to allow of the formation of an opinion of any value as to ultimate absolute recovery.

TREATMENT.

In the management of these cases, symptomatic treatment was the line adopted. This was directed in the first place towards the hygiene of the mouth and throat which tended to become very dry and clogged with mucus, and towards the relief of constipation which is usually a troublesome feature of the disease. Attention must also be paid to the bladder, retention of urine being a fairly common symptom, and tending if neglected, to go on to overflow incontinence. In addition, particular attention must be paid to the skin, especially in long-standing cases, bed-sores, to judge from the French literature on the subject, being a common and distressing occurrence in the disease. Personally, I have not seen this complication.

In spite of the prevailing lethargy, sleeplessness may sometimes be a feature of this disease and sedative treatment may be required. This was so in one of my cases where the patient was very restless all day in a state of low muttering delirium, which tended to become noisy at night, and no real sleep was obtained until he was put on to 10 minims of Battley's Solution nightly. This gave him several hours of quiet, refreshing sleep with very beneficial result.

Urotropine has been recommended in this disease as in other affections of the central nervous system on account of its supposed disinfectant action in the cerebro-spinal fluid. I used it in one case, where 5 grains were given every four hours for two days at the end of which time patient had a severe haematuria, which persisted for several days although the urotropine was stopped immediately. I was of the opinion that the haematuria was a direct result of the administration of urotropine, but I have since found two cases recorded by Combemale and Duhot in which very severe haematuria occurred in lethargic encephalitis where no urotropine or any other drug was being administered, so that it is possible that the haematuria in this case may have had

nothing to do with the urotropine. In another of my cases although no haematuria was found during life very intense congestion of the kidneys was found post-mortem.

Serum Treatment. In two cases serum from a convalescent patient was made use of in treatment. The serum in each case was taken from Case 7 at a time when all the symptoms of the disease had passed off except occasional diplopia and some sensory disturbance in the fingers of on e hand. The cases treated were numbers 9 and 10. In Case 9 the serum was given intra-thecally in one dose of 20cc. on the 16th day of illness, when stupor was very marked so that it was with very great difficulty that patient could be roused at all to answer questions, and respiration was very laboured and sighing. The serum apparently had no effect whatever, as evidenced by any improvement in the general condition, or any alteration in temperature or pulse and patient became more stuporose still till death took place on the following day.

In Case 10 15cc. of serum were injected intra-thecally on the 16th day of illness. Patient was then very drowsy with unequal pupils and a coarse tremor of the arm. No effect was noticed on the pulse or temperature and next day the drowsiness seemed to be worse than before. The dose was repeated on the following day but with no beneficial resultso far as could be seen, the drowsiness continuing to increase steadily during the next 10 days. No further administration of serum was made but ultimately this patient recovered, although his illness was very protracted. I have since thought, that since in this disease, as in acute poliomyelitis, invasion of the central nervous system may be only a part of a more or less generalised systemic infection in which the virus seems to reach the nervous system, by way of the lymph channels, in close connection with the blood stream, and the disease process is situated chiefly within the brain tissue, intravenous administration of serum would have given

better results, especially if combined with the removal of 20 to 30 cc. of spinal fluid by lumbar puncture, so as to promote lymph drainage towards the spinal canal and so facilitate the arrival of immune serum at the disease processes within the brain and cord tissue. In acute poliomyelitis certainly, the most recent evidence is in favour of intravenous as against intrathecal administration of immune serum, extraordinary good results having followed this method of treatment in Rosenow's[52] hands.

In the literature of lethargic encephalitis I have only been able to find one case in which convalescent serum was employed. Wegeforth and Ayer gave 50 cc. of convalescent serum intravenously in combination with 350 cc. of normal saline solution to one of their cases, giving an intrathecal injection of 30 cc. of serum at the same time. A marked febrile reaction resulted but no improvement. Two days later the intravenous injection was repeated but with no beneficial result, death taking place on the following day.

The success of the serum treatment of acute poliomyelitis has been found to depend on the serum being administered early in the disease and it is probable that the same is the case with lethargic encephalitis. Unfortunately I have had no opportunity of treating a case early in the disease with convalescent serum, but the treatment seems certainly much more hopeful than any other. In selecting a donor of convalescent serum care should be taken to see that the Wassermann Reaction is negative and the strictest aseptic precautions should be observed in withdrawing the blood and separating the serum.

Prophylaxis. If it be the case as seems most likely, in view of the multiple cases which have been recorded as occurring in the same household, that lethargic encephalitis is spread by human contact, isolation of the patient should be the first step in prophylaxis. Local prophylactic measures to be adopted

in treating contacts, convalscents and possible carriers should be directed towards attacking the virus at its most li kely point of entry into the system, the nasopharynx. Douching or spraying with mild antiseptic lotions might be advised, but as it has been demonstrated by Amoss and Taylor that in acute poliomyelitis the nasopharyngeal secretion contains neutralising bodies to the virus of that disease, the same may be the case with lethargic encephalitis, in which case, at least strong antiseptics should be avoided, as more likely to do harm than good, and only the mildest lotions employed.

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4. [illegible] pons, cut obliquely showing perivascular infiltration.

5. [illegible] nerve cells showing Nissl granules.

6. [illegible] nerve cells close to infiltrated vessel.

7. Nerve cells showing distinct chromatolytic change. The upper [illegible] in the left cell of the field shows commencing [illegible].

8. [illegible] round cell infiltration. The nerve cells [illegible] stained and have lost their Nissl granules.

9. [illegible] engorgement in the lenticular nucleus.

10. [illegible] congestion in the cerebellum.

11. [illegible] perivascular and interstitial infiltration in the pons.

12. [illegible] through the lower part of the [illegible] showing the central canal. The epithelial cells lining the canal are proliferating and the proliferated cells infiltrating the [illegible] tissue.

Description of Photographs.

1. Venule in medulla showing well marked perivascular infiltration.
2. Vessel showing rupture of wall and effusion of blood into surrounding tissue. Mixed with blood cells are infiltrating white cells. These are mostly small lymphocytes but many large mononuclear cells are also seen.
3. Perivascular infiltration under a high magnification. The majority of the cells seen are small lymphocytes but larger granular cells are also seen. One large cell in the centre of the field shows two nuclei.
4. Venule in the pons, cut obliquely showing perivascular infiltration.
5. Healthy nerve cells showing Nissl granules.
6. Healthy nerve cells close to infiltrated vessel.
7. Nerve cells showing distinct chromatolytic change. The upper nerve cell in the left half of the field shows commencing neuronophagia.
8. Dense interstitial round cell infiltration. The nerve cells seen are faintly stained and have lost their Nissl granules.
9. Small haemorrhage in the lenticular nucleus.
10. Capillary congestion in the cerebellum.
11. Slight perivascular and interstitial infiltration in the pons.
12. Section through the lower part of the medulla showing the central canal. The epithelial cells lining the canal are proliferating and the proliferated cells infiltrating the surrounding tissue.

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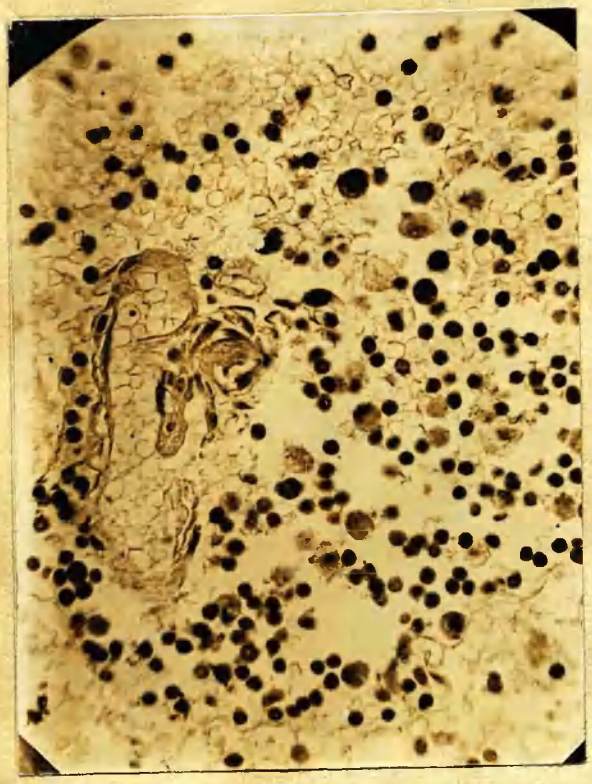

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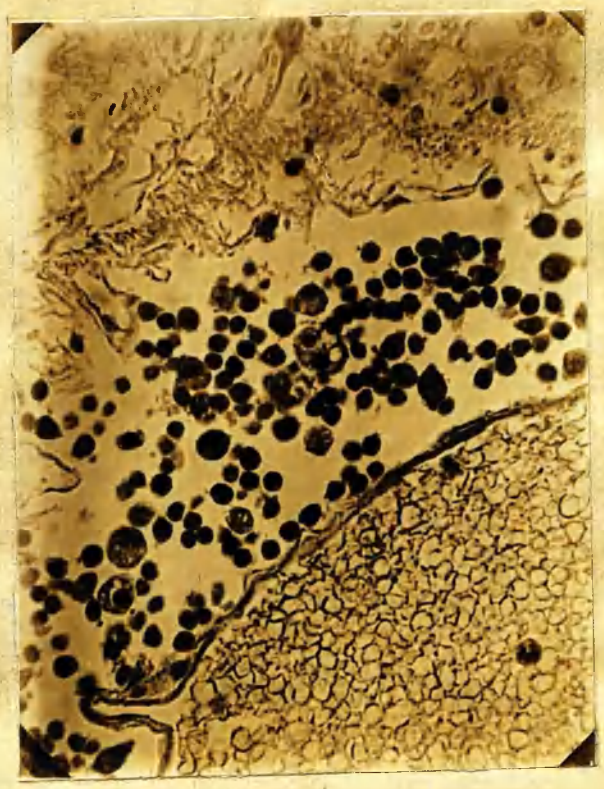

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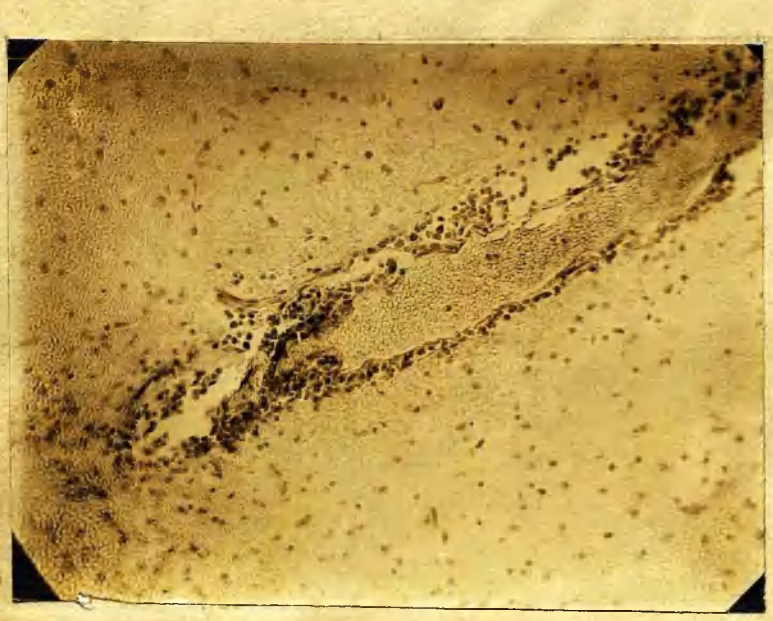

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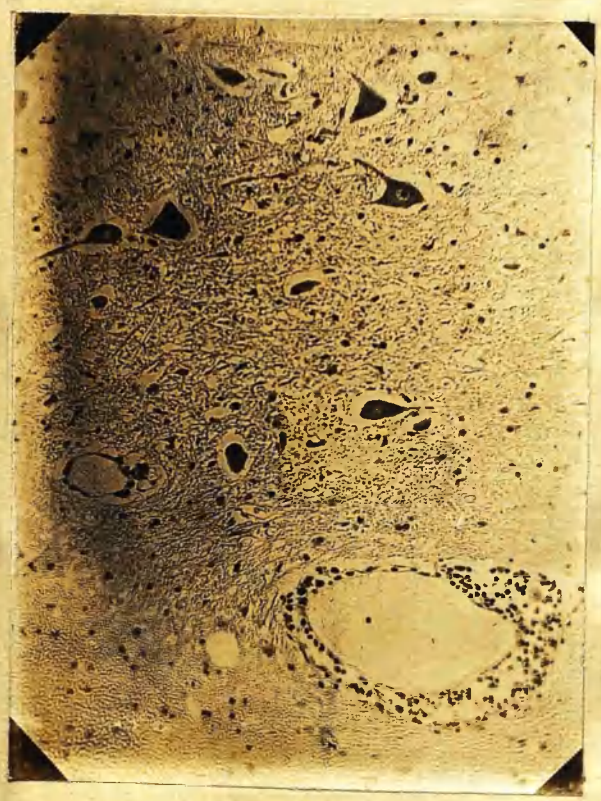

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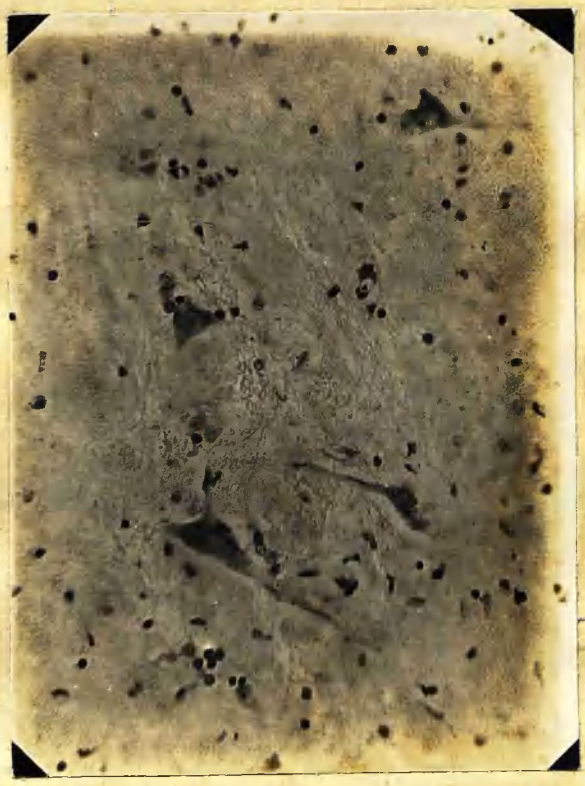

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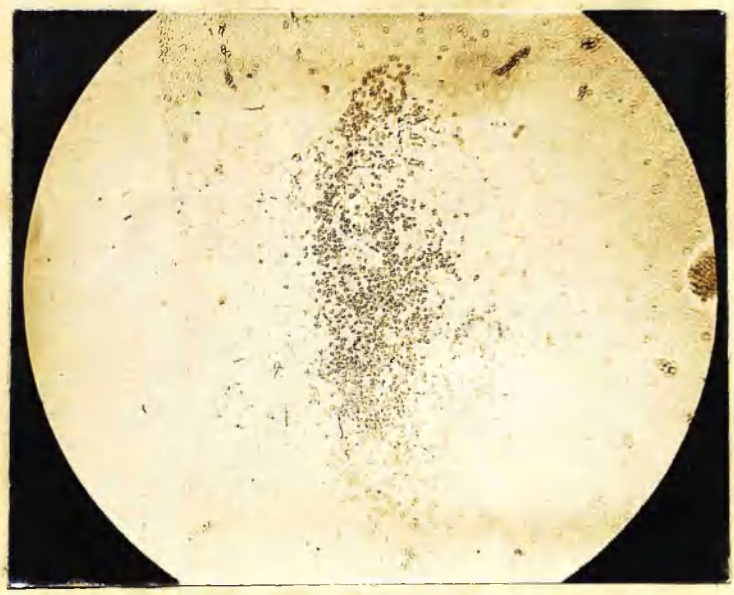

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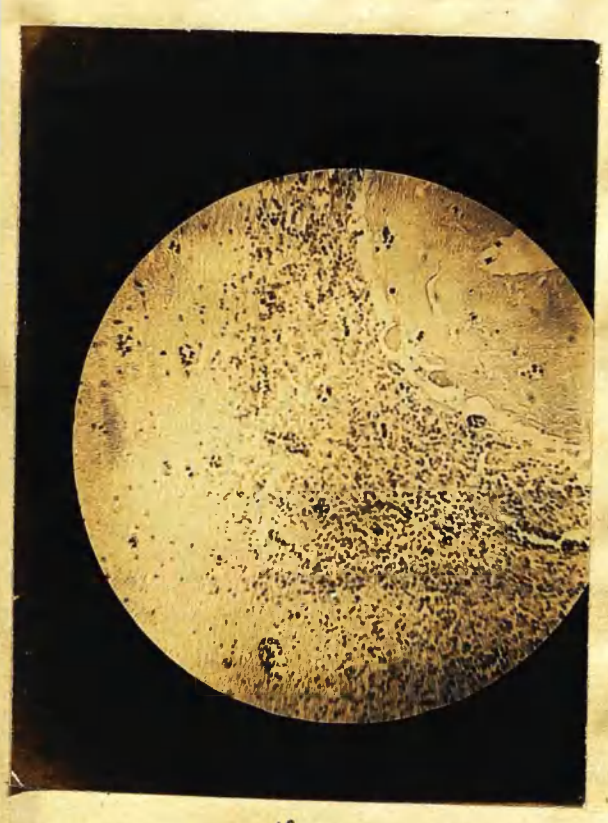

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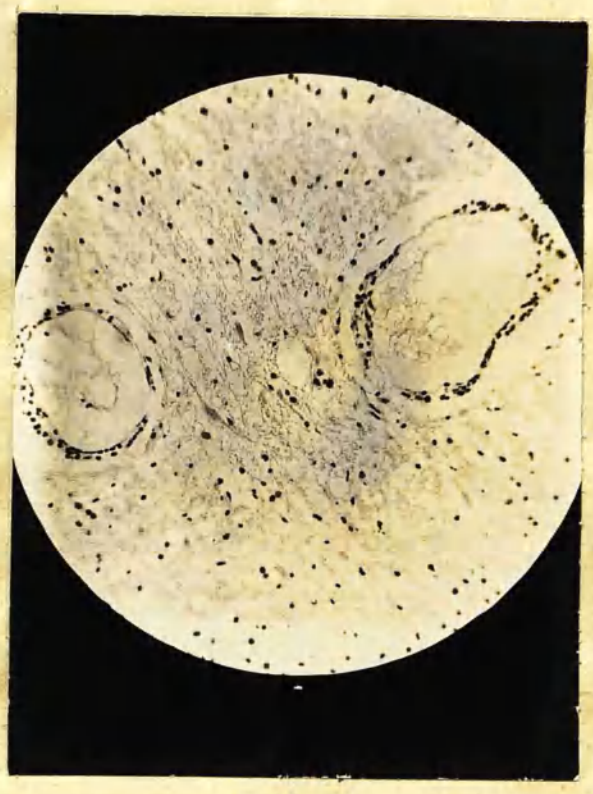

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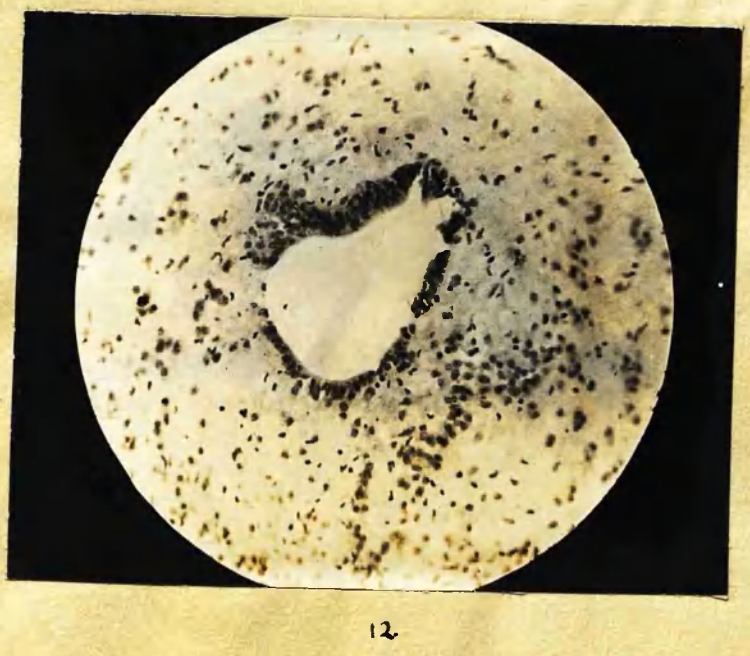

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