

# LETHARGIC ENCEPHALITIS: SYMPTOMATOLOGY AND HISTOPATHOLOGY\*

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Our present literature is teeming with symptomatology and case reports of lethargic encephalitis. Since v. Economo,<sup>1</sup> in the spring of 1917, reported his first thirteen cases in detail, similar clinical conditions have been observed on the Eastern Continent as well as in this country. It first manifested itself on our Eastern coast in the fall of 1918 (Abrahamson<sup>2</sup>), gradually spreading westward. In the spring and summer of 1919, cases were reported throughout the Middle West (Bassoe,<sup>3</sup> Riggs,<sup>4</sup> Hammes<sup>5</sup>), and in October, 1919, it appeared almost simultaneously in Portland (House<sup>6</sup>), in Seattle and in Tacoma (Winslow<sup>7</sup>).

We have had an opportunity to observe twenty-seven cases, six of which occurred since the recent influenza epidemic and in which the clinical picture differed somewhat from those observed earlier.

The onset was usually gradual. Severe diffuse headaches, disappearing rapidly after the first four to ten days, occurred eleven times in our series. Asthenia, lethargy, general muscle rigidity with masklike features (the paralysis agitans syndrome, usually without the tremor), any or all three of these symptoms manifested themselves in every case in a greater or less degree. Cranial nerve palsies were observed, the third and sixth were involved most frequently, and diplopia or blurred vision was a common complaint. The seventh nerve was involved unilaterally twice and bilaterally once, the tenth nerve once and the twelfth nerve in two cases. Eight cases gave no evidence of cranial nerve involvement at any time during the disease.

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\* Histopathologic Studies made in Neuropathologic Laboratory, University of Minnesota Medical School.

1. v. Economo, C.: Encephalitis lethargica, Wien. klin. Wchnschr., May 10, 1917.

2. Abrahamson, I. Prevalence of Infectious Lethargic Encephalitis, Proc. New York Neurolog. Soc., J. Nerv. & Ment. Dis. **50**:61 (July) 1919.

3. Basso, P.: Epidemic Encephalitis (Nona), J. A. M. A. **72**:971 (April 5) 1919.

4. Riggs, C. E.: Epidemic Lethargic Encephalitis, Minnesota Med. **3:49** (Feb.) 1920.

5. Hammes, E. M.: Lethargic Encephalitis (with Report of Twelve Cases), Minnesota Med. **3**:118 (March) 1920.

6. House, W.: Epidemic (Lethargic) Encephalitis, J. A. M. A. **74**:372 (Feb. 7) 1920.

7. Winslow, K.: Epidemic Lethargic Encephalitis (Nona) in Seattle, Northwest Med. **18**:209 (Oct.) 1919.

In seven cases the pupils did not respond to light or accommodation; in two the pupils were miotic, in one mydriatic, and in three irregular in size.

Partial atrophy of the hand muscles (right) was observed in one case; three cases manifested weakness and one definite paralysis of one arm. Tremor of variable amplitude and location occurred in five cases. Ticlike contractions of the facial or arm muscles were observed four times. Choreiform twitchings, hemiplegic and suggestive of Huntington's type, were marked in one patient. Another patient had two general convulsions in one day two weeks after the onset of the illness, followed by motor paralysis of the right arm which improved gradually.

Urinary retention, necessitating catheterization, was present five times. Involuntary urination or dribbling occurred in only two cases.

The temperature varied between normal and 103.4 F. Five patients had a normal temperature throughout, and although they presented a typical clinical picture, the disease ran an uneventful course and the patients made a satisfactory recovery.

The mental picture has been a variable one. Delusions and hallucinations occurred. Temporary disorientation and confusion were not infrequent. One patient presented the picture of a catatonic type of dementia praecox; another one developed a typical Korsakoff's psychosis; a toxic delirium was observed in four cases associated with a high temperature. Wilson<sup>8</sup> described a case in which typical "Witzelsucht" was manifested through the entire course of the illness. House<sup>6</sup> states that euphoria in a greater or less degree occurred in every one of his patients.

The deep reflexes have been either normal, increased or absent. The youngest patient was 14 years of age, and the oldest, 54. Eight of our patients were females and nineteen were males. Of the first twelve patients, six died. Of the remaining fifteen patients, all are still living. Judging from our observation, the clinical course was gradually becoming milder until the occurrence of our recent influenza epidemic (January and February, 1920). Since then the cases (six) have been of a very severe and more toxic type, although none have been fatal as yet.

In the shortest case entire recovery occurred within three weeks. The longest one in our series began in December, 1918. At present the patient is still lethargic, and has epileptiform attacks involving the left side of his face. Another case in our series began Sept. 16, 1919. The patient remained lethargic for more than two months, had a tem-

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8. Wilson, S. A. K.: Epidemic Encephalitis, *Lancet* 2:7 (July 6) 1918.

perature between 100 F. and 103 F. for about one month. At present, he is able to sit up, feeds himself, takes some interest in his surroundings, but it unable to walk or talk.

The laboratory findings were quite uniform in our cases. There usually was a mild leukocytosis (average, 14,000). The spinal fluid gave a mild globulin test, a lymphocytosis varying between normal and fifty-seven per c.mm. The colloidal gold curve was of no aid in the diagnosis. In some cases, the most marked changes occurred in the syphilitic zone, in others in the meningitis zone and in several there was no change in any dilution. All blood and spinal fluid cultures were negative. No animal inoculations were done.

Tucker<sup>9</sup> reported two cases of lethargic encephalitis in which post-mortem examination revealed some involvement of the hypophysis. His opinion was based on macroscopic examination alone, as no microscopic report was given. In our three cases which came to postmortem nothing abnormal was noted in the hypophysis on gross examination, but one of our patients presented a clinical picture suggestive of pituitary gland involvement.

#### REPORT OF CASES

CASE 1.—A male, 24 years of age, was first seen Nov. 25, 1919. His family and personal history are unimportant.

He contracted influenza in October, 1918. One week later he became drowsy and sleepy, and a few days afterward he became unconscious. This condition continued for about ten days, after which he gradually improved. Two weeks later he had a generalized epileptic attack which recurred at irregular intervals until Dec. 9, 1919. The attacks varied from four a day to one a month. They would commence with a "feeling of faintness," then the patient would become unconscious and have a generalized convulsion, bite his tongue and have involuntary urination. When he awakened he would feel tired and fall asleep for an hour or two. He, furthermore, described periods during which he would be confused mentally. At times he also had involuntary urination. He would be quite free from this for several weeks and then it would become very annoying for a week or so and clear up again. Mentally he is somewhat sluggish.

Since his influenzal attack, he has noticed that his breasts are enlarging, that he is losing the hair in his axillae and that he has to shave only every week or ten days, where formerly it was necessary to do this every other day. He has impairment of his sexual desire. His weight fluctuates considerably; within a week he would gain or lose ten pounds without any apparent reason.

The *neurologic examination* is negative, except for a slight Romberg. The fundi are normal; fields of vision normal. The physical examination shows a well built young man, with a dozen scant hairs on his chin only, although he has not shaved for six days. The hair on his head appears to be normal. In both axillae are a few scattered hairs. His pubic hair and his sexual organs are apparently normal. His breasts are somewhat enlarged and slightly tender on pressure. A roentgenogram of the skull is negative. There is no enlargement of the sella turcica.

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9. Tucker, B. R.: Epidemic Encephalitis Lethargica or Epidemic Somnolence, or Epidemic Cerebritis with Report of Cases and Two Necropsies, J. A. M. A. **72**:1448 (May 17) 1919.

The *laboratory findings* are: hemoglobin, 80 per cent.; erythrocytes, 4,800,000; leukocytes, 7,900; differential count, normal; blood Wassermann, negative; blood pressure, 120 systolic, 70 diastolic. The spinal fluid was under normal pressure, gave a trace of globulin, two lymphocytes per c.mm., a negative Wassermann and a negative colloidal gold curve.

Under *treatment* with whole pituitary extract 2 grains three times a day, and luminal,  $\frac{3}{8}$  grain, three times a day, he has been free from attacks since Dec. 9, 1919, but has noticed no other change in his condition.

CASE 2.—This case was suggestive of a thalamic syndrome. A young woman, age 29, was seen in consultation with Dr. Goltz, Jan. 27, 1920. She gave a history of having had a severe chill Jan. 17, 1920, accompanied by severe headache, fever, vertigo and general malaise. Jan. 24, 1920, she complained of blurred vision, drowsiness and nervousness. She had a slight general tremor of both arms which was not present when she was seen three days later. At this time she complained of diplopia, drowsiness, stiffness in her extremities and difficulty in starting the flow of urine. Her face was masklike, she was lethargic and answered questions sluggishly. On examination, the left pupil was larger than the right, and it was irregular. There was no response to light or accommodation. There was a paralysis of the left internal rectus. The fundi were negative. The upper extremities were normal, the lower extremities rigid, all deep reflexes normal.

About February 1, she developed irregular choreiform movements of her left arm and leg. These also involved the left facial muscles and the left sternomastoid. The movements were irregular and jerky, simulating a Huntington's chorea. They were aggravated when the patient attempted to use either left extremity. Since February 15 this has become so marked in her left facial muscles that it was difficult to understand her. She protruded her tongue normally, but there was a slight tremor present. Her right side was entirely free from these movements and the posture of the right extremities was almost catatonic. Her muscle strength was good in all four extremities. The neurologic findings have remained the same.

The laboratory findings were: leukocytosis, 14,000; negative blood Wassermann; spinal fluid under normal pressure, gave a heavy trace of globulin, fifty-seven lymphocytes per c.mm. and a negative Wassermann. Urine negative.

The lethargic condition had entirely subsided by February 24, but the choreiform movements were marked and the patient complained of difficulty in going to sleep because of them. She had a temperature of 101 F. during the first week, which gradually became normal and has remained so. She has had difficulty in taking sufficient food and is gradually losing weight and strength.

Howe<sup>10</sup> describes very completely a thalamic syndrome in one of his cases of lethargic encephalitis.

Six cases of lethargic encephalitis seen during the past month have presented an onset somewhat different from the previous cases. There was more evidence of meningeal irritation and mental confusion. The following case was seen Feb. 16, 1920, in consultation with Dr. Sanford at Farmington, Minn.

CASE 3.—The patient was a farmer, age 52, with a negative family and personal history, except that he had an attack of pneumonia in November, 1918. About Feb. 2, 1920, he noticed a mild left conjunctivitis with severe pain in the eyeball. This gradually subsided, and within a few days he developed severe

10. Howe, H. S.: Thalamic Syndrome in Epidemic Encephalitis, *Neurolog. Bull.*, N. Y. **2**:190 (May) 1919.

neuralgic pains in both occipital nerves. Soon after, this same condition extended into both arms, the pain being so severe that it was necessary to resort to morphin for relief. Two days later, he complained of similar pains in his lower extremities. These attacks of pain occurred frequently during the day and night. In the intervals the patient was quite comfortable.

About this time he became confused and disoriented, and during the night, he became quite delirious. His temperature was normal during the first week, but gradually increased until it was 102 F. at the end of two weeks. He also complained of blurred vision, and that if he looked to the right, the wall appeared at an angle and the pictures on the wall seemed to be at the foot of the bed. On the evening of February 15, he became drowsy and the next morning he was very lethargic, but could be aroused readily.

The *neurologic examination* was negative throughout.

The spinal fluid was under normal pressure, gave a trace of globulin, seven lymphocytes per c.mm., a negative Wassermann and a colloidal gold curve 1344210000. Since then he has developed a typical picture of lethargic encephalitis; his neuralgic pains have subsided, but he is still confused and delirious at night.

Our histopathologic studies have been based on the following three cases:<sup>11</sup>

CASE 4 (147).—Male, age 53, admitted Oct. 16, 1919, to the Neurologic Service, City and County Hospital, St. Paul, gave a negative family and personal history. Oct. 12, 1919, the patient complained of an acute coryza, severe headache, general malaise and joint pains. He began to wander around his home in an aimless manner. The following day he became drowsy and sluggish mentally, and soon after he became stuporous. He was disoriented, but answered all other questions intelligently. He was lethargic but could be aroused readily.

The *neurologic examination* showed the following: Pupils were moderately dilated and did not respond to light or accommodation. There was weakness of the right external and left internal rectus eye muscles. The fundi were negative. The face was masklike, but the patient could move all the facial muscles. He protruded his tongue with difficulty. The upper extremities were normal, but mildly spastic. The lower extremities showed absent knee and Achilles jerks, no Babinski, no spasticity.

Leukocytosis, 11,850, blood culture negative, urine normal, except for a trace of albumin. Blood Wassermann negative. Spinal fluid gave increased pressure, a trace of globulin, fifteen lymphocytes per c.mm., a negative Wassermann and a colloidal gold curve 2334300000. Repeated lumbar punctures gave similar spinal fluid findings. The patient progressively grew worse and died eighteen days after the onset of the illness.

CASE 5 (149) is of interest because of the involvement of the respiratory centers early in the disease. Male, age 45, admitted on the Neurologic Service, City and County Hospital, St. Paul, Oct. 29, 1919. His family and personal history were negative. October 15, the patient noticed that he felt weak, drowsy and wanted to close his eyes. He continued his work as a teamster for three days, until he went to sleep while driving his truck; fell down and injured his knee. He remained home for eleven days during which he "slept" most of the time. He also noticed difficulty in breathing at times. Patient was examined October 20; he was in bed motionless and with eyes closed. He could be aroused readily, answered questions, got up and walked around, and presented the typical gait and posture of a paralysis agitans. Occasionally, he would have

11. These three cases have been previously reported from the clinical standpoint by one of us (E. M. H.) in *Minnesota Med.* 3:145 (March) 1920.

a general coarse tremor. At irregular intervals, he would get attacks of cog-wheel respiration of from one to two minutes' duration, during which his respiration would go up to 72 per minute. He was markedly rigid.

*Physical examination* was negative, except for an atrophy of the left calf muscles, which patient stated he had had all his life. His pupils were normal. The light and accommodation reactions were sluggish and disappeared after three days. There was a paralysis of the right internal rectus. The face was masklike, but all movements were normal. All other cranial nerves were normal. All deep reflexes were normal, except for an absence of the left Achilles jerk.

Blood culture was negative, Widal negative, Wassermann negative; leukocytes, 12,200. Spinal fluid was under pressure, contained ten lymphocytes per c.mm., and a trace of globulin, but was otherwise normal. His temperature varied between 100 and 102 F.; his pulse was around 130; his respirations varied between normal and 72. His stupor gradually deepened and he died Nov. 9, 1919.

CASE 6 (151).—Male, age 23, was admitted on Dr. A. Hoff's medical service, City and County Hospital, St. Paul, Nov. 16, 1919, with a diagnosis of suspected typhoid. A lethargic encephalitis was suggested, and Dr. Hoff kindly permitted one of us (E. M. H.) to see the patient. His family and personal history were negative. About November 9, he began to feel drowsy and weak. Soon after he had two severe attacks of epistaxis. About November 12, he developed marked photophobia, also a slight general muscle rigidity and he became stuporous. We first saw the patient November 18; he was drowsy but could readily be aroused, and he answered questions coherently. His mental condition was normal. He could not open his eyes because of marked photophobia.

*Neurologic examination* showed the following: Pupils equal and responded to light and accommodation. He had a paresis of the left internal rectus. All other cranial nerves were normal. All deep reflexes were normal. He had a positive right Babinski.

Blood culture was negative, Widal negative, Wassermann negative; leukocytosis, 17,000; urine normal. Spinal fluid was normal, except for a positive globulin and fifty-four lymphocytes per c.mm. November 19, he seemed confused and disoriented and developed a typical mental picture of a Korsakoff's psychosis. He died Nov. 21, 1919.

#### PATHOLOGY

The pathologic findings in the three cases we have studied microscopically correspond in the main to the other cases described in the literature (Bassoe,<sup>3</sup> Bassoe and Hassin,<sup>12</sup> Wegeforth and Ayer,<sup>13</sup> Neal,<sup>14</sup> Calhoun,<sup>15</sup> special article in *Journal American Medical Asso-*

12. Bassoe, P., and Hassin, G. B.: A Contribution to the Histopathology of Epidemic ("Lethargic") Encephalitis, *Arch. Neurol. & Psychiat.* **2**:24 (July) 1919.

13. Wegeforth, P., and Ayer, J. B.: Encephalitis Lethargica, *J. A. M. A.* **73**:5 (July 5) 1919.

14. Neal, J. B.: Lethargic Encephalitis, *Arch. Neurol. & Psychiat.* **2**:271 (Sept.) 1919.

15. Calhoun, H. A.: Histopathology of brain and Spinal Cord in a Case Presenting a Postinfluenzal Lethargic Encephalitis Syndrome, *Arch. Neurol. & Psychiat.* **3**:1 (Jan.) 1920.

ciation,<sup>16</sup> Marinesco,<sup>17</sup> Netter,<sup>18</sup> von Economo,<sup>19</sup> and Vaughan<sup>20</sup>). Our findings consist in congestion, edema, petechial hemorrhages, pigmentation, perivascular and diffuse infiltration of round cells, proliferative changes in the endothelial and interstitial tissues, and degenerative changes in the nerve cells and myelin sheaths. The whole central nervous system, including the meninges, shows evidence of involvement in the disease process, but the most marked changes are uniformly in the lenticulo-striate complex, the midbrain, pons and medulla. No extensive review of the literature on the pathology of lethargic encephalitis is contemplated in this report, but differences noted in our cases as compared with some of the others reported will be brought out in the description of the histopathology.

At the time of necropsy no gross lesions were noted in the central nervous system, aside from the fact that the meningeal vessels were markedly congested in Case 151 and moderately congested in Case 149. No recognizable hemorrhages or areas of softening were encountered. No pathologic changes having any significance in connection with this report were noted in other parts of the body. The postmortem examinations were performed by Dr. Kramer, pathologist at the City and County Hospital of St. Paul. The brains and cords (no cord received from Case 147) were delivered to us in 10 per cent. liquor formaldehydi.

Blocks of tissue were taken from various areas of the cerebral and cerebellar cortices, the basal ganglia, midbrain, pons, medulla and cord. Sections from these blocks were stained with thionin, Weigert's myelin sheath stain, Marchi's stain, Bielschowsky's stain, sudan III, stains for hemosiderin, and Dominici's stain (toluidin, Orange G, and eosin—an especially good stain for the study of free cells in sectioned material).

For the most part, aside from congestion of the vessels, the meninges show only very mild involvement in the inflammation. Occasional areas are to be seen in which there is a slight increase in the number of nuclei in the meninges, due to an infiltration of small round cells of the same type as will be described later in the brain substance. In one case (151), the sections passing through the attach-

16. Special Article: Epidemic or Lethargic Encephalitis (Nona), J. A. M. A. **72**:794 (March 15) 1919.

17. Marinesco, G.: Contribution à l'étude de l'histologie pathologique de l'encéphalite léthargique, Bull. de l'Acad. de méd., Par. **80**:411 (Nov. 5) 1918.

18. Netter, A.: L'encéphalite léthargique épidémique, Bull. de l'Acad. de méd., Par. **79**:337 (May 7) 1918.

19. v. Economo, C.: Wien. klin. Wchnschr. **31**:850 (July 25) 1918.

20. Vaughan, V. C.: Encephalitis Lethargica, J. Lab. & Clin. M. **4**:381 (April) 1919.

ment of the trigeminal nerve show marked perivascular and diffuse infiltration of these and other cells together with hemorrhage into the subarachnoid spaces in the region of the fifth nerve root. The changes at this point involve not only the meninges, but also the nerve trunk itself and the underlying region of the pons (Fig. 1, B and C). This area presents a decided departure from the picture of the meninges seen in any of the other sections from our cases. It appears that the meninges are even less involved in our cases than in the majority of those reported in the literature.

In the cerebral cortex of all three cases there is marked congestion of the vessels. There is slight diffuse and perivascular infiltration of small round cells (lymphocytes and plasma cells) with an evident tendency for these cells to collect especially about the bases of the pyramidal cells (Fig. 2, B). While examples of satellitosis are fairly common, no true neuronophagia is to be seen; that is, there is no evidence of actual destruction and phagocytosis of the cortical cells by the satellite cells, none of these cells are intracellular within the nerve cell bodies, the cortical cells are in a state of good preservation, showing only mild chromatolytic changes. No hemorrhages are seen within the cortical layers. No proliferative glial or endothelial changes have been noted.

The cerebellar cortices of Cases 147 and 149 appear quite normal except for a rather marked congestion of all the vessels. In Case 151, however, the molecular layer of the cerebellar cortex shows a decided diffuse infiltration of small round cells (lymphocytes) along with the congestion. Deep in the sulci of the cerebellum in this case the vessels are surrounded by scattered round cells. There are no noteworthy changes in the cells of Purkinje; our cases do not confirm the changes described by Calhoun<sup>15</sup> in regard to these cells. The granular cell layer appears normal in each of the three brains.

The thalamus, caudate nucleus, globus pallidus, putamen, midbrain, pons and medulla all show great uniformity in their pathology in all of our cases; hence they can be discussed together.

Perivascular infiltration of round cells about the congested vessels is the most evident change noted. These cells have invaded the walls of the vessels to a very marked extent, leaving the perivascular space of His relatively free, however (Fig. 3, A). Diffuse infiltration of these cells into the surrounding tissues is also marked. On high power examination it is seen that the majority of these cells are slightly larger than erythrocytes, and are made up of a rounded nucleus containing relatively large masses of chromatin arranged more or less wheel-like around the inside of a definite nuclear membrane, and a small amount

of, or no visible cytoplasm (Fig. 4, A). It is probable that these cells should be classified as small lymphocytes rather than plasma cells, as Bassoe and Hassin<sup>12</sup> have suggested. That there are plasma cells among the infiltration cell types is not at all to be doubted, however, for we have found a number of cells with relatively large amounts of cytoplasm, eccentric, rounded nuclei containing chromatin granules with a very definite wheellike arrangement and often a vacuole or vacuoles bordering on the nucleus (Fig. 4, A and B, pl). Plasma cells in our cases are distinctly in the minority, being very scarce perivascularly, and only occasionally found scattered in the tissues.

Another type of cell making up a part of the infiltration, much less numerous, however, than either the lymphocytes or plasma cells and most in evidence in the area of infiltration and hemorrhage around the origin of the fifth nerve in Case 151, is that which might be called a macrocyte, an endothelial cell or a large mononuclear cell, depending on who might be describing it. This cell is considerably larger than the lymphocytes, contains a large, rather irregular (sometimes spherical) nucleus whose chromatin material is not very dense and does not tend towards any particular arrangement about the nuclear membrane which is more delicate than that of the lymphocytes or plasma cells. The cytoplasm stains purplish (neutrophilic) with Dominici's stain and is rather granular and sometimes vacuolated. These cells are certainly phagocytic for many of them contain nuclear and other cell debris (Fig. 4, A, and Fig. 1, B). Polymorphonuclear leukocytes are absent, except in such places as contain hemorrhages; here they are not present in any great numbers and probably have simply escaped from the blood stream along with the extravasated erythrocytes. The lymphocytes and plasma cells are situated not only perivascularly, but have also wandered out into the brain substances so that in the affected areas a low power examination gives one the impression of a very marked increase in the number of nuclei in the field (Fig. 3, A).

In the basal ganglia of one case (151) is a small abscess large enough to be seen in the stained section with the naked eye, consisting almost exclusively of lymphocytes. The tissues surrounding it are infiltrated with lymphocytes and are definitely fragmented. Fortunately, we obtained practically serial sections through this region which show that the abscess has not been confused with perivascular infiltration as no vessels larger than precapillaries are in that vicinity (Fig. 3, C).

Hemorrhage is not a marked feature of the pathology in any portions of the central nervous system we have studied. Small hemorrhages, or, at least, areas in which red blood corpuscles are to be seen

in the perivascular space of His are not at all uncommon in the regions in which pathologic changes are marked—basal ganglia, midbrain, pons and medulla—and are altogether absent elsewhere (Fig. 3, B). Neal<sup>14</sup> states that "Frequent small and occasional large extravasations of blood are seen anywhere, but especially in the gray matter." In view of the evident vascular injury it would certainly be easy to understand how sizable hemorrhages could take place, but none of noteworthy size have been observed in any of our sections. Such hemorrhages as we have seen must have occurred shortly before death as the erythrocytes are in a state of good preservation and there is no blood pigment out in the tissues; stains for hemosiderin are negative.

Separation of the tissues of the brain in the more severely injured areas, giving the appearance of much dilated tissue spaces, is a constant feature of our sections. This looseness of the tissue meshwork is taken by us to be evidence of a marked edema, though the possibility of artifacts has been constantly kept in mind. The occurrence of this change in the affected areas and its absence in the relatively normal areas makes us feel safe in stating that there is edema present (Fig. 3, A; compare Fig. 4 and Fig. 2, A, with Fig. 2, B and C).

Glial proliferation in the affected regions is not marked at first glance. As the slides are studied, however, it appears that there is a definite increase in the number of glial nuclei. Furthermore, young types of glial cells are not uncommon with their relatively large nuclei and definitely increased cytoplasm. In one section (Fig. 4, C) an undoubted example of mitosis in a glial cell is present. No free cells of definitely glial origin have been found. Proliferative changes in the endothelial cells are also not marked in the central nervous system with the exception of the region of the meninges about the origin of the fifth nerve in Case 151. Here one finds numerous vessels slightly larger than capillaries in which the endothelium is made up of cells with marked increase in their cytoplasm and large rounded or oval, usually vesicular nuclei. Since the nucleus and cytoplasm of these endothelial cells simulate very closely the appearances in the macrocytes, and since the macrocytes are definitely phagocytic, we feel that these large free cells are undoubtedly endothelial in origin (Fig. 1, B).

Various changes are noted in the nerve cell bodies located within the severely affected areas. In these regions it is exceptional to find a normal neuron; they all show evidences of one or another type of degeneration. Examples of satellitosis about the nerve cells are very common, those of actual neuronophagia considerably less frequent, though present (Fig. 2, B and C). The satellite cells are indistinguishable in their morphology from the lymphocytes described above. Chromatolysis is the rule in these localities, usually evidenced by loss

of Nissl bodies around the nucleus and collection of the remaining tigroid substance about the periphery of the cell (Fig. 2, A). The nucleus of the cell may be relatively clear and swollen or it may be somewhat darker and shrunken. Some of the nerve cells are vacuolated (Fig. 2, A); they are seldom actually fragmented. Most of them show an apparent, if not an actual decrease in the number of their processes. Pigmentation of the nerve cells is a marked feature of all the affected areas. The pigment is extremely abundant in some of the cells, completely filling the cell body and even obscuring the nucleus. The pigment granules are small, rounded, regular and yellowish brown in all the sections excepting those stained by Sudan III when they take the red color of the stain; therefore, they are lipochrome granules. The pigment is located not only within the neurons but occurs free in the interstitial tissues and also within the cytoplasm of the glial cells (Fig. 4, B). Stains for hemosiderin are negative even in the presence of hemorrhages; hence this pigment is not a derivative of the blood pigments.

Weigert sections show no involvement of the long tracts in the brain and cord. In the nuclei within the affected areas, however, the finer myelinated fibers show definite evidences of degeneration. Some of the myelin sheaths are actually fragmented; others show the peculiar swelling and knobbing characteristic of early myelin sheath changes. These changes are particularly noticeable within the nucleus of the third nerve (Fig. 1, A), but are found even in the projection fibers of the cerebral cortex.

The spinal cord is involved to the extent of considerable congestion, some increased pigmentation of the nerve cell bodies and fairly common examples of chromatolysis.

There are no changes of any significance in the ependyme of the ventricles of the brain or the central canal of the cord.

It is worthy of mention that in the rootlet of the trigeminal nerve in Case 151 there is very marked perivascular and some diffuse infiltration of lymphocytes (Fig. 1, C). We have seen no inflammatory changes in any of the other nerve rootlets.

#### DISCUSSION

The laboratory findings in our cases have thrown no light on the etiology of lethargic encephalitis. This is in accord with most investigators. v. Wiesner<sup>21</sup> cultured a gram-positive diplococcus from a monkey which had previously been inoculated subdurally by an emul-

21. v. Wiesner, P. R.: Die Aetiologie der Encephalitis lethargica, Wien. klin. Wchnschr. **30**:933, 1917.

sion of the brain and cord from one of v. Economo's patients. Strauss, Hirshfeld and Loewe<sup>22</sup> also successfully inoculated monkeys with an emulsion of the human brain and produced the characteristic lesions of lethargic encephalitis. In a later report they state that they have isolated a gram-positive organism resembling that described by Flexner and Noguchi in poliomyelitis.

Although no definite relationship has been established between influenza and lethargic encephalitis, the clinical evidence is very suggestive for every epidemic of lethargic encephalitis has been preceded by a pandemic of influenza.

Neal,<sup>14</sup> Bassoe and Hassin,<sup>12</sup> and Calhoun<sup>15</sup> have pointed out the similarity pathologically between lethargic encephalitis, acute anterior poliomyelitis and trypanosomiasis, and have considered the possibility of a common etiology, but have been able to reach no definite conclusions.

#### SUMMARY AND CONCLUSIONS

1. No definite etiologic factor has yet been established in lethargic encephalitis. The relationship clinically to influenza is very suggestive.

2. Although the general symptomatology is profound, the localizing symptoms are not so marked as the widespread pathologic findings would lead one to expect.

3. Asthenia, lethargy, muscle rigidity and cranial nerve involvement are the outstanding features of lethargic encephalitis clinically.

4. Pathologically, the picture is an inflammation of the brain and cord characterized by a perivascular and diffuse infiltration of lymphocytes especially in the basal nuclei and gray matter of the brain stem.

We wish to express our appreciation for criticism and advice cheerfully given by Drs. A. S. Hamilton and C. E. Nixon in the preparation of this paper; also, credit is due Miss Margaret Graham for her intelligent interest in preparing the tissues on which our pathology is based.

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22. Strauss, I., Hirshfeld, S., and Loewe, L.: Studies in Epidemic Encephalitis (Encephalitis Lethargica), New York M. J. **109**:722 (May 3) 1919.

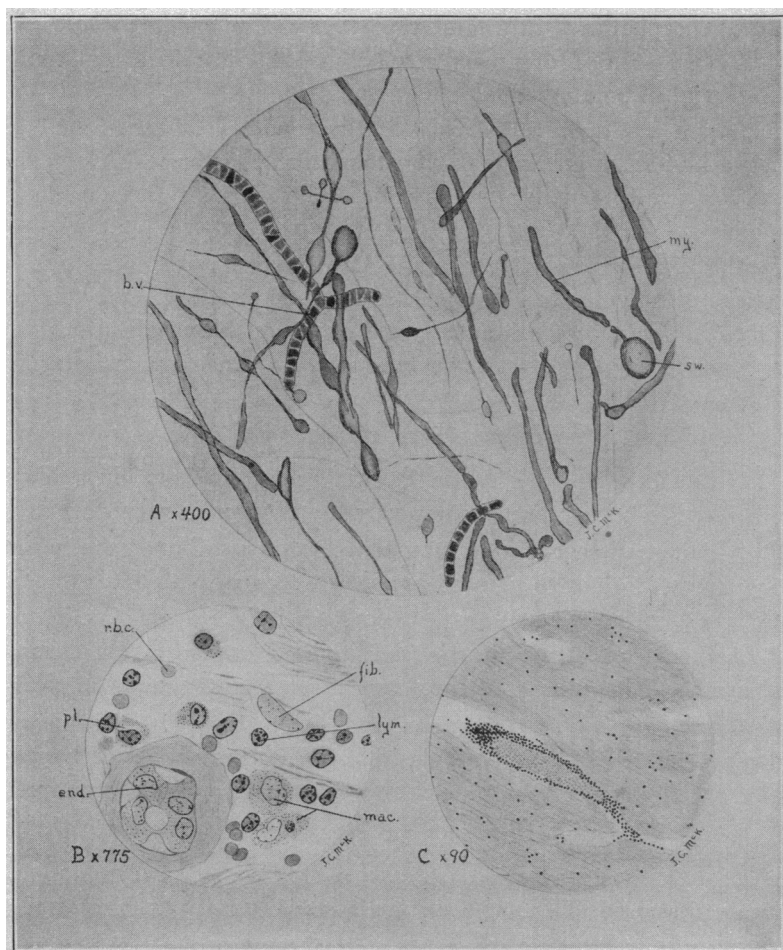


Fig. 1.—A.  $\times 400$ . Nucleus of oculomotor nerve in Case 151 stained with Weigert's myelin sheath stain. Knobbing and fragmentation of the myelin sheaths. b.v., blood vessels; my., myelin sheath fragmented; sw., swelling or knobbing of the same sheath. B.  $\times 775$ . Meninges near the attachment of the fifth cranial nerve in Case 151. Swollen endothelial cells still attached to a vessel wall, apparently ready to break loose and give rise to macrocytes. Hemorrhage and infiltration. end., swollen endothelial cells; fib., fibroblast nucleus; lym., lymphocyte; mac., macrocytes, one of them containing cell debris; pl., plasma cell; r.b.c., erythrocytes in the subarachnoid spaces. C.  $\times 90$ . Perivascular infiltration in the root of the fifth nerve in Case 151.

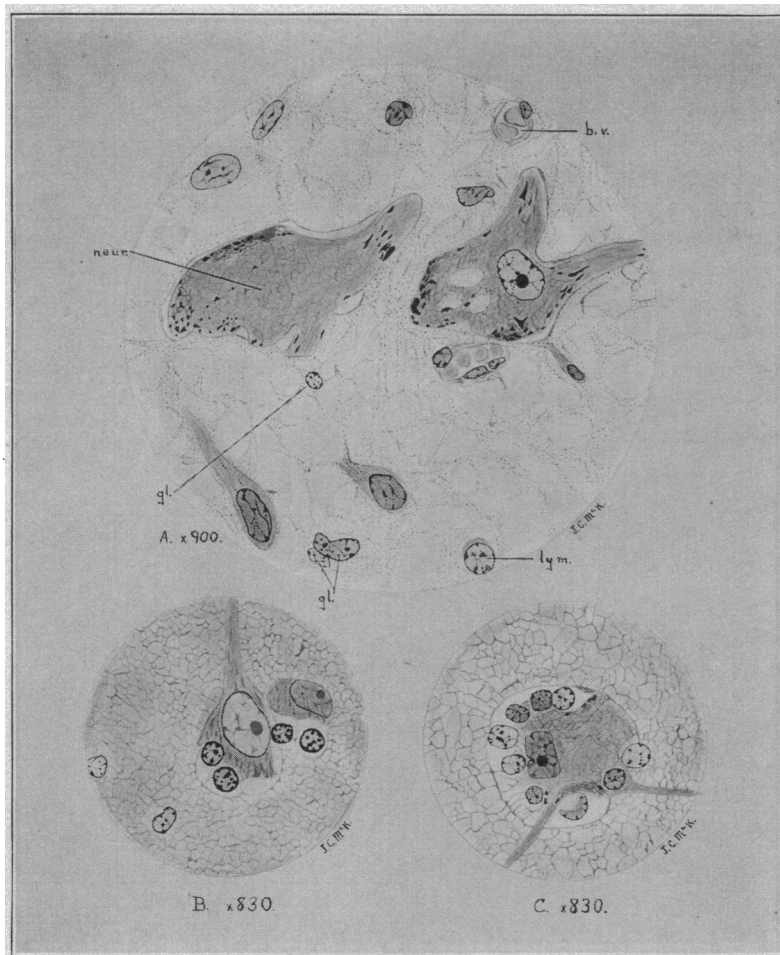


Fig. 2.—A.  $\times 900$ . Basal ganglia from Case 149. Chromatolytic, swollen nerve cells, one of which is vacuolated. b.v., blood vessel; gl., glial cell; lym., lymphocyte; neur., neuron. B.  $\times 830$ . Cortex from Case 147. Satellitosis about the bases of two pyramidal cells. C.  $\times 830$ . Basal ganglia from Case 151. Neuronophagia. Chromatolytic ganglion cells with pyknotic nucleus.

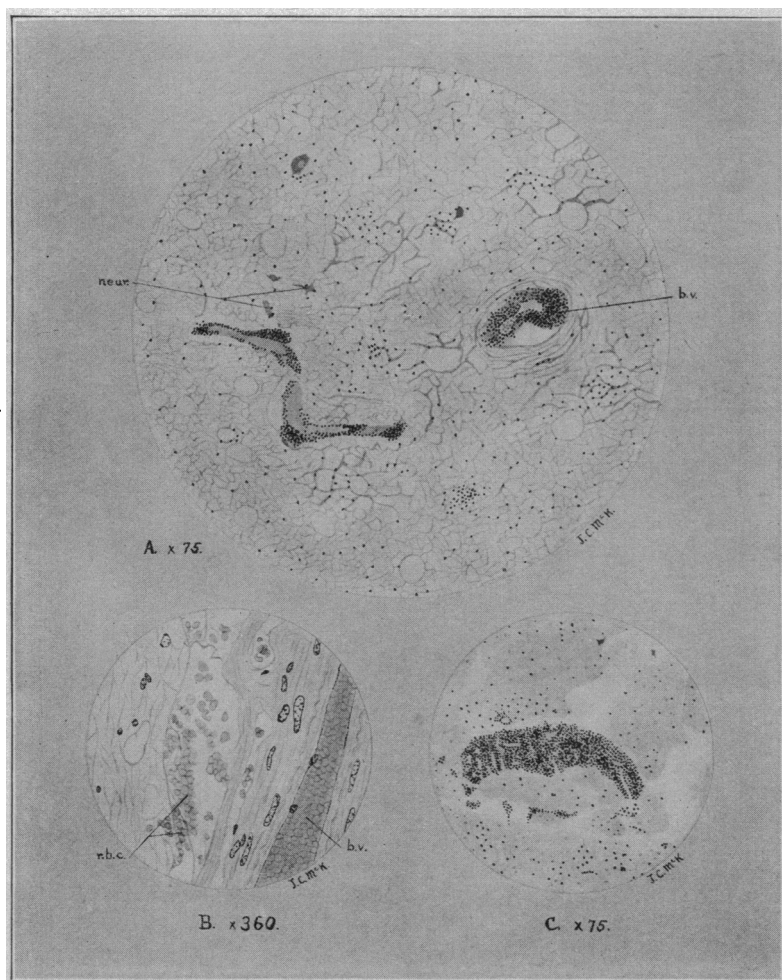


Fig. 3.—A.  $\times 75$ . Midbrain from Case 147. Perivascular and diffuse infiltration of lymphocytes. Marked edema. Satellitosis about the nerve cell bodies. b.v., blood vessel; neur., neurons with satellite cells. B.  $\times 360$ . Basal ganglia from Case 147. Small hemorrhage about a vessel. b.v., blood vessel; r.b.c., extravasated erythrocytes in perivascular space of His. C.  $\times 75$ . Basal ganglia from Case 151. Small abscess made up of lymphocytes. Fragmentation of the surrounding tissues.

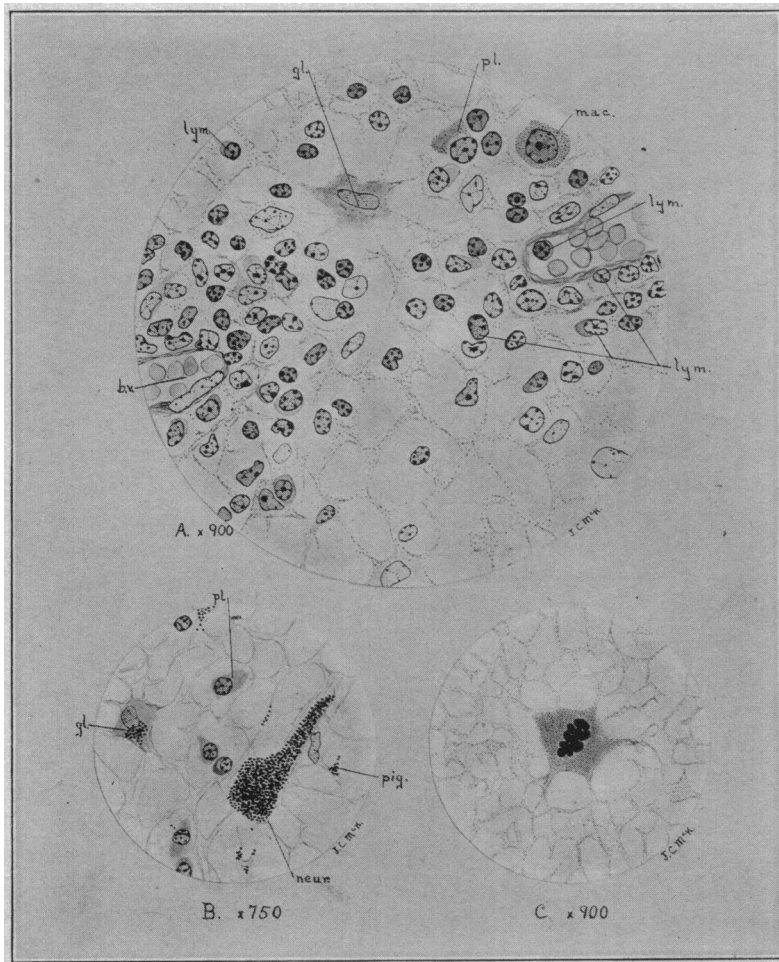


Fig. 4.—A.  $\times 900$ . Pons from Case 149. Cell types making up the infiltration. b.v., blood vessel; gl., glial cell; lym., lymphocyte; mac., macrocyte; pl., plasma cell. B.  $\times 750$ . Midbrain from Case 147. Pigment granules in a nerve cell body, in a glial cell and free in the tissues. gl. glial cell; neur., neuron filled with pigment; pig., pigment granules; pl., plasma cell. C.  $\times 900$ . Basal ganglia from Case 151. Mitosis in a glial cell.