missions which may give a false sense of security. These symptoms will return or other more urgent symptoms develop.

Unfortunately early symptoms are ill-defined or minor in character, and the diagnosis may be indicated only by an association of mild complaints, none of which are remarkable by themselves, but which when added together point to the correct conclusion. By the time symptoms are severe enough to take the patient to the doctor, the growth has likely been present for a considerable period of time. This probability is what makes it so important that one should act quickly, once symptoms become definite enough to arouse suspicion. It also explains the fact that the prognosis, in the average case, without treatment, is suggested to be as short as six months from the establishment of the diagnosis. The old maxim of "better to be safe than sorry" is very appropriate at this point. It is far better to have a negative investigation than a doomed patient.

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NEUROLOGICAL COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS*

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NUMEROUS reports have appeared in the past several years of cases diagnosed infectious mononucleosis and showing neurological complications. The various reported neurological symptoms can be grouped as serous meningitis, encephalitis, myelitis, neuritis and convulsive states. These are non-specific types of neurological inflammatory reactions which one encounters more commonly as sporadic illnesses unrelated to any known systemic infection or illness. The same type of inflammation in the nervous system are encountered with known virus infections such as measles, mumps, rabies, herpes and vaccinia. The small group of cases occurring with mononucleosis is of interest in relation to the diagnosis and clinical assessment of the whole field of virus infections of the nervous system. Though we have little to contribute to the problems of etiology and treatment it is our purpose to present three further cases of infectious mononucleosis with neurological complications and to review the related literature.

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CASE 1

M.S., male, aged 17, was admitted to hospital in a semi-stuporous state. A two day history of feeling "seedy" and of mild, non-localized headaches, was obtained from relatives. In the morning of the day of admission he had felt generally unwell and complained of weakness in his legs. A few hours later he had become drowsy and had a sudden severe convulsion, following which he remained in a stuporous state, although responding to painful stimuli. At this time his rectal temperature was 103° and he vomited several times. Urinalysis was negative. In the evening consciousness began to return but he was sent to hospital because a subdural hæmatoma was suspected, as he had suffered a minor head injury two weeks previously. Examination showed a semi-stuporous, resistive, restless, well developed young man. There was moderate neck rigidity but no other positive neurological signs were present. There were a few small non-tender, firm cervical glands and also some redness of the pharynx. Laboratory findings: hæmoglobin 100%, white blood cell count 14,000, polymorphonuclear leucocytes 65%, lymphocytes 35%; spinal fluid was clear with the protein content slightly raised, and a cell count of 16. The cerebrospinal fluid pressure could not be estimated due to the patient's restlessness. The following day the patient was conscious but somewhat confused, and a left Babinski response had developed. During the next night widespread lymphadenopathy occurred and the spleen could be palpated 2 cm. below the costal margin. A repeat blood count showed white blood cells 12,600, with a differential count of 83% lymphocytes, most of which were of a large atypical variety, and thought characteristic of infectious mononucleosis. A Paul-Bunnell titre was positive, in 1:1,280. During the next seven days there was rapid symptomatic improvement and disappearance of the lymphadenopathy, splenomegaly, and the atypical lymphocytes from the peripheral blood. The patient was discharged asymptomatic on the ninth hospital day. There was some residual easy fatigability for a further three weeks, but no new symptoms developed.

CASE 2

W.D., male, aged 24, developed low back pain three weeks prior to admission to hospital. The pain had been made worse by movement, and over a period of three to four days it had spread to include the neck, shoulders and back. Generalized headache had also developed at that time and had persisted. Over the next week the back pains had gradually disappeared but general malaise persisted. The low back pain returned four days before admission, and in addition there was some neck stiffness and soreness. Aching discomfort in both legs occurred next and rapidly developed to stiffness, with numbness and tingling, so that he could not walk. Two days before admission retrobulbar pain and difficulty in micturition began. Small amounts of urine only were voided with difficulty. This latter complaint led to his seeking medical help. Examination showed a temperature of 102°, a reddened pharynx without soreness, moderate neck stiffness, generalized small, non-tender lymph nodes and a palpable, firm spleen extending 2 cm. below the costal margin. The urinary bladder was palpated above the pubis and contained 25 ounces of urine. Neurological examination showed questionable early papilloedema and otherwise normal cranial nerves. There was weakness of all muscle groups in both lower limbs, more marked in the proximal groups. Sensation to pain and touch was impaired below a level at the seventh thoracic dermatome. There was some dysæsthesia over the upper few dermatomes. Postural and vibration sense were grossly impaired in the lower limbs. The abdominal reflexes were absent and there were bilateral Babinski responses. Hæmoglobin 90%, white blood count 7,000 with 67%

lymphocytic forms of which 61% were large and atypical. Lumbar puncture: initial cerebro-spinal fluid pressure 230 mm. of spinal fluid, normal dynamics, protein estimation 64 mgm. %, cells 29, all lymphocytes. A Paul-Bunnell titre 1:40.

The patient showed progressive improvement for nine days with diminishing lymphadenopathy and splenomegaly, improved motor power of the lower limbs and the sensory deficit became less marked. The white blood cells had increased to 12,000 on the fourth hospital day but returned to 7,000 with only 15% atypical lymphocytic forms. On the ninth hospital day the patient had a generalized convulsive seizure without loss of consciousness. Four days later there were two more similar seizures. Clinically there was return of the lower limb weakness and the sensory level again became clearly evident. Dermatographia was transiently present. An electrocardiograph showed frequent intermittent runs of 2-3 per second high voltage slow waves, tending to be rhythmical. These were mainly bisynchronous and frontal in origin but occasionally clearly arose from the left frontal region. A few days after the last seizure improvement again began, the sensory level disappeared, bladder control returned and the reflexes became physiological except for absent abdominals. Motor power returned to normal in three weeks, but position sense in both feet remained slightly impaired. A few atypical lymphocytic forms were still present in the peripheral blood. A lumbar puncture showed 23 cells but was otherwise normal. The electrocardiograph still showed frequent short runs of 4-6 per sec. medium and high voltage slow waves arising in the right frontal and temporal regions. The patient's only complaint on being sent for convalescence was slightly increased fatigability. At six weeks' physical examination, blood and spinal fluid studies were all normal. However, the electrocardiograph still showed considerable abnormality, from both frontal lobes. Three and a half months after the onset of his illness an electrocardiograph still showed a few short runs of medium voltage 6 per sec. slow waves. The record was otherwise normal with well regulated 2 per sec. symmetrical alpha rhythm. The patient felt perfectly well.

CASE 3

B.W., male, aged 24. This patient reported being in excellent health until three weeks prior to being seen at the hospital. He first noted a sudden onset of moderately severe, generalized headache, more marked in frontal distribution. This persisted, unaffected by symptomatic therapy, for three days while he continued attending at work. Mild chills accompanied by excessive perspiration then developed, with which his headaches improved. Accompanying fatigue and anorexia resulted in the patient voluntarily going to bed for the next four days. He was then seen by a physician because of general lack of improvement and splenomegaly and lymphadenopathy were reported, white blood cells 17,000, and a differential count revealed 65% lymphocytes, many of which were atypical forms. A diagnosis of infectious mononucleosis was made. During the second week the patient made rapid subjective improvement.

On the fourteenth day of this illness he noted the onset of weakness in the muscles of the face which made it difficult to hold food in his mouth, he was unable to chew adequately, and could neither smile nor whistle. Two days later he was unable to close his eyes or raise his eyebrows and these complaints continued until seen on the twenty-first day of his illness. It is interesting to note that with the onset of difficulty referable to his eyes his throat became quite sore, painful on swallowing, and continued so for five days.

The patient was a very well developed young man whose only complaints were referable to a bilateral facial weakness. The pharynx was inflamed although the tonsils were small and atrophic. General examination was otherwise normal. There was no evidence of lymphadenopathy or splenomegaly. Neurological examination revealed a complete, bilateral, peripheral seventh cranial nerve paresis, with loss of taste to standard test substances on the anterior two-thirds of his tongue. The remaining cranial nerves and the remainder of the neurological examination was normal. White blood count was 12,000, 4% lymphocytes with persistence of some atypical forms considered compatible with the diagnosis of infectious mononucleosis. The heterophile agglutination test was positive in a titre of 1:160. Spinal puncture was normal. An electroencephalogram showed a few random, low voltage, 4-6 per sec. slow waves only and was not considered definitely pathological.

Over the following six weeks the patient showed gradual clearing of clinical and laboratory evidence of his infectious mononucleosis. The facial diplegia began to subside within a few weeks of its onset and recovery was almost complete in three to four weeks. This patient was under the care of Dr. E. J. Clifford to whom we are indebted for permission to report this case.

REVIEW OF LITERATURE

"Glandular fever" was first described by Pfeiffer in 1889 but has really only aroused clinical interest since 1920, at which time the name infectious mononucleosis was coined.[1] Since then many accounts of the disease have been published. The variety of the clinical manifestations is noteworthy and, aptly or not, this disease has been stated to be second only to syphilis as an imitator of clinical syndromes. This is well exemplified in the excellent review by Bernstein.[2] In 1932 Paul and Bunnell described the presence of heterophile antibodies in the sera of patients with infectious mononucleosis and although the reaction is not specific[3] its value in the identification of this condition is well established.

In reviewing the literature for cases with central nervous system complications a number of general reviews (not particularly studying the nervous complications) were encountered.[4 to 13] In the ten reviews noted there were a total of 4,393 cases of infectious mononucleosis recorded. Of these a total of 17 cases, or an incidence rate of 0.37%, were recorded as showing definite neurological complications. An additional two cases showed a polymorphonuclear pleocytosis in the spinal fluid, probably due to a concurrent unrelated central nervous system infection.[7, 8] Also cases of headache, dizziness, vomiting, etc., were mentioned but in these the cerebrospinal fluid was either normal or not investigated and in the absence of other neurological signs and symptoms they were omitted from these figures.

In addition to the above, a number of other reports of the neurological complications of infectious mononucleosis have appeared in the medical literature since 1931 when the first two such reports by Johansen[14] and by Epstein and Damashek[15] appeared. The neurological com-

plications that have been reported can be roughly grouped into four main types: (*a*) lymphocytic or serous meningitis; (*b*) encephalitis, including varieties of meningo-encephalitis, encephalo-myelitis, etc.; (*c*) polyneuritis, acute, of the Guillain-Barre type; (*d*) neuritis (see Table I). A total of 59 cases have been collected, of which eight fatalities are reported.[15, 16, 17] One case reporting psychosis as a complication is not included in this report.[18]

The following tables classify the literature according to types of neurological involvement in cases of infectious mononucleosis:

LYMPHOCYTIC (SEROUS) MENINGITIS

	No. cases
Johansen[14]	1
Epstein and Damashek[15]	1
Gsell[33]	3
Schmidt and Nyfeldt[34]	5
Pietsonka[36]	3
Marshall[22]	1
Thelander and Shaw[19]	1
Holcrow *et al.*[8]	4
Immerman[10]	1
Coogan *et al.*[23]	2
Vander Meer *et al.*[12]	2
Wechsler and Rosenbloom[13]	1
Total	28

ENCEPHALITIS (MENINGO-ENCEPHALITIS, ENCEPHALO-MYELITIS, ETC.)

	No. cases
Fledelius[31]	1
Sucher and Swartz[32]	2
Davidsohn[28]	1
Huber[35]	1
Thompson and Vimtrup[5]	4
Landes *et al.*[20]	1
Slade[26]	2
Geliebter[29]	1
Schneider and Michelson[27]	1
Bercel[40]	2
Present report	2
Total	19

GUILLAIN-BARRÉ TYPE POLYNEURITIS

	No. cases
Sohman and Silverman[24]	1
Hiller and Fox[39]	1
Coogan *et al.*[23]	1
Ricker *et al.*[16]	2
Haymaker and Kernohan[17]	2
Total	7

NEURITIS

	No. cases
Gsell[33]	2
Richardson[38]	1
Salsena[21]	1
Stevenson and Brown[9]	1
Total	5

FATALITIES FROM NEUROLOGICAL COMPLICATIONS

	No. cases
Thompson and Vimtrup[5]	4
Ricker *et al.*[16]	2
Haymaker and Kernohan[17] (plus 6 suspect)	2
Total	8

The commonest manifestation reported was that of a meningitis and this was well exemplified in a case reported by Thelander and Shaw.[19] They report the case of a 22 year old girl whose presenting symptoms were headaches, neck rigidity and slight fever. Spinal fluid examination showed 630 cells mostly lymphocytes. Thirteen days after the onset of symptoms peripheral blood changes of infectious mononucleosis developed and the Paul-Bunnell titre rose to 1:640. Spinal fluid cell count decreased to 85 and remained elevated at that level for some months. The patient became rapidly asymptomatic on general treatment.

Those cases presenting as, or developing, the clinical picture of an acute encephalitis were next in frequency of occurrence. Great variety of symptomatology was reported. The neurological signs variously began before, or after, the systemic signs of the infectious mononucleosis were evident. For example, Landes, Reich and Perlow[20] describe the case of a 21 year old male who was admitted to hospital with a seven day history of severe headache, dizziness, vomiting and staggering gait. Temperature was 101°. The patient was first irritable, then lethargic and finally irrational. Speech was poorly articulated and explosive, co-ordination was poor. Sensation and reflexes were normal. The blood picture was that of infectious mononucleosis and the Paul-Bunnell titre was 1:1,024. Spinal fluid pressure was normal, protein estimation 175 mgm. %, and cells up to 10. Lymphadenopathy and splenomegaly developed 22 days after the onset of the symptoms.

Cases with the clinical picture of acute infectious polyneuritis were noted on seven occasions with a fatal termination in four cases.

A brief account of one of the cases reported by Ricker *et al.*,[16] illustrates this type of complication. A 22-year old male presented with headaches, chills, fever and generalized muscle pain. There were slightly enlarged lymph nodes present, blood findings were those of infectious mononucleosis and the Paul-Bunnell titre was 1:1,792. On the second hospital day the headache increased and the cell count was 97 of which 94 cells were lymphocytes. On the third day flaccid paralysis of all four extremities with hyperæsthesia of hands and feet, developed. A right facial paralysis and a decreased gag reflex were found. All reflexes were absent. The

sensorium was clear but the patient was very apprehensive. He died in a respirator of respiratory paralysis on the seventh day.

Finally, there are a few reports of single peripheral nerves being affected during the clinical course of proved infectious mononucleosis. Such a complication is a case reported by Saksena[12] in which the patient complained of pain in the shoulder in the area of the right deltoid muscle ten days after the onset of typical infectious mononucleosis. The pain persisted for ten days, at the end of which time the pain subsided and paralysis of the serratus anterior muscle occurred. In this case the spinal fluid pressure, protein and cell estimations were all in normal limits. The paralysis recorded is still present fourteen months after its onset. (We have recently encountered a case with bilateral facial neuritis which has not been included in this report.)

Variations of the above rough grouping of neurological complications are, of course, the rule. The clinical signs or symptoms were ushered in suddenly[15] or gradually[22] were very mild[23] to very severe[24] and the generalized manifestations could develop before,[21] with[10] or after[19] the neurological signs. Sudden convulsive seizures are also reported as initial symptoms.[25] While complete recovery is the rule persisting sequelæ do occur[26, 27] and, as noted, death followed in eight instances. No deaths were reported in the meningitic or neuritic groups. In 20 of the included cases, where cerebrospinal fluid cell counts and protein estimations were recorded, the protein was elevated in all, while the cell counts varied from 0 to 9 c.mm. in seven cases. Thus, albumino-cytological dissociation was a relatively common finding. Spinal fluid pressures were noted infrequently but definite elevation of pressure was recorded in three cases.

Since the clinical use of the Paul-Bunnell test was first recorded by Davidsohn in 1937[28] almost all cases of infectious mononucleosis with neurological manifestations are reported as having had elevation of the titre values, varying from 1:64, the usually accepted minimal value, to 1:28,000.[27] In the one case where the Paul-Bunnell titre of the spinal fluid was done it was negative. There appears to be a rough correlation of the neurological signs and the value of the titre. Attention is drawn to our second new case report where the highest titre obtained was 1:40. It may be that this case falls into the sero-negative grouping of Davidsohn[28] but it was felt that the general features of splenomegaly, glandular hypertrophy and the blood picture warranted the diagnosis of infectious mononucleosis. With one exception[29] the total white blood cell counts reported were over 5,500; in all cases there was a lymphocytosis. The spleen was enlarged in the seven cases in which its size was noted.

Pathology. — Two excellent papers on the pathology of the neurological changes in infectious mononucleosis have recently appeared.[16, 30] Central nervous system material from six autopsies was examined. In two cases the patient had died of the neurological complications[16] and here the veins and capillaries of the meninges were engorged, a few perivascular hæmorrhages were seen in the cervical portion of the spinal cord and there was a mononuclear infiltration of the anterior nerve roots at all levels. The spinal nerves showed congestion and œdema and the peripheral nerve axis cylinders were distorted and the myelin sheaths swollen and disrupted, with some perivascular infiltration of the nerve sheaths. In three of the other four cases there was evidence of mild to moderate meningo-encephalitis with occasional small perivascular hæmorrhages in the brain and mild ganglion cell degeneration. In the spinal cord the changes were minor, but cellular infiltration of the anterior roots was noted at all levels, particularly in the periphery of the blood vessels.

Because of our experience as mentioned above, and in view of the findings of Haymaker and Kernohan[17] as reported to the American Neurological Society in 1948 where a clinico-pathological review of 50 cases of the "Landry-Guillain-Barre" syndrome showed two cases to be neurological complications of infectious mononucleosis and a further six cases were suggestive of this condition, a review was made of relevant autopsy material at this hospital to see if infectious mononucleosis could be incriminated as a causal agent. The cases selected were those in which death followed an acute clinical course of what appeared to be a generalized virus infection and in which the findings had not been those of specific known disease processes. Twenty-two such cases were selected from the autopsies performed between

1928 and 1948. The diagnoses which had been made were:

Acute encephalitis	9
Acute infectious polyneuritis	5
Landry's paralysis	3
Acute encephalitis lethargica	2
Acute encephalo-myelitis	1
Acute meningo-myelitis	1
Acute cerebritis	1
Total	22

A review of the pathology of these cases was undertaken with special attention being paid to sections of the spleen and lymph nodes. In no case was the evidence even suggestive of a generalized reaction of infectious mononucleosis.

DISCUSSION

It appears self-evident from the foregoing that infectious mononucleosis must be kept in mind in the etiology of a variety of neurological syndromes and particularly in acute infections where the etiological agent is not at first apparent, but thought to be of a virus nature. Repeated blood and heterophile agglutination studies should be performed and persisted in even weeks after the onset of the illness. Only thus can this condition be excluded in the differential diagnosis of viral diseases affecting the central nervous system. The reaction of the nervous system to the virus of infectious mononucleosis both clinically, as in the neurological examination, spinal fluid and electroencephalographic studies, and pathologically, would not appear to be in any way specifically diagnostic. The identification relies upon the general system manifestations of infectious mononucleosis in conjunction with any of the types of central nervous system reactions described.

It should be made clear that diagnosis is not always certain even at autopsy. Recently, we have seen a case of a 19-year old boy, with a one week's history of mild headache and malaise who, on examination had lymphadenopathy, splenomegaly, white blood count 4,100 of which 50% were lymphocytes and 23% of these atypical forms. He developed major convulsive seizures and rapidly passed into a state of deep coma with serial seizures in which he died. Encephalitis complicating infectious mononucleosis appeared to be the most likely clinical diagnosis. However, the Paul-Bunnell titre never rose above 1:40. At autopsy it was disconcerting to find the spleen had become shrunken and small and examination of all organs, including the lymph nodes, revealed no systemic evidence of infectious mononucleosis. Virus studies were non-informative.

The present state of our knowledge as to sporadic cases of encephalitis tends to leave us most humble in incidents of this nature. However, it would appear well established that a very small percentage of such cases can, with a degree of certainty, be diagnosed as neurological complications of infectious mononucleosis.

SUMMARY

Three cases of infectious mononucleosis with neurological complications have been reported. In the first case the presenting symptoms of a major convulsion and stupor preceded the other general symptoms of the disease. The second case had a severe myelitis with recovery and then a neurological relapse with repeated convulsions. The third case showed facial diplegia. A fourth is mentioned in which death occurred from status epilepticus and the clinical features strongly supported a diagnosis of infectious mononucleosis. The neuropathological findings in that case were surprisingly slight.

The literature has been reviewed in some detail with a grouping of the types of neurological complications.

The varied and non-specific types of neurological symptoms in mononucleosis have been discussed in comparison with unexplained sporadic cases of encephalitis, myelitis, meningitis and polyneuritis.

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PULMONARY CALCIFICATION AND HISTOPLASMIN SENSITIVITY

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IN 1906 Darling,[1] working in the Panama Canal Zone, encountered at autopsy cases of what appeared to be kala-azar, a disease which had not been reported from the western hemisphere. Closer study of the apparent causative organism in these cases disclosed differences between it and that which was found in kala-azar. Darling therefore felt that he was dealing with a different and previously undescribed disease. He considered the organism to be a protozoan, and called it *Histoplasma capsulatum*, and the disease histoplasmosis.

It was accepted that Darling had indeed described a new disease, but because it seemed to be a very rare tropical disease, little general interest was shown in it. In 1926 Watson and Riley encountered a case in Minnesota, the first case to be reported from the United States proper. By 1937 only 13 cases had been recognized, and the disease was still regarded as an uniformly fatal medical curiosity. DeMonbreum in 1934 restudied the organism which he isolated from a fatal case, and showed that it was a fungus and not a protozoan.

Since 1937 more and more cases have been reported and by 1946 88 cases were gleaned from the literature. Most of these were encountered in the United States, but some had also been reported from other areas. It was also recognized that the disease was not uniformly fatal.

In 1941 Zarafonetis and Lindberg[2] prepared antigens from cultures of the *H. capsulatum* and used this "histoplasmin" to determine the incidence of skin sensitivity in the same manner as tuberculin is used to determine tuberculin skin sensitivity. In surveys of positive histoplasmin skin sensitivity it was discovered that there were striking geographical differences.[3, 4] In the Mississippi basin a very high incidence of positive reactors was found, and the incidence of positive skin reactors tended to diminish the further from this region that testing was done. However, occasional pockets of increased incidence of histoplasmin sensitivity are encountered.

It had been known for many years that the incidence of pulmonary calcification as detected by x-ray films of chests also varied geographically. Thus in American Army recruits the incidence of calcification varied from 6% of inductees in Oregon to 28% in Kentucky.[5] In most regions it had been assumed that pulmonary calcification was evidence of old tuberculosis infection, and indeed some inductees with marked pulmonary calcification were rejected on this ground. It was also known that many of these individuals were negative reactors to tuberculin, but this was explained on the gradual loss of tuberculin sensitivity as the individual became older. However it has been shown[6] that tuberculin skin sensitivity is lost very slowly, and this is probably true particularly in urban areas where repeated contact with tuberculosis is likely.

Great interest was evidenced, therefore, when it was shown[7, 8, 9] that the incidence of pulmonary calcification showed a much closer relationship to positive histoplasmin skin sensitivity than to positive tuberculin skin sensitivity. It therefore appeared likely that pulmonary calcification was not necessarily evidence of old tuberculosis, but in certain areas at least, represented old histoplasmosis.

The next step was to demonstrate that infection with *Histoplasma* could produce this picture, and that recovery could occur, leaving calcified nodules that could be detected by x-ray. This has been done. Sontag and Allen[10] observed school children who were histoplasmin and tuberculin negative, and who had negative