In conclusion I can only reiterate the opinions I expressed earlier: that it is unfortunate in the extreme to limit the application of chemical analysis of the blood to any selected group of technical procedures or to any one class of diseases, or to treat the information secured by these analyses as if it were separable or distinct from other types of clinical information.

CLINICAL OBSERVATIONS AND LABORATORY INVESTIGATIONS ON THE 1933 EPIDEMIC OF ENCEPHALITIS IN ST. LOUIS*

RALPH S. MUCKENFUSS
St. Louis

Encephalitis, as it appeared in the epidemic in St. Louis in the summer of 1933, was an acute febrile disease, characterized by prominent signs of meningeal irritation, a comparatively short course, and a relatively low incidence of sequelae.

Early in the epidemic, hospitalization was strongly recommended by the Health Division, with the result that over 90 per cent of the reported cases were observed in hospitals. In the Isolation Hospital, where nearly 400 cases were treated, a senior student, responsible for the completeness of the records, was placed by Dr. Barr. The present report covers 300 of these cases, and free use has been made of the tabulations prepared by Mr. Robert L. Drury, a member of the senior class at Washington University.

Classification. The cases have been divided into three groups by Dr. T. C. Hempelmann[1]. The first two groups differ in the mode of onset, and the third group consists of abortive or very mild attacks in which the diagnosis was difficult and frequently uncertain.

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* Department of Internal Medicine, Washington University, School of Medicine, St. Louis.

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Onset and Initial Symptoms. The first type of onset was abrupt, and preceded by no prodromal symptoms. Headache and fever appeared, frequently associated with vomiting. Very rapidly the patients became somnolent, spoke slowly and with some difficulty, and at times went to sleep without finishing a sentence. A stupor from which the patient could be aroused to answer simple questions frequently followed closely on the appearance of somnolence, and in some cases true coma occurred. Mental confusion was commonly present. Instead of somnolence and stupor, many patients showed irritative phenomena, such as restlessness, constant irrational talking, or, rarely, active delirium.

The second type of onset was characterized by a prodromal period, usually lasting one to four days, in which slight fever and "grippy" feelings were usually present. At the termination of this period a sharp rise in temperature occurred, and the subsequent picture was similar to the first type.

The predominant features of the disease were meningeal

TABLE I.

TYPES OF ONSET

*Sudden	57.0%
Gradual	42.3%
Doubtful	0.6%

or meningo-encephalitic. Some degree of rigidity of the neck muscles was present in 86 per cent of the cases, and a positive Kernig's sign in 72 per cent. The abdominal reflexes were ordinarily absent, and the deep reflexes were diminished or absent. Plantar reflexes were abnormal in 40 per cent of the cases, but this was variable, and the findings would sometimes change from hour to hour. Tremors of the tongue and lips were frequent, and were especially noticeable when the patient attempted to speak.

* Any onset of less than three days duration was arbitrarily classified as sudden for purposes of tabulation.

Symptoms or signs referable to the eyes were comparatively rare, and usually consisted of small and sluggish pupils, blurred vision, or photophobia. Nystagmus and diplopia each occurred in 8 per cent, and strabismus and ptosis in 3 per cent and 2.6 per cent respectively. The accuracy of these last two figures is still open to some

TABLE II.

NEUROLOGICAL SIGNS

Abnormal deep reflexes	74.0%
Absent abdominal reflexes	59.6%
Tremors	55.6%
Abnormal plantar reflexes	40.6%
Aphasia or speech difficulty	12.0%
Facial weakness	6.0%

question, since it has not been possible to determine the condition of all of these patients prior to their attack of encephalitis, and since ptosis was more a weakness and slight drooping of the lids than an actual paralysis.

Mild and Abortive Cases. In some cases a slight fever of one or two days duration, with perhaps some stiffness of the neck or headache, prompted lumbar puncture, which revealed the increase in cells characteristic of encephalitis. At times an unexplained fever was the only symptom. In children the findings were more variable and mild cases seemed to be more common.

Spinal fluid. Lumbar puncture usually yielded a clear fluid under moderately increased pressure. In the majority of instances from 100 to 300 cells were present per c. mm., but this was subject to considerable variation, and one count as high as 1100 cells per c. mm. was recorded. Lymphocytes predominated, but in a few instances polynuclear cells constituted from 30 per cent to 50 per cent of the total count. At times the fluid withdrawn on the first puncture was normal, while a second puncture a day or two later showed the characteristic increase in cells. When the results of spinal punctures are tabulated, it is seen that 81 per cent showed 10 or more cells per c. mm. If, how-

ever, as is probably more correct, counts of 3 or more cells per c. mm. are considered abnormal[2], only 7 per cent of the cases showed normal cell counts.

A slight increase in globulin was demonstrated in 41 per cent by means of the Pandy test.

Sugar determinations usually showed from 50 to 90 mg. per cent, and very rarely was the result low enough to lead to a suspicion of tuberculous meningitis. Spinal fluid was precipitated as soon as collected, and the filtrate was used in determining sugar by the Shaffer-Hartmann method.

Blood. Blood counts most frequently showed white cells ranging from 10,000 to 14,000, with extremes of 2,800 and 36,000. With the Schilling differential, the usual result was a shift to the left.

Clinical Course. The clinical course was rather characteristic. Fever continued high, quite commonly between 104 and 105° F., for a few days, and then gradually diminished, in the majority of instances reaching normal in six to ten days after admission to the hospital. Frequently there was a critical drop in temperature, which then usually remained normal in uncomplicated cases. A few times the elevation of temperature was more prolonged, and in fatal cases the temperature usually remained elevated up to the time of death. Somnolence and stupor, when present, usually persisted until about the time of defervescence, and then rapidly disappeared, as did the other symptoms and physical signs. The rapidity of recovery in many instances was amazing, and at times a patient who at one visit could only be aroused with difficulty, would on the next day be alert and apparently perfectly normal.

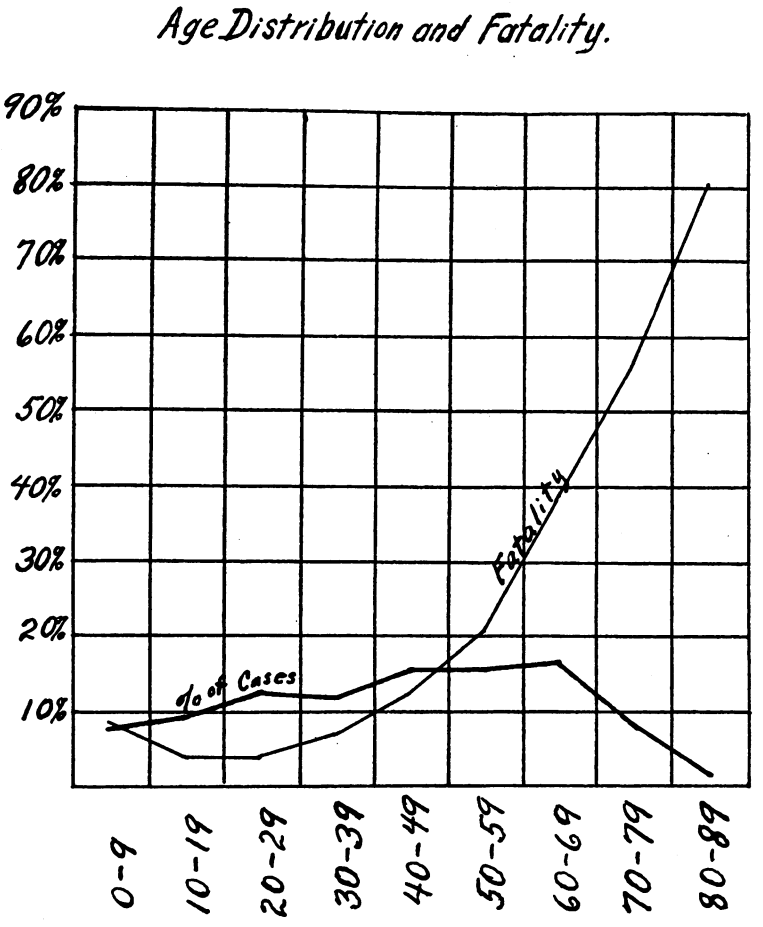
TABLE III.

*DEFERVESCENCE (200 CASES)

By lysis	55.8%
By crisis	44.2%

* For purposes of tabulation a return of temperature to normal in 36 hours or less was considered critical; more than this was considered defervescence by lysis.

*CHART I.



Complications. Most of the deaths were associated with some other condition. Of the 68 deaths occurring in this group, 42 were complicated by bronchopneumonia. Nephritis, hypertension, and arteriosclerosis were also frequent concomitant conditions, and were probably present before the appearance of encephalitis. Of the deaths occurring

* These curves are prepared from the data on 1091 cases of encephalitis reported to the St. Louis Health Division.

in the Isolation Hospital only about 10 per cent were without some complication diagnosed clinically.

Prognosis. The prognosis was much more favorable in younger individuals, as is shown by the fact that while 41.3 per cent of the cases reported in the epidemic were under 40 years of age, only 11.4 per cent of the deaths occurred in this group (Reports on 1091 cases to the St. Louis Health Division). The rise in the death rate with advancing age is graphically demonstrated when the curves of incidence and fatality are plotted on the same chart (Chart I).

Condition on Discharge. The condition of most patients on discharge from the hospital was surprisingly good except for some general weakness. Only 4.6 per cent showed any residua, and half of these consisted of such difficultly definable conditions as were recorded as mental or emotional abnormality. Only a detailed observation over a long period by the psychiatrists will make an evaluation of such findings possible. Photophobia was still present at discharge in two patients. Parkinson's syndrome appeared only one time. Lumbar puncture at the time of discharge, after three weeks isolation, showed a pleocytosis still present in several instances, although such examinations were not made routinely. No relapses or second attacks have been observed in this group of cases.

Treatment. Treatment was symptomatic. The most commonly employed measures were lumbar puncture for increasing headache or other evidence of advancing disease, and the intravenous administration of hypertonic glucose. A number of other therapeutic agents were employed, but none on a large enough scale for the results to be of significance.

Differential Diagnosis. Some cases of non-paralytic poliomyelitis probably cannot be differentiated with certainty from encephalitis. Poliomyelitis was present in St. Louis during the past summer, but the number of cases was not unusually large, so that mistakes in all probability were very few.

Tuberculous meningitis presented much more difficulty, but the onset is ordinarily more insidious, the spinal fluid sugar is usually markedly lowered, and the demonstration of tubercle bacilli would eliminate any doubt.

Follow-up. Plans have been made to follow the recovered cases for a period of two years. An examination of some of the patients 3 months after recovery has not shown any significant deviation from their condition at the time of discharge from the hospital.

Identity of the Disease. The relation of this illness to the lethargic encephalitis of v. Economo[3] naturally comes into question. The sudden, stormy onset, the acute and relatively short course, the predominance of signs of meningeal involvement, the low incidence of cranial nerve paralyses, and the rarity of residua seem to justify placing it in a separate clinical group. It is realized that cases indistinguishable from these have occurred in previous epidemics, but they were only a small fraction of the total number of cases. The clinical manifestations that we have observed, and the seasonal occurrence, correspond quite closely to encephalitis occurring in Japan[4] which has been classified as Type B.

Pathological changes occurring in the two types are quite similar, and consist of perivascular infiltration and some nerve cell destruction. Differentiation is probably more difficult for the pathologist than for the clinician.

Nevertheless, the clinical uniformity of such a large group of cases, which differ from most cases of lethargic encephalitis (v. Economo) requires that the possibility of different etiological agents be kept in mind.

EXPERIMENTAL

Early in the epidemic, research was centralized in the laboratories of the Departments of Medicine and Pathology of Washington University. This enabled experimental study of all cases in which collection of material would not interfere with work planned by the institution in which the patient was treated. Dr. Charles Armstrong, of the

National Institute of Health collaborated in this investigation throughout the course of the epidemic[5].

Many cultures of blood and spinal fluid were made with uniformly negative results, and animals of a number of species were inoculated with blood, spinal fluid, and filtered nasal washings from acute cases, and with brain tissue removed aseptically at autopsy. Shortly after beginning this work, some of the rhesus monkeys developed symptoms suggestive of encephalitis, and work with other animals at the time was to a large extent discontinued.

Emulsified brain tissue from fifteen cases was inoculated intracerebrally into rhesus monkeys, and in seven instances these animals developed fever, weakness, tremors and incoordination after an incubation period of from 8 to 21 days. These symptoms varied in degree, and sometimes were quite mild. The majority of animals showing symptoms were sacrificed, and passage in series through 5 monkeys was successful with four strains. Histological examination of the central nervous system showed changes consistent with human encephalitis, namely, perivascular cuffing and nerve cell degeneration. No bacteria were demonstrable.

Passage in monkeys was attended with considerable difficulty. Only about 40 per cent were susceptible, a large inoculum was necessary, and reinoculations were usually made after an interval of five days. At the time that this phase of the work was discontinued at Washington University and transferred to Dr. Armstrong at the National Institute of Health, one strain was still active in monkeys in our laboratory.

Among other animals, six horses and mules were used. One mule developed fever, lasting a few days, about ten days after inoculation but showed no other evidence of illness. Another mule, inoculated with monkey brain, developed fever and became obviously ill after about ten days. This animal was sacrificed, and histological examination of the brain revealed perivascular cuffing. Passage in this species was not successful, so the significance of the observation is open to question.

During the course of this work, glycerinated brain tissue was shipped to a number of laboratories. Dr. Webster[6], of the Rockefeller Institute, used a strain of mice, bred in his laboratory, which is highly susceptible to neurotropic viruses. In four out of eight attempts he was able to isolate a virus causing encephalitis in these mice. This virus was neutralized by sera from convalescents and was not neutralized by sera collected from normal individuals in New York.

Dr. Webster informed us of his findings, and we accordingly inoculated stock mice with brain tissue of monkeys showing signs of encephalitis. On first inoculation the takes were irregular, but on passage the virus became capable of causing the death of nearly 100 per cent of the animals. Three of the strains that were being passed in monkeys were established in mice. We have confirmed Dr. Webster's observation that the virus is neutralized by the serum of individuals convalescent from attacks of encephalitis during this epidemic.

This virus differs from that of herpes in a number of its characteristics, and at this point it should be stated that over thirty rabbits and eight cebus monkeys were inoculated with brain, blood, spinal fluid, or nasal washings without once encountering herpes virus. These results make it seem evident that herpes virus did not play a part in the St. Louis epidemic.

After intracerebral inoculation, the incubation period that we have observed in mice ordinarily varies between four and eight days, and is most commonly five or six days. At the expiration of this period the mice become hyperirritable and many have convulsive seizures. In a few hours they become quiescent, respiration is barely perceptible, and they will move only when strongly stimulated. Death follows shortly, and histological examination of the brain reveals perivascular cuffing and nerve cell degeneration.

The virus deteriorates fairly rapidly on standing, as is shown by the following experiment. An emulsion of fresh brain was diluted serially and inoculated immediately.

All of the mice given a dilution of 1-1,000,000 died. After standing for five hours at room temperature, only the dilutions up to 1-1,000 caused the death of all inoculated animals; and after 24 hours at room temperature this occurred only with the 1-10 dilution.

TABLE IV.

DETERIORATION OF VIRUS ON STANDING

	Immediate Inoculation	After 5 hours room temperature	After 24 hours room temperature
1-10	*3/3	3/3	3/3
1-100	3/3	3/3	2/3
1-1,000	3/3	3/3	1/3
1-10,000	3/3	1/3	
1-100,000	3/3		
1-1,000,000	3/3		

* These fractions indicate the number of mice dying over the number inoculated.

There is a gradual deterioration in 50 per cent glycerine in the ice box, but after 5 weeks we have demonstrated active virus, although only a few of the inoculated animals have succumbed, and the incubation period was prolonged.

The frequency with which this virus has been encountered, and its neutralization by the serum of patients convalescent from encephalitis lead one to think that it was of etiological significance in the St. Louis epidemic.

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