

## LETHARGIC ENCEPHALITIS \*

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For the past nine years we have had at the research laboratory of the health department of New York City a meningitis division, the function of the members of which is to see in consultation all kinds of meningeal conditions for differential diagnosis and treatment. In this connection we have seen over 1,000 cases of meningitis of various kinds, 600 or more cases of poliomyelitis and over 700 cases of meningism with various diseases, besides small numbers of cases of numerous other conditions, so that we have had a fairly good background for the study of a new type of meningeal or cerebral disease.

Last October, as a member of the research laboratory of the health department of New York City, I began to see a new type of disease. The majority of these patients gave a history of influenza followed in a varying length of time by headache, drowsiness and apathy, usually accompanied by a low irregular fever, strongly suggesting a slowly developing tuberculous meningitis. One of the earliest patients, "X," showed extreme restlessness instead of drowsiness, marked muscular weakness and some paralysis of the cranial nerves. These conditions suggested a variety of diagnoses. Meningism seemed possible in certain instances, perhaps caused by some gastro-intestinal disorder, or it may have followed, instead of accompanied, influenza; this, however, was ruled out as the spinal fluid showed a marked increase in the protein elements and cells instead of being normal, as is the rule in meningism. Syphilitic disease was suspected, especially in "X," but this was disproved by the negative Wassermann test and by the character of the gold chlorid curve. Brain tumor must be differentiated in certain of the more severe cases, and this differentiation has proved a stumbling block to some very eminent neurologists. Tuberculous meningitis was considered in many cases, but this diagnosis was discarded because of failure to find the tubercle bacillus either by smear or by animal inoculation, the normal reduction of Fehling's solution and the favorable termination. In some instances the encephalitic type of poliomyelitis was suggested by the clinical picture and by the spinal fluid findings, but this type is rare even in epidemics of poliomyelitis,

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TABLE 1.—SALIENT FEATURES OF FORTY CASES OF LETHARGIC ENCEPHALITIS

Case No.	Age	History of Influenza	Type of Onset	Lethargy	Asthenia	Headache	Palsies	Reflexes	Temperature	Vomiting	Miscellaneous	Duration	Outcome	Remarks
14	12 wk. M.	+	Slow	Slight	.....	.....	—	—	100	+	Slight convulsions.....	?	Recovered	
388	8 mo. M.	+	Slow	+	.....	.....	Int. strabis.	—	102	—	Irritability.....	7 days	Died	
368	9 mo. F.	+	Sudden	++	++	.....	.....	—	105	+	Mask-like expression, spasticity, marked tremors, convulsions just before death, marked arrhythmia	3 weeks	Recovered	
32	15 mo. M.	+	Slow	++	++	.....	.....	—	Slight	—	.....		Died	
5	15 mo. M.	+	Slow	+	+	.....	—	?	+	+	Tremors.....	4-5 weeks	Recovered	
9	18 mo. F.	+	Slow	++	.....	.....	Int. strabis.	N.	102-103	+	.....	1 week	Died	
371	20 mo. F.	+	Slow	++	.....	.....	rt. facial	—	Slight	+	Convulsions.....	3 months	Died	
94	2 yrs. M.	+	Slow	++	+	.....	.....	N.	101	+	.....	10 days	Recovered	
40	2 yrs. M.	+	Slow	++	?	.....	.....	—	104	+	Rotating of eyeballs, twisting of lips, difficult respiration, convulsions, arrhythmia	6 days	Died	
54	3 yrs. M.	+	Sudden	+	+	+	—	—	104	+	.....	4 weeks	Recovered	
16	3 yrs. M.	+	Slow	++	++	.....	.....	—	Slight	—	.....	3 weeks	Recovered	
87	3½ yrs. M.	—	Sudden	++	++	.....	.....	—	100	+	.....	10 days	Recovered	
351	4 yrs. F.	Probable	Sudden	+	?	.....	.....	—	Slight	+	.....	Less than 1 month	Recovered	
137	4 yrs. M.	—	Sudden	+	?	.....	.....	N.	Slight	+	.....	2 weeks	Recovered	
391	6½ yrs. F.	+	Slow	++	++	.....	.....	N.	100.5	+	.....	2 weeks	Recovered	
395	7 yrs. F.	+	Slow	++	++	.....	.....	N.	101.5	+	Tremors.....	2-3 weeks	Recovered	
19	7 yrs. M.	+	?	++	++	.....	.....	.....	104	—	Spasticity of legs, vacant expression	3 weeks	Died	
41	7 yrs. M.	+	Slow	++	++	.....	.....	— left N. rt.	104	—	.....	4 weeks	Recovered	
80	9 yrs. M.	—	Sudden	++	+	.....	.....	N.	Slight	—	Babinski.....	2 weeks	Recovering	
357	9 yrs. M.	—	Slow	++	++	.....	Facial Slight dysphagia	N.	104	—	.....	1 month	Recovered	
46	9 yrs. M.	—	Slow	++	++	.....	.....	+	+	—	Babinski, mask-like expression, tremors at times, arrhythmia	3 months	Improving	
35	10 yrs. M.	+	Sudden	++	+	+	.....	N.	+	+	.....	2 weeks	Recovering	
100	10 yrs. M.	+	Slow	++	++	+	.....	D.	Slight	+	Babinski, pupils unequal, Delirious during convalescence, arrhythmia at times	7-8 days	Died	Mental examination showed it had been abnormal some years, not sequel of encephalitis
38	11 yrs. M.	+	Slow	+	+	+	Rt. facial	—	101	—	.....	2 months	Recovered	

331	14 yrs. M.	?	Sudden	+	+	+	+	+	+	102	+	Delirium.....	3 weeks	Recovered	
332	16 yrs. M.	—	Sudden	+	+	+	+	+	+	To 106.6	—	.....	3 days	Died	
Y	18 yrs. M.	—	Sudden	++	++	+	+	+	+	102	—	Slight delirium at times.....	3-4 weeks	Recovered	
24	20 yrs. M.	+	Slow	+	+	+	+	+	+	103	—	Paralysis after 1 week, delirium	1 month	Recovered	
48	20 yrs. M.	—	Sudden	+++	+++	+	+	+	+	103	..	Leg spastic, marked sweating, mask-like expression, tremors, delirium	1 week	Died	
353	23 yrs. M.	+	Slow	++	++	+	+	+	+	+	+	.....	1 month	Recovered	
393	25 yrs. ?F.	+	Slow	+++	+++	+	+	+	+	103	+	Pregnant, normal delivery, delirium at times	Over 2 months	Recovered	
66	30 yrs. ?M.	+	Slow	+++	+++	+	+	+	+	99-103	—	Restlessness, marked tremors, mask-like expression	6 weeks	Recovered	
103	30 yrs. M.	+	Slow	+	+	+	+	+	+	—	—	Disturbance of vision, variant expression, delirium at times	?	Recovering	
27	32 yrs. M.	+	Slow	+++	+++	+	+	+	+	102	—	Nystagmus, dizziness, diplopia, tremors, mask-like expression, spasticity	4 months	Recovered	
59	35 yrs. M.	—	Slow	++	++	+	+	+	+	101-102	—	Diplopia, difficult speech, dizziness	2 months	Recovering	Mental depression, slight paralysis
72	43 yrs. M.	+	Sudden	++	++	+	+	+	+	—	—	Dizziness, diminished sensitivity on right upper and lower extremities	2 weeks	Recovering	Slight weakness
392	45 yrs. M.	+	Slow	++	++	+	+	+	+	103	—	B a b l n s k i incontinence, sweating, mask-like expression, delirium	4 months	Recovered	Rapid pulse
68	50 yrs. M.	—	Slow	+++	+++	+	+	+	+	Slight	—	Babinski, mask-like expression	3 months	Recovered	
X	50 yrs. ?M.	+	Slow	—	+	+	+	+	+	+	+	Irritability, pain, restlessness	3 mo.: facial par. after 5 mo. nearly gone at 6	Practically recovered	Slight paralysis remaining
52	50 yrs. M.	—	Sudden	++	++	+	+	+	+	Slight	—	.....	1 month	Died	

and during the fall and winter the number of cases of even the spinal type has been extremely small. Finally, I began calling these cases influenzal encephalitis, since the symptoms were those of encephalitis and since they so often followed influenza. Not until midwinter did I designate these cases lethargic encephalitis, as it was not until that time that I encountered patients with lethargy, asthenia and oculomotor palsies, the characteristic triad of symptoms described by the English and French. Table 1 gives some of the salient features of forty cases in which the diagnosis seems to be well established. A study of the table shows: (1) wide age distribution—from twelve weeks to over fifty years. From the nature of our work we see an unusually high proportion of children. (2) The large proportion of males, thirty-three out of forty. Tucker reports nine males out of eleven cases. In other reports, usually of smaller numbers, there has not been this marked difference. (3) The history of an attack, clinically influenza, in twenty-seven of the forty cases. It will be noted that the onset is more often slow than sudden, and that lethargy and asthenia are nearly constant symptoms, while cranial nerve or other palsies are present in less than half of the cases. It is possible that our list includes a rather high proportion of mild cases, since we are called in consultation where an early tuberculous meningitis is suspected. Where lumbar puncture is not so freely resorted to, I fancy that many of these milder cases are unrecognized.

#### REPORT OF CASES

Certain patients are perhaps of sufficient interest to deserve special attention.

**CASE 1.**—Patient 357 had a typical mild case. He had influenza early in October. About the middle of October he became gradually worse, with headache, vomiting, constipation (which the French call the meningitic triad), irregular fever (102 to 104 F.), and marked apathy. This history was very suggestive of tuberculous meningitis. I saw him October 27. He was then somewhat improved. His mental condition was nearly normal, there was no well-marked stiffness of the back, but he still had fever, his patellar reflexes could not be obtained, and there was a moderate Kernig's and Macewen's sign. Lumbar puncture revealed clear fluid under pressure showing only a slight increase in the proteid contents. The case cleared up quite promptly.

**CASE 2.**—Patient 66 was a physician about 30 years of age. He had an attack of influenza which began February 18 and lasted for six or seven days. While there was general improvement after the attack, he continued to suffer with severe headache, and late in February he began to have fever, which ran as high as 103 F., and marked apathy. I saw him March 12. His face was entirely expressionless and he made no response whatever when requested to smile; apparently there was great weakness of the facial muscles on both sides. At times there was ptosis. He was unable to move, but frequently asked to be turned as he was uncomfortable if left long in one position as a tremor involving all the limbs was then most likely to develop. His pupils

were equal and reacted to light; the knee jerks were slightly increased and he was entirely clear mentally and very anxious about his condition. As Dr. Foster Kennedy very aptly expresses it, these patients are emotionally stuporous and intellectually bright. About 35 c.c. of clear spinal fluid was withdrawn, showing great increase in cells and proteid contents; a negative Wassermann test was made. He was able to be out of bed by the end of March and after another month had quite recovered, though he was still a little weak and suffered slightly from insomnia.

CASE 3.—Patient 393, five months pregnant, had an attack of influenza two weeks before the onset of the encephalitis, which began gradually early in December with headache, chill and fever, vomiting, sweating and delirium. I saw her December 14, at which time she was stuporous. There was some stiffness of the neck, and a right facial paralysis. About 25 c.c. of clear spinal fluid were withdrawn, which showed great increase in cells and in the protein elements, and a negative Wassermann test. A guinea-pig inoculated with the fluid gave a negative reaction for tuberculosis. Her condition remained the same for two weeks or more and then she gradually recovered. The facial paralysis cleared up, and she had a normal delivery at term.

CASE 4.—Patient 38, a boy of 11 years, was seen February 4. Late in January he had what had been diagnosed as a mild attack of influenza. On the 31st he began to have gradually increasing headache, apathy, and low fever. When examined, February 4, he was stuporous, the pulse rapid (120), and quite arrhythmic. His temperature was between 100 and 101 F. The right pupil reacted sluggishly to light, the left was normal. The right patellar reflex was increased, and there was a right facial paralysis. Fifteen c.c. of spinal fluid withdrawn on this occasion and 25 c.c. withdrawn two days later showed slight increase in cells, albumin and globulin. The Wassermann test was negative. The patellar reflexes became equal in a few days. By the 11th he was greatly improved. The stuporous condition had disappeared, and the pulse, though still rapid, had ceased to be arrhythmic. Later, however, he became mentally disturbed and was violent. By the middle of April, he seemed to have recovered, but his mother reported that he had a voracious appetite and was very troublesome and difficult to manage. At first it seemed that his condition was due to the encephalitis but an investigation of the case revealed the fact that he had been in classes for atypical children for two or three years. He was examined by Dr. Coffin of the department of education for New York City, and was found to belong to the hyperactive, precocious type of children that it is so difficult to deal with satisfactorily.

CASE 5.—Patient 46, a boy of 9 years, is of interest on account of the long duration of his disease. He was admitted to Willard Parker Hospital with a history of being ill for three days. He was then comatose, had slight rigidity of the neck and Kernig's sign, exaggerated knee jerks, positive Brudzinski sign and Babinski reflex. He ran an irregular temperature, from 100 to 103 F. until February 19, after which it was below 100 until March 14. At times his pulse and respiration were irregular. He became progressively worse and by February 20 had marked rigidity of the entire body, and a mask-like, expressionless face. He became unable or unwilling to swallow and had to be tube fed. The white blood count was 15,000, 81 per cent. polymorphonuclears. The first lumbar puncture, February 13, showed a clear fluid with moderate increase in cells, 60 per cent. polymorphonuclears, moderate increase in protein elements, normal reduction in Fehling's sign and negative Wassermann test. Fluid withdrawn February 14, was slightly blood-tinged so that it had a

somewhat hazy appearance. Therefore, with the clinical picture resembling meningitis so strongly, and an excess of polymorphonuclears in the first fluid, serum was given. Of course, this obscured the spinal fluid picture for some time. During all this time the child did not speak and has not up to the present time. There were frequent muscular twitchings. Early in March he began to move his head and a little later his legs and arms, and seemed to be progressing toward recovery. On March 14, however, the temperature rose to 106 F., he perspired profusely and seemed to be in a desperate condition. A blood culture at this time was negative. Twenty c.c. of spinal fluid were withdrawn under some pressure, showing a moderate increase in cells, 80 per cent. mononuclears, increase in albumin and globulin, and a normal reduction of Fehling's. On March 15 he began to improve; his temperature dropped to 100 F. Since that time his condition has shown some improvement, and he has gained in weight. A peculiar hairiness has appeared on the trunk, legs, arms and forehead. He looks about and has an intelligent expression but does not respond in any way when spoken to. He still has to be tube fed but can swallow if one is dexterous enough to insert food when his mouth is open. His arms, and especially his legs, are still somewhat spastic and the right leg shows contracture, though it is now possible nearly to straighten it without his evidencing much discomfort. Being naturally optimistic, we are expecting his ultimate recovery.

CASE 6.—The patient (48) 20 years old, became ill while he was in a hospital being treated for flatfoot. The onset, which was sudden, came on February 13, with severe pain in the chest, side, and shoulder, temperature of 102 F., pulse from 80 to 100. February 14 the condition was about the same except that he complained of pain in his eyes and during the night he became irrational. On the 15th and 16th the condition became worse, with severe headache and active delirium. His jaw was so rigid that his throat could not be examined and the arms and legs became spastic. There was slight rigidity of the neck and the Kernig sign was present, which may have been due to the general spasticity. The patellar reflexes were present, the pupils reacted rather sluggishly to light, there were a few large, moist râles in the right base posteriorly and no bronchial breathing. The pulse was rapid and of poor quality at times. His temperature went as high as 104 F. A diagnosis of cerebrospinal meningitis was made and an unsuccessful attempt was made to perform a lumbar puncture. The patient was sent to the Willard Parker Hospital on the evening of February 16. Twenty c.c. of clear fluid were withdrawn showing a moderate increase in cells and mononuclears, albumin and globulin greatly increased, and a normal Fehling's reduction. There were no organisms by smear or culture and a negative Wassermann reaction. The second puncture, February 19, showed practically the same picture except that there was a greater increase in cells. The blood count was normal, 10,000 leukocytes, 65 per cent. polymorphonuclears. His temperature ranged from 103 to 105 F. His pulse was between 120 and 130, but was not irregular until slightly before his death, which occurred February 20. He lay on his back with his eyes tightly closed and his whole body markedly spastic. His neck was rigid. It was impossible to obtain the knee jerks, but the plantar reflexes were increased. At times there was a tremor, especially of the legs. He was generally comatose but at intervals there was muttering delirium, and he frequently perspired freely. He was able to swallow until near death though he often refused unless urged to do so by one of the nurses whose directions he usually followed. His death was described as being particularly

painful with evidences of respiratory difficulty, probably of central origin, since it did not develop until shortly before he died. There was no evidence of paralysis at any time. A necropsy was performed which showed marked congestion of all the organs. The report on the brain and upper part of the cord will be given under pathology.

#### CLINICAL PICTURE

The characteristic clinical picture of lethargic encephalitis is generally as follows: a gradual onset, often following influenza, a low irregular fever, headache, marked lethargy and asthenia, with or without cranial nerve palsies.

#### TREATMENT

While there is no specific treatment, a lumbar puncture has been followed in many cases by temporary improvement. The spinal fluid is usually under increased pressure and it seems to me desirable to relieve it. Of course, every effort should be made to keep the patient comfortable and general eliminative and supportive measures should be carried out. Symptomatic treatment should be instituted as the indications arise.

#### LABORATORY FINDINGS

The blood picture is not characteristic. It is usually normal or shows a slight leukocytosis, perhaps up to 15,000. Blood cultures are sterile. The urine is usually negative (Table 2). The spinal fluid shows practically the same picture as in poliomyelitis. The cells are usually slightly or moderately increased, seldom greatly, perhaps up to 150 to 200 in some cases. While cell counts may run higher in poliomyelitis, the great majority do not. As in poliomyelitis, there is usually an excess of mononuclears, but an excess of polymorphonuclears may occur. The albumin and globulin are greatly increased, the reduction in Fehling's is normal. The increase in cells and protein content is not always in the same ratio. No organisms are shown by smear or culture. The gold chlorid curve depends on the amount of albumin and globulin present and duplicate curves may be selected from those in poliomyelitis fluids. In some instances, most often in convalescent or mild cases, the findings may depart little from the normal. This is true also in poliomyelitis. Most reports of encephalitis show that the cell count (which, unfortunately, is often the only information given) falls off very quickly. In two of our cases of long duration, the character of the fluid did not change materially over a period of several weeks, but the condition of the patients also showed little change. This comparison with poliomyelitis is made, not because I believe the two diseases are at all identical, but to emphasize the fact that in each instance the spinal fluid is not specific, but shows the

reaction of the meninges to an inflammation of the brain substance. A somewhat similar condition exists in the various syphilitic involvements of the central nervous system, but in these conditions the gold chlorid curve and the Wassermann test are helpful in making the diagnosis.

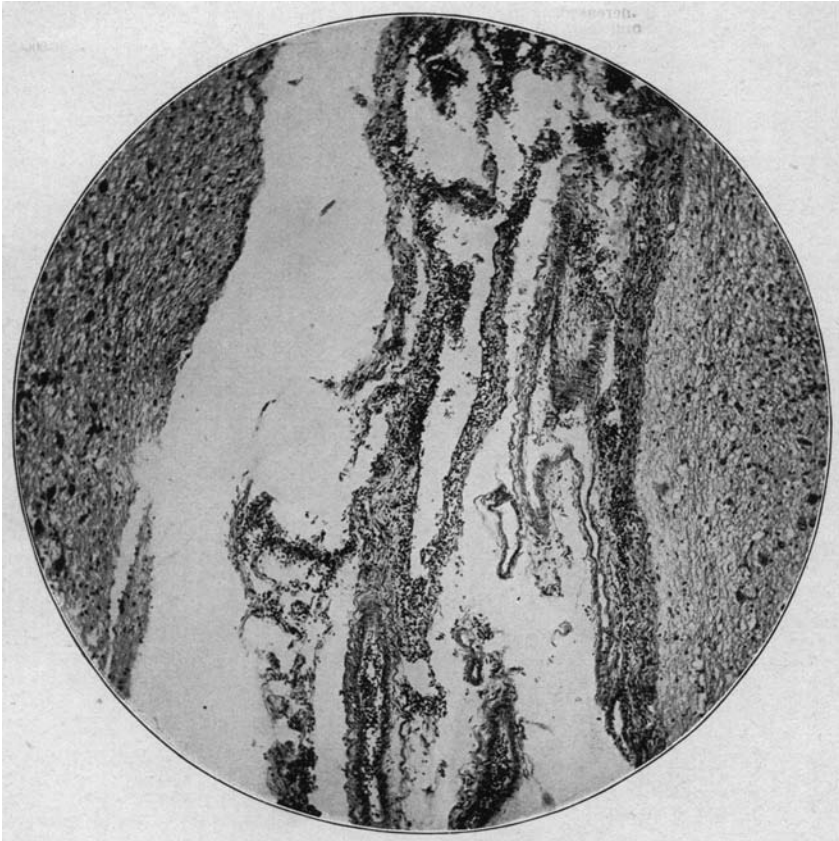


Fig. 1.—Meninges of the anterior fissure of the cord, showing fibrosis and round-cell infiltration, mostly in the vessel walls. Diffuse round-celled infiltrations of the arcuate nucleus of the pyramids is shown in either side.

The most difficult and the most needed diagnosis is that made from the fluid of tuberculous meningitis. While generally the number of cells and the increase in albumin and globulin is greater in the latter disease, it is by no means always so, and it is sometimes necessary to examine more than one fluid before one can be certain of the diagnosis, as it is often difficult to find the tuberculosis bacillus in early tuberculous meningitis and the reduction of Fehling's may be normal at that time. The following table shows the findings in the spinal fluids in our cases of lethargic encephalitis.



TABLE 2.—LABORATORY FINDINGS IN CASES OF LETHARGIC ENCEPHALITIS

Case No.	Amount in C.c.	Cytology	Protein	Fehling's Reduction	Animal In- oculation	Wassermann Reaction	Onset to Puncture	Gold Chlorid
14	30	Greatly increased.....	+++	+++	.....	.....	?	
		Mononuclears 80%						
388	25	Greatly increased.....	++++	.....	—	.....	3 days	
		Mononuclears 90%						
368	15 sl.	Greatly increased.....	++	+++	.....	.....	3 days	
	cloudy	Mononuclears 90%						
32	60	Greatly increased.....	++ 1	+++	—	—	14 days	1234321000
		Mononuclears 80%						
	35	Greatly increased.....	+++	+++	.....	.....	15 days	
		Mononuclears 80%						
	30	Slight to moderate in- crease, Monos. 90%	+++	++	.....	.....	16 days	
	30	Greatly increased.....	++++	++	.....	.....	18 days	
		Mononuclears 80%						
5								
9	30	No increase.....	+ 1	+++	.....	.....	5 days	
371	10	Greatly increased.....	++	+++	.....	.....	18 days	
		Mononuclears 80%						
94								
49	12	Slight increase.....	±	+++	.....	.....	4 days	
54	5	Slight increase.....	+ 1	+++	.....	.....	5 days	
16	30	No increase.....	+	+++	.....	.....	?	
87	20	Very great increase.....	+	+++	—	.....	4 days	
		Mononuclears 90%						
351	20	No increase.....	++ 1	+++	.....	.....	4 days	
137	10	No increase.....	+ 1	+++	.....	.....	3 days	
391	25	Slight to moderate.....	+ 1	+++	—	—	7 days	
		Mononuclears 90%						
395	15	Slight increase.....	+	+++	.....	.....	4 days	
19	35	Moderate increase.....	++	+++	.....	—	4 days	
		Mononuclears 90%						
41	20	Greatly increased.....	++ 1	+++	.....	.....	3 days	
		Mononuclears 95%						
80								
357	35	No increase.....	+	+++	.....	.....	14 days	
46	15	Moderate increase.....	++	+++	.....	—	3 days	
		Polys. 60%						
	25	Bloody fluid.....	++	+++	.....	.....	4 days	
	30	Bloody fluid.....	++ 1	+++	.....	.....	5 days	
	20	Moderate increase.....	+++	+++	.....	.....	6 days	
		Mononuclears 80%						
	20	Moderate increase.....	++	+++	.....	.....	8 days	
		Mononuclears 80%						
	15	Moderate increase.....	++	+++	.....	.....	32 days	
		Mononuclears 95%						
	20	Slight to moderate.....	+++	+++	.....	.....	50 days	
35	10	Moderate increase.....	+++	+++	.....	—	2 days	
100	20	Very great increase.....	++++	++	—	—	2 days	
		Mononuclears 90%						
	30	Great increase.....	++++	+	.....	.....	4 days	
38	15	Slight increase.....	+	+++	.....	—	4 days	
	25	Slight increase.....	+	+++	.....	.....	6 days	
331	30	Slight increase.....	+	+++	.....	.....	21 days	
382	20	No increase.....	+	+++	.....	—	1 day	
Y								
24	25	Greatly increased.....	++ 1	+++	.....	.....	14 days	
		Mononuclears 80%						
48	20	Moderate increase.....	+++	+++	.....	—	?	
		Mononuclears 60%						
	20	Greatly increased.....	+++	+++	.....	.....		
		Mononuclears 80%						
353	5	Slight increase.....	++	+++	.....	.....	3 days	
393	25	Moderate increase.....	++ 1	++ 1	—	—	10 days	
		Mononuclears 85%						
66	30	Moderate to great incr.	++ 1	+++	.....	—	15 days	
103								
27	30	Moderate increase.....	+ 1	+++	.....	—	2 days	1232100000
		Mononuclears 80%						
59	25	Moderate to great incr.	++ 1	+++	.....	—	14 days	
72	25	No increase.....	+ 1	+++	.....	.....	3 days	
392	20	Greatly increased.....	++	+++	—	—	10 days	
		Mononuclears 90%						
	25	Greatly increased.....	++	++ 1	.....	.....	18 days	
		Mononuclears 80%						
	35	Moderate increase.....	++	+++	.....	.....	20 days	
		Mononuclears 80%						
	20	Moderate to great incr.	++	+++	.....	.....	44 days	
		Mononuclears 90%						
68								
X	30	Slight increase.....	+++	+++	.....	—	7 days	00012455560
52	30	Moderate increase.....	+	+++	.....	—	17 days	

The inoculation of monkeys with the emulsified brain and cord of fatal cases has given far from uniform and conclusive results. The English reported failures in their attempts, though the same workers had been almost uniformly successful in dealing with material from cases of poliomyelitis. Von Weisner reported an instance in which the infected monkey died in forty-six hours, his brain on necropsy showing gram-positive cocci. The short period of incubation and the



Fig. 2.—Meninges of the cortex showing marked injection of the vessels and hemorrhage invading the cortex for a short distance. The cortical tissue otherwise is negative.

finding of the organisms make it much more probable that the monkey died from bacterial infection than from encephalitis. Flexner reported inconclusive results; Strauss, Hirshfeld and Loewe have published a preliminary report that indicates that the disease may be reproduced in monkeys by inoculation. I regret that up to the present time the lack of monkeys has made it impossible for us to do any work along this line at the research laboratory.

## PATHOLOGY

Lethargic encephalitis belongs to the class of inflammatory diseases, in which also are included poliomyelitis, syphilitic lesions of the central nervous system and trypanosomiasis. While these different diseases have, broadly speaking, certain characteristics, the cases in a given class differ so widely that it is difficult, if not impossible, to accurately diagnose, by a study of the pathology alone, the less typical cases.

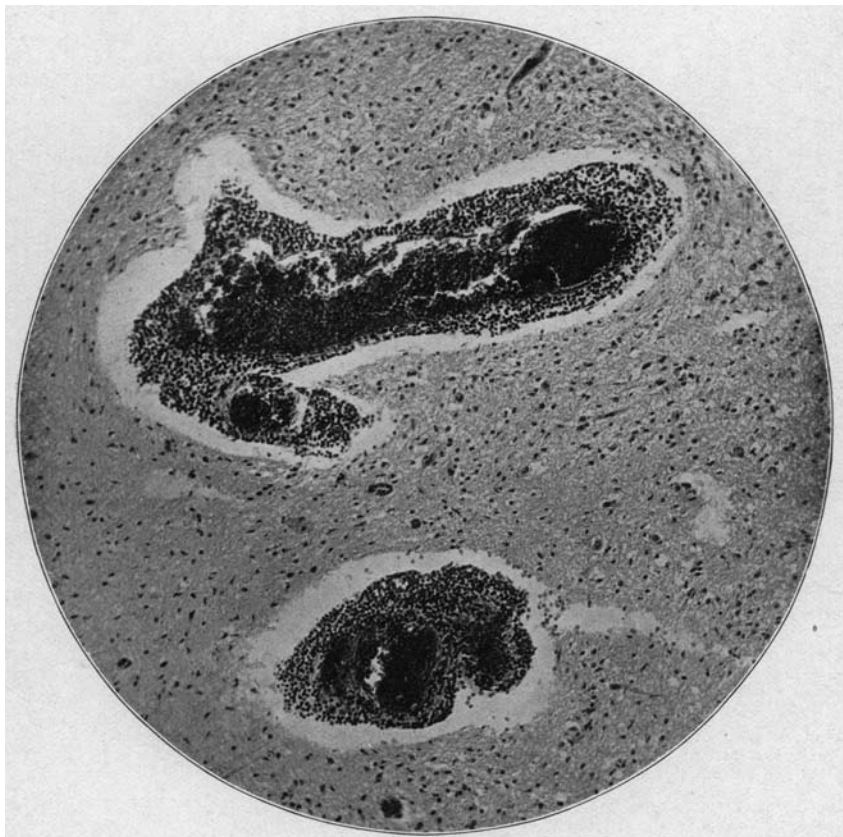


Fig. 3.—Cord, just below the olivary body, showing dense perivascular, round-celled infiltration and edema.

The meninges are usually described as showing only slight changes—an increase in the cellular elements particularly in the neighborhood of the blood vessels of the pia-arachnoid.

The cerebral cortex is generally normal except for congestion of the vessel of the leptomeninges.

In the brain substance, the changes are most marked in the basal nuclei of the brain, the upper part of the pons and peduncles, the gray matter of the floor of the fourth ventricle, and the aqueduct of

Sylvius. The changes in the medulla and cord are often reported as less pronounced, though observers have noted the same changes occurring in the upper section of the cord. This was certainly observed in the case of 48, which came to necropsy. To the localization in the mesencephalon, particularly in the vicinity of the nucleus of the third nerve, McNalty attributes the stupor, since a lesion in this locality cuts off the afferent stimuli. The relation of the paths of the rubro-

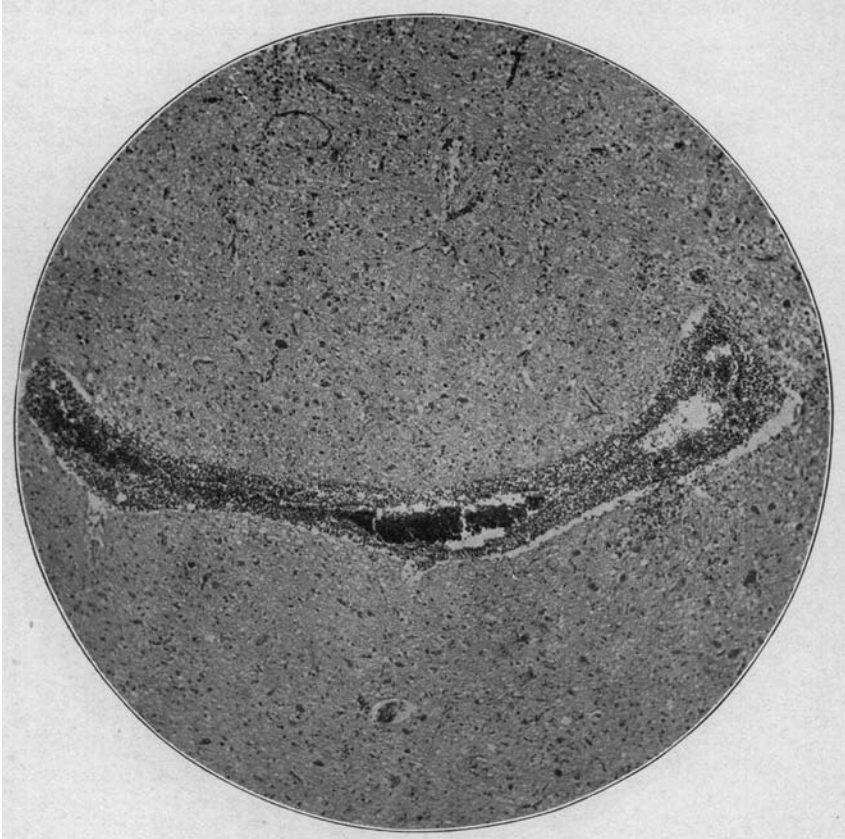


Fig. 4.—Cord, a higher level, showing dense perivascular and also diffuse round-celled infiltration.

spinal and pyramidal tracts to the region of the nucleus of the third nerve also explains the tremor and the frequent presence of the Babinski sign. It must be borne in mind that a virus affecting the nervous tissue, although it may have a predilection for a certain part of the central nervous system, may attack any part.

The lesions are generally described as consisting of four kinds:

1. Infiltration of the walls of the small vessels with lymphocytes and plasma cells.

2. Foci of interstitial and parenchymatous infiltration with round cells. In this reaction neuroglia cells may take part.

3. Lesions of the nerve cells—usually not so extensive as in poliomyelitis, and with less neuronophagia. These lesions of the cells usually occur when the inflammatory process takes place in the gray matter, but they may develop in the absence of any inflammatory reaction. Such is the case with regard to the cells of Purkinje in the cerebellum where inflammatory changes are almost entirely absent.

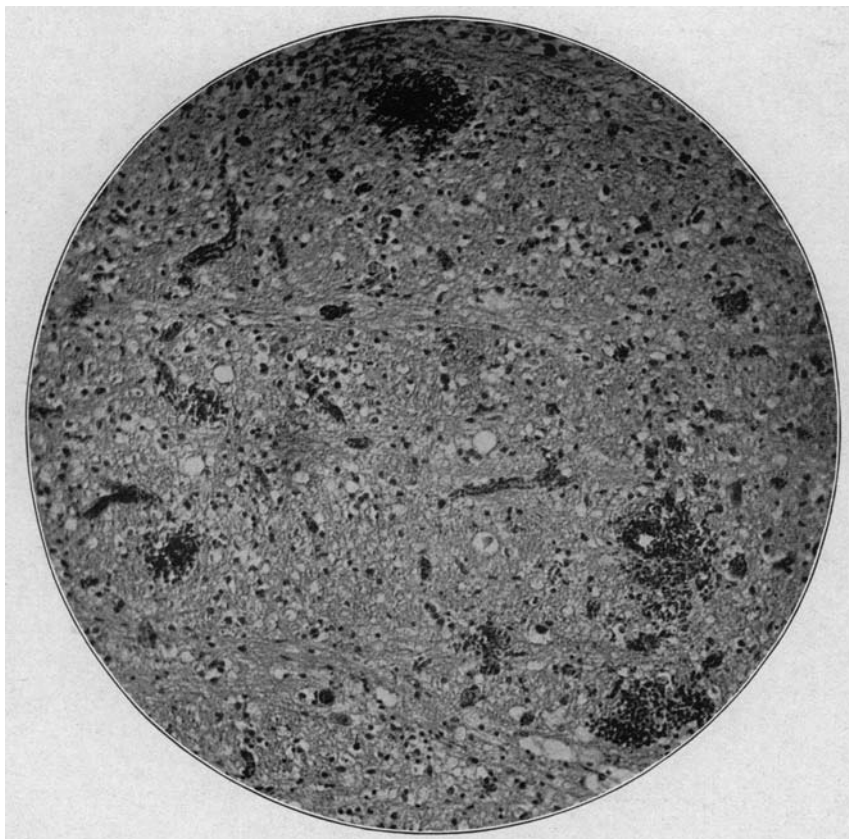


Fig. 5.—Medulla oblongata showing numerous petechial hemorrhages, diffuse round-celled infiltration and degeneration of ganglion cells.

4. Foci of perivascular hemorrhage. The vessel walls are usually not necrosed.

In connection with the statement that lesions of the cells may occur in regions where there is no evidence of inflammatory reaction, it is interesting to recall that Abramson, in a very excellent study of the pathology of poliomyelitis made at the research laboratory during the epidemic of 1916, brought out the same fact in regard to the lesions of poliomyelitis.

Perhaps an idea of the pathologic picture may best be obtained by a description of a case, No. 48. The brain was studied at necropsy by Dr. Alexander Fraser of Bellevue Medical School, to whom I am indebted for the following report.

#### MACROSCOPIC

The pia-arachnoid of the whole brain, including the medulla oblongata and a small part of the spinal cord accompanying it, shows

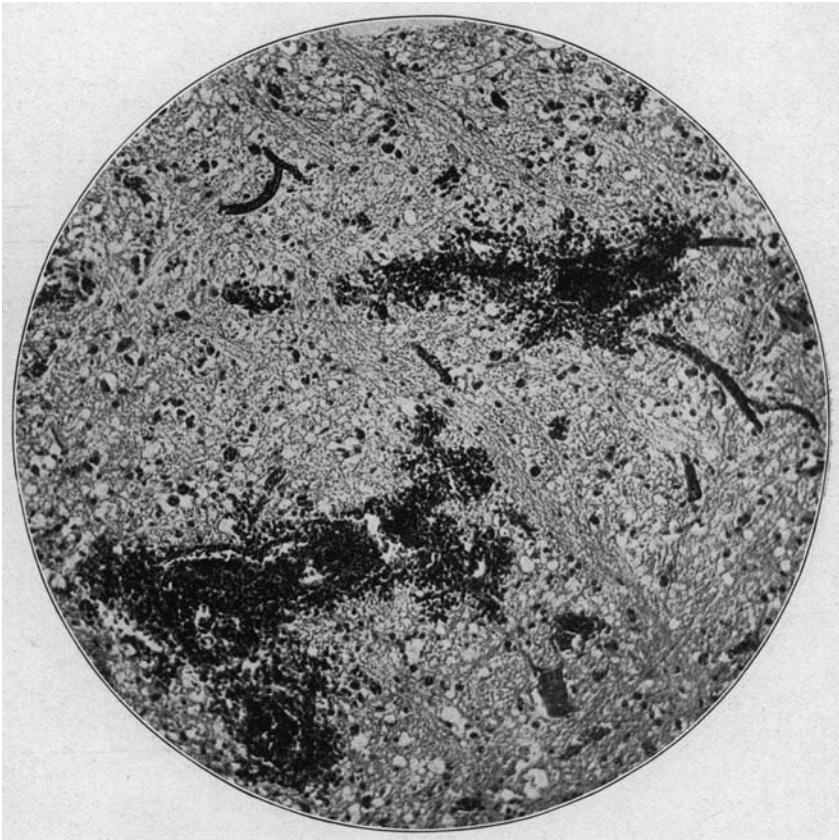


Fig. 6.—Another section from the medulla showing larger hemorrhages.

marked congestion of the vessels and numerous small hemorrhages. The portion covering the medulla, pons and peduncles is considerably thickened and brownish-gray in color. No free exudate is present. The brain tissue is firm in consistency. On section, the cerebral hemispheres show considerable distention of the vessels with blood and an occasional small splotchy hemorrhage especially in the outer cortex.

The ventricles seem large, but contain little fluid which is of a reddish tinge. The ependyma, especially over the thalamus and floor

of the fourth ventricle is lustreless, dull grayish-white in color and "mushy." In one place in the fourth ventricle it projects into the cavity in the form of a polypoid mass. The choroid plexus of the lateral ventricles is markedly congested and in places cystic. Section of the cerebellum shows distended vessels but apparently no hemorrhages. Section of the medulla, pons, crura and basal ganglions shows very marked distention of the vessels with numerous small and a few fairly large, irregularly outlined extravasation of blood.

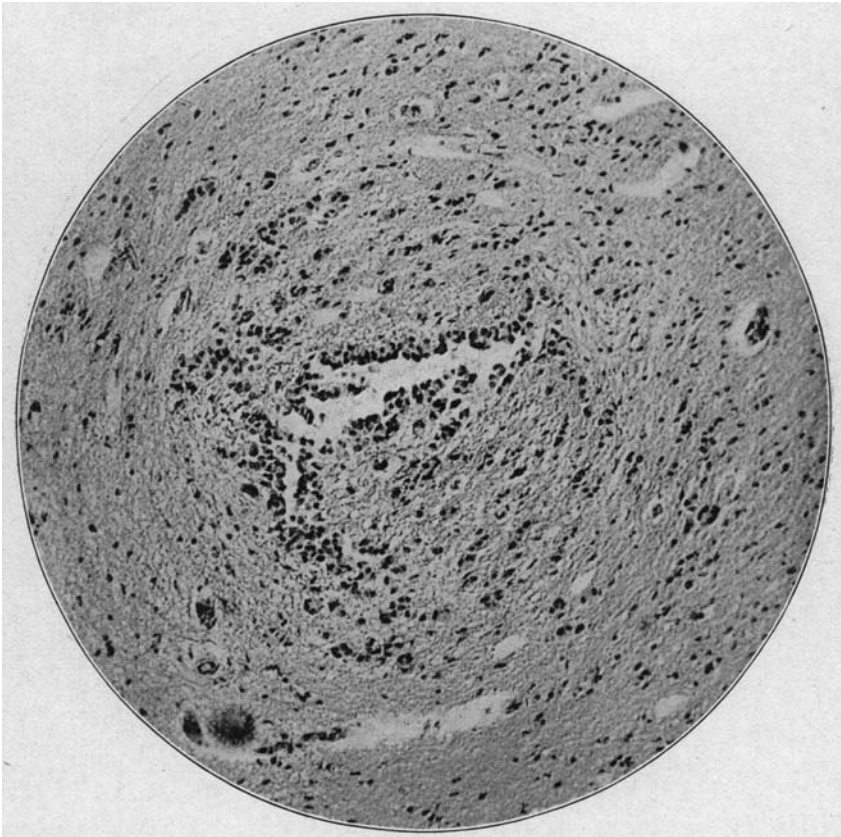


Fig. 7.—Section of the cord showing central canal. Note disintegration of the epithelium and exudate in the lumen.

The color of the tissue in these regions is a fine and irregular mottling of dull gray and white. These features are especially marked just beneath the floor of the fourth ventricle.

#### MICROSCOPIC

The pia of the cerebrum and cerebellum shows distention of the vessels with blood, round cell infiltration especially marked around and

in the vessel walls, thrombosis and hemorrhages. Only very rarely does the perivascular infiltration follow the vessels into the brain substance, and then only for a short distance. Occasionally, a hemorrhage from one of these vessels is seen in the outer part of the cortex. In such areas the ganglion cells show various degrees of degeneration.

In the medulla, pons and basal ganglions, the pia shows the same pathologic features, but in a much more marked degree. In these

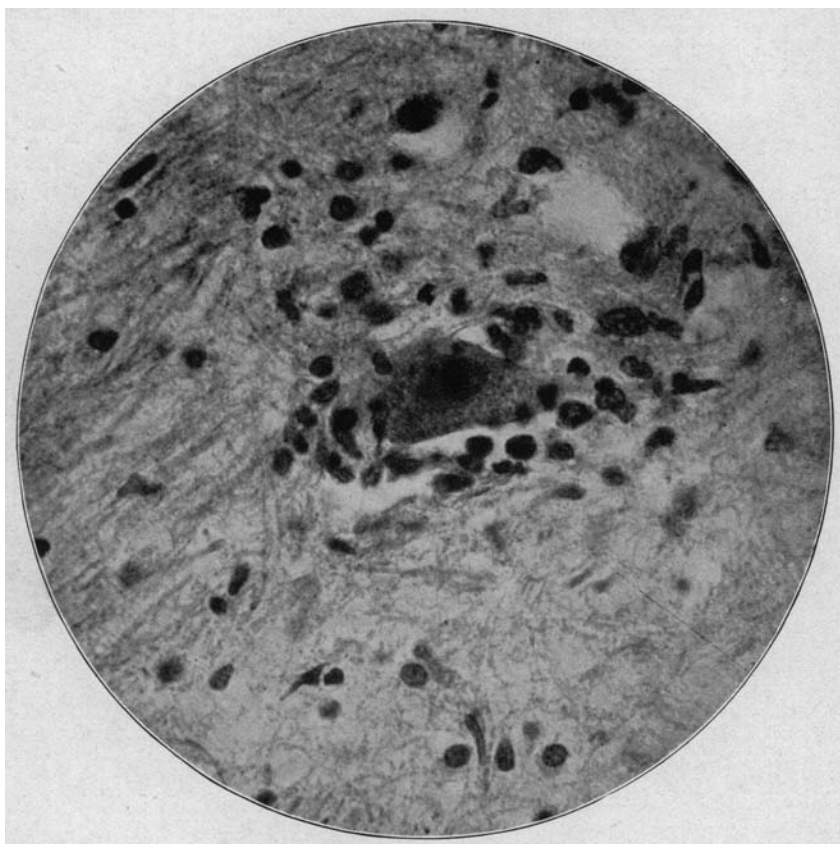


Fig. 8.—Same section as Fig. 7. Ganglion cell undergoing disintegration surrounded by phagocytes.

regions, too, the perivascular infiltration follows the vessels deeply into the brain tissue, and focal and diffuse areas of round cell infiltration are scattered throughout the tissue apart from the vessels. Frequent small and occasional large extravasations of blood are seen anywhere, but especially in the gray matter.

The cellular infiltrations, too, are practically always in the gray matter. The cells of the infiltrate are mostly lymphocytes with a few plasma cells and an occasional large mononuclear.



The blood vessels, though densely infiltrated, show no endarteritis.

In the affected areas, ganglion cells are seen in all stages of disintegration, some having been completely destroyed and replaced by groups of phagocytes. Sections stained by the Levaditi method were negative.

#### CONCLUSIONS

1. The histologic picture of the condition is that described by English authors for lethargic encephalitis, also that of trypanosomiasis.

2. The picture is very much like poliomyelitis, but such extensive infiltration of meninges and larger vessel walls would, at least, be very unusual.

3. The picture is also very much like syphilis. In syphilis, however, the infiltration sticks to the vessels. Syphilis shows an endarteritis, and usually gummata in vessel walls.

#### POSSIBLE RELATION TO POLIOMYELITIS AND INFLUENZA

Three theories have been advanced to explain the occurrence of lethargic encephalitis. When it first appeared in England, it was suggested that it was caused by food—botulism or some poison derived from substitutes or solanin accumulating in sprouts of potatoes or other vegetables. This theory has been definitely disproved and discarded. According to a second theory, it is a form of poliomyelitis; and, according to a third, it is connected with the epidemic of influenza.

The theory that it is a form of poliomyelitis has not been definitely proved or disproved. Epidemic poliomyelitis usually occurs in hot weather, the majority of the victims are children, and the lower motor neuron type of paralysis constitutes the great majority of the cases with paralysis. The onset is usually sudden and the greatest number of deaths occur in the first week. Lethargic encephalitis has occurred in its present appearance during the cool weather, the majority of cases having been adults (my own list of cases shows a large number of children, but this is undoubtedly because I am so often called to see the milder type of case where tuberculous meningitis is suspected). Very few cases of the lower motor neuron type of poliomyelitis are occurring, and among the cases diagnosed as lethargic encephalitis there are evidences of involvement of the higher centers in the way of cranial nerve palsies and prolonged lethargy which are rare even in epidemics of poliomyelitis. Certainly among the hundreds of cases of the latter disease that came under my observation during the epidemic of 1916 there were no cases at all approaching the characteristic pic-

ture of lethargic encephalitis, and only a few of the encephalitic type of poliomyelitis, with which some of these milder cases might easily be confused. Moreover, in lethargic encephalitis the onset is usually slow, and death occurs oftenest in the third week. The similarity of the spinal fluid findings is of little significance, since in neither case are they specific. The same may be said in regard to the pathology, though here there are, as a rule, more points of difference. As regards animal inoculation, it is certainly much more difficult to reproduce the disease in monkeys than is the case in poliomyelitis. For all these reasons it seems to me probable that lethargic encephalitis is not a form of poliomyelitis though the causative agents in the two diseases may perhaps be closely allied.

In regard to the possible relation between influenza and lethargic encephalitis, the evidence is as yet entirely circumstantial. In the first place, attention may be called to the fact brought out by historical study that on several occasions epidemics of a disease resembling lethargic encephalitis and influenza have occurred together. The impression is gained from these studies that encephalitis has not appeared in anything like an epidemic form except with influenza. It is certain that in their last appearance, 1889-1890, they occurred simultaneously, and it would seem that enough time has elapsed since for either to appear by itself if there were no direct connections between them. Then again, in a large proportion of cases, occurring in this country at least, the onset has been preceded by an attack clinically influenza. Moreover, that influenza has a marked effect on the central nervous system is shown in two ways: First, in nearly every instance, the convalescence from influenza is characterized by a profound mental depression and nervous exhaustion out of all proportion to the severity of the disease; secondly, as indicated by the reports of Jelliffe, Menninger, Burr and others, influenza is far more likely than any other acute infection to be followed by disturbances of the nervous system either psychic or organic. Therefore, it seems to me probable that there is a definite connection between influenza and lethargic encephalitis. Just what the relation is, I am not prepared to state. In view of the fact that we do not know the cause of either disease, one cannot say that the two diseases have the same origin. The causative agents may be identical or closely allied or the virus causing influenza may make the individual more susceptible to the causative agent of encephalitis or it may enhance its virulence. It is easy to speculate on the unknown.

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## DISCUSSION

DR. JOHN F. HOGAN, Baltimore: In Baltimore we wished to ascertain the number of cases of encephalitis lethargica, as only a few were diagnosed. I saw all of the cases reported to the health department and there was one constant symptom or rather complication. I think it should be classed as a complication rather than a symptom, because it comes on later in the progress of the disease. This constant complication of diplopia seemed to set in after-

ward, within three to five weeks after the onset. In all the cases that I saw, the complication was present or developed later. The first patient I saw was a big husky man, 20 years of age. I did not know what his trouble was. He had been sent to a camp in that vicinity because he was a member of the Dental Reserve Corps. In February or March I heard that this man had recovered. He had had a slight facial paralysis which afterward disappeared, and as I questioned him and read the article to him, which appeared about that time in the report of the Surgeon-General of the U. S. Public Health Service, and I described diplopia he said he had it. He spoke of attending a lecture at the camp and while at the lecture he thought he saw two lecturers on the platform and, in fact, questioned a soldier who was next to him and asked him if there were two persons on the platform. I wonder if others had the same experience.