Outbreak of Encephalitis in Man Due to the Eastern Virus of Equine Encephalomyelitis*

ROY F. FEEMSTER, M.D., DR.P.H., F.A.P.H.A.
Director of the Division of Communicable Diseases of the Massachusetts Department of Public Health, Boston, Mass.

ABOUT the middle of August, 1938, cases of encephalomyelitis in horses were recognized in Massachusetts and it was soon ascertained that an epidemic of considerable proportions existed. On August 12 a child from Brockton died of encephalitis, and when a second child from the same city died on August 30 a rumor spread that the two had been victims of the disease prevalent among horses.

On September 1 the Massachusetts Department of Public Health began to be bombarded with questions as to the truth of the rumor. The answer given was that there had never been an authenticated case of human disease due to the equine virus. On September 2 a death from encephalitis was reported in a child from Marshfield, not far from Brockton. On the same day it was learned that a child, reported on August 31 from Abington as poliomyelitis, had been sent to the Haynes Memorial Hospital where a diagnosis of encephalitis was made. Likewise, on the same day a telephone request was received for aid in making a diagnosis of an illness in a child from Rockland. A consultant of the department, sent to see the case, found that the symptoms were those of encephalitis.

All five of these cases occurred within 15 miles of each other, the nearest being 20 miles southeast of Boston. An interesting coincidence was that they had occurred in essentially the same area as the equine disease. Because of this fact and also on the chance that this was just the beginning of an outbreak similar to the one at St. Louis, the department arranged for virus studies on any fatal cases that might occur. Over the Labor Day week-end the child, seen by the department consultant and transferred to the children's Hospital, died. Two other cases admitted to the Haynes Memorial Hospital on September 1 and 3 also proved fatal. Brain tissue from the first case was put into experimental animals in the Department of Bacteriology of Harvard Medical School, and brain tissue in glycerine from all three was sent to the Rockefeller Institute at New York.

NOTE: The author is merely acting as spokesman for the Department, most of the members of the Division having taken part in the investigation. The Department wishes to acknowledge its indebtedness to Dr. J. E. Gordon, Dr. C. F. McKhann, and Dr. S. Farber of Harvard Medical School and the Children's Hospital for assistance in guiding the investigation and evaluating the epidemiological, clinical, and pathological findings; to Dr. L. D. Fothergill and his associates of Harvard Medical School and Dr. L. T. Webster of Rockefeller Institute for making virus studies; to Dr. C. Wesselhoeft and Dr. E. C. Smith of the Massachusetts Memorial Hospitals for information in regard to their cases; and to Dr. James P. Leake of the U. S. Public Health Service, and Lt. Col. J. S. Simmons and Lt. Col. Raymond Randall of the Office of the Corps Area Surgeon, First Corps Area, Boston, for valuable suggestions and information.

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During the next few days a number of additional cases of encephalitis were discovered in the same area, and brain tissue from other fatal cases was obtained for virus study.

Information was received by the Massachusetts Department of Public Health simultaneously from Fothergill, Dingle, Farber, and Connerley [1] of Harvard Medical School and the Children's Hospital, and Webster and Wright [2] of the Rockefeller Institute that the eastern strain of the equine encephalomyelitis virus had been isolated from the brain tissue. The investigation immediately assumed a new importance. The existence of a new human disease had been established. The virus is known to be widespread in horses along the Atlantic coast. If the western strain can also cause human infections, a public health problem of some magnitude may confront us.

The U. S. Public Health Service had been informed of the increased prevalence of encephalitis, and when cases were definitely proved to be due to the equine virus Dr. James P. Leake and an entomologist were sent to Boston to aid in the investigation. Because Kelser [3] and others had demonstrated that mosquitoes can transmit the disease in laboratory animals, a mosquito survey * was begun on September 19. It was found that Aedes mosquitoes, the probable vector among horses, had already practically disappeared for the season. *Culex pipiens* was the mosquito most frequently encountered in the area. Mosquitoes were collected in homes of cases and around stables where fatal disease in horses had occurred, in the hope of discovering some that might be carrying the virus. So far no virus has been recovered from such mosquitoes.

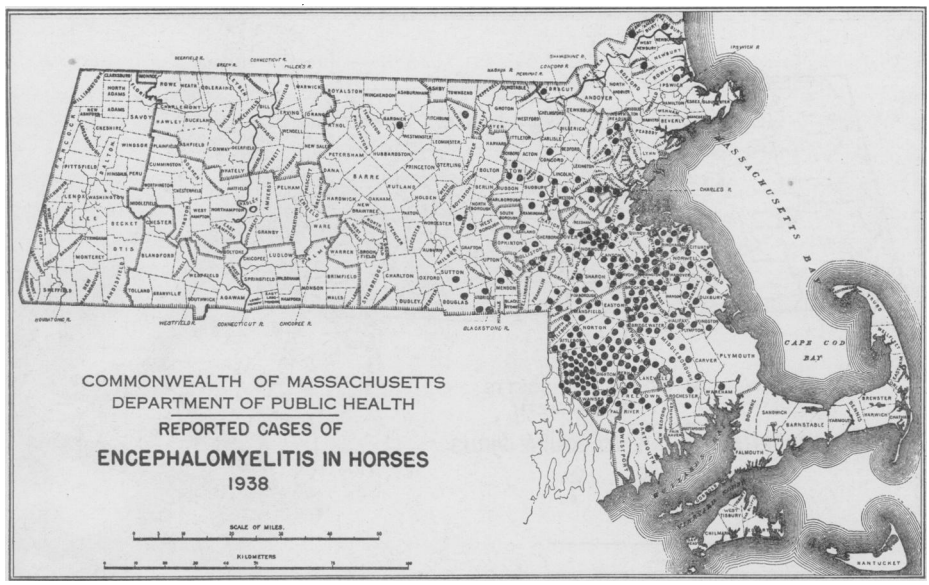
* Valuable assistance in the survey was rendered by Virgil I. Miles, entomologist, of the U. S. Public Health Service.

THE DISEASE AMONG HORSES

While the etiology of equine encephalomyelitis in this country was not definitely established until 1930, it is believed that outbreaks had been occurring in previous years. Conditions formerly called forage poisoning and botulism are mentioned by Meyer as probable cases. When the disease became epidemic in Southern California in 1930 and 1931, Meyer and his coworkers isolated the virus [4] and described the disease [5] and its pathology.[6] When cases were recognized in the East it was noted that the case fatality rate was twice as great east of the Appalachian Mountains. This led workers to suspect that a different virus was present in the East. Ten Broeck and Merrill [7] and Howitt [8] have demonstrated that the eastern and western strains are immunologically different from each other and also different from the strain causing Borna disease in Europe which had been proved to be due to a virus in 1926.[9] Strains from Argentina and certain other South American areas behave the same as the western strain. Those from Panama are identical with the eastern strain.

There is very little evidence that the disease has been present in New England in recent years. Veterinarians now believe that cases occurred in Massachusetts in about 1913 and 1914 and that the highly fatal epidemic among horses in 1872 was probably encephalomyelitis. The disease, however, is known to have been present in various states along the Atlantic seaboard from Florida to New York in recent years.

While the disease among horses was not definitely recognized in Massachusetts in 1938 until after the middle of August, it was eventually found that cases had occurred in that state as early as July 12 (one questionable case reported June 4). The number increased with considerable rapidity, reaching a peak in the week ending August 27 and



rapidly decreasing thereafter (Table I). The number of cases reported to the Massachusetts Division of Livestock Disease Control has now reached 251. This probably does not represent all of the cases, since horses must have died without coming to the attention of veterinarians. Other delayed reports continue to come in. The number of horses on the tax lists in the counties (Table II) most seriously affected was 5,738 (Bristol, Norfolk, and Plymouth Counties). The total number of cases reported from these counties was 204, which gives an attack rate of about 3.5 per cent (see map). This compares with 10 per cent noted by Meyer [5] in California at the time the causative organism was first recognized.

TABLE I

Reported Cases of Encephalomyelitis in Horses *

Dates of Onset

Week Ending	*Number*
June 4	1
July 16	2
23	1
30	1
Aug. 6	3
13	18
20	55
27	68
Sept. 3	56
10	16
17	13
24	8
Oct. 1	2
8	1
15	3
Total	248

* Supplied by Massachusetts Division of Livestock Disease Control. These figures are incomplete. Additional cases are being added to the list as rapidly as investigations justify their inclusion.

The disease appeared to be unusually fatal, very few recoveries being reported. It is estimated that well over 90 per cent of the horses affected have died. The eastern strain has been isolated from the brains of 6 horses. It is definitely known, therefore, that the disease in Massachusetts in both man and horse is due to the eastern strain. Schoening [10] has just been able to produce the disease in a horse with a virus from one of the human cases.

Kelser [3] and other workers have demonstrated that several varieties of Aedes mosquitoes can transmit either the eastern or western strain of the virus in laboratory animals. Three of the varieties (*Aedes solicitans, Aedes vexans,* and *Aedes cantator*) are usually found in considerable numbers in Massachusetts, and a fourth (*Aedes dorsalis*)

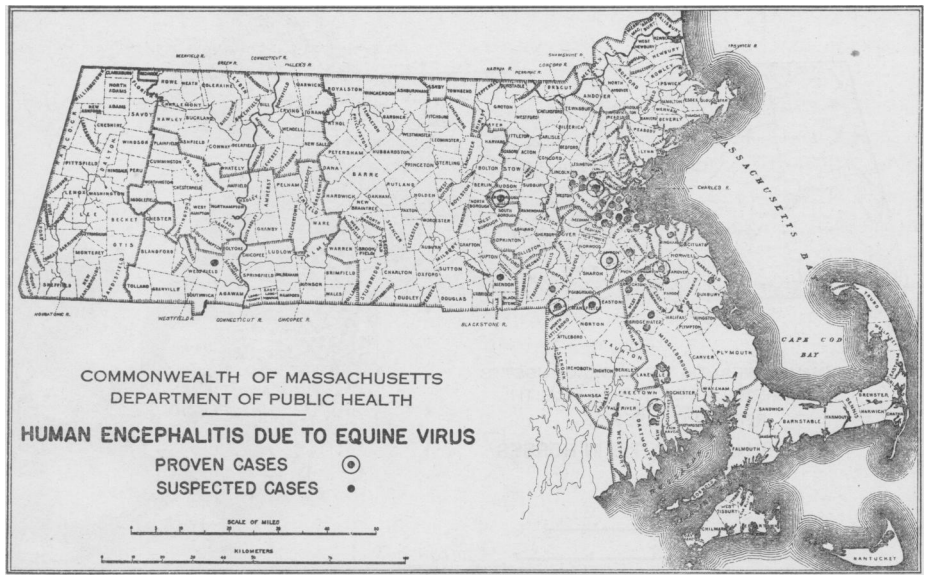


TABLE II

Encephalomyelitis in Horses

Attack Rate by Counties *

	Horses	*Cases*	*Attack Rate*
Barnstable	278	0	
Berkshire	2,960	0	
Bristol	2,647	95	3.6
Dukes	123	0	
Essex	2,467	4	.16
Franklin	2,392	0	
Hampden	2,119	0	
Hampshire	2,625	1	.04
Middlesex	3,887	26	.7
Nantucket	45	0	
Norfolk	1,698	51	3.0
Plymouth	1,393	58	4.2
Suffolk	815	2	.2
Worcester	5,430	11	.2
	28,879	248	

* Compiled from figures supplied by the Massachusetts Division of Livestock Disease Control

has been reported occasionally. If the mosquito is the vector of the natural infection in horses, the spread of the disease in the state can easily be accounted for once a case is introduced.

DISTRIBUTION OF HUMAN CASES

It is, of course, impossible at present to state how many cases of encephalitis due to the equine virus have occurred in the state during the outbreak. Some 38 cases have been under investigation. These are being classified into 4 groups as information becomes available:

I. Cases proved by isolating the virus from brain tissue taken at post-mortem. Thus far, 8 cases * have been so identified.

II. Cases in which the gross and microscopic pathology is characteristic. Including the 8 cases from which virus was recovered, fifteen cases already examined fall into this group.

III. Recovered patients who show neutralizing antibodies in the blood. Specimens have been collected from several individuals who have survived illnesses in which symptoms compatible with the disease were observed. Four of these have shown high titers of neutralizing antibodies, two were negative and the remainder have not yet been examined.

IV. Patients who have died without an autopsy, but in whom the clinical picture seems suspicious. Additional information on these cases may come from the examination of bloods taken from contacts. If neutralizing antibodies are found, infections caused by the virus in the family will be indicated.

Theoretically there should possibly be a 5th group: cases from which the virus is isolated from the blood or

* Four of these died at the Haynes Memorial Hospital, 2 at the Children's Hospital, 1 at the Truesdale Hospital, Fall River, and 1 at St. Elizabeth's Hospital, Boston.

spinal fluid early in the disease. So far, all specimens of this kind have failed to yield a virus. Meyer [11] and Ten Broeck [12] and their coworkers have observed that the virus is found in the blood of experimentally inoculated animals during the period of invasion and rise in temperature, but disappears before any symptoms are observed. Virus has not been recovered from naturally infected horses. It seems unlikely, therefore, that human cases will be seen early enough to obtain virus from the blood.

It is quite certain that some of the cases under investigation will have to be thrown out either because another diagnosis will be established or because evidence will not be sufficient to classify them into any of the 4 groups. This should be borne in mind in interpreting the following tables.

It will be noted (see maps) that there was a marked concentration of cases within the area where the equine disease was prevalent. Search was made among hospitals and physicians in other parts of the state to make sure that cases were not being overlooked elsewhere, but no additional ones were found. The earliest cases under investigation had onsets (Table III) early in August and the peak occurred early in September, a week later than the peak of the disease among horses.

TABLE III

Human Cases under Investigation

Dates of Onset

Week Ending	*Suspected Cases*	*Proved Cases*
Aug. 13	1	0
20	1	0
27	4	0
Sept. 3	9	4
10	8	2
17	6	1
24	4	0
Oct. 1	4	1
8	..	..
15	1	..
Totals	38	8

The cases are fairly evenly divided between the sexes (Table IV). The age distribution, on the other hand, is quite striking. Children under 2 years seem particularly vulnerable, 37 per cent of the cases being in that group. One-half were under 5, and 69 per cent under the age of 10.

The families in which cases have occurred have been visited and epidemiological records obtained. Suspicious illnesses have occurred in some, but multiple or secondary cases of frank disease in families have not been found.

TABLE IV

Human Cases under Investigation

Age and Sex

	Suspected Cases						
	Male		*Female*		*Total*		
Age	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Proved Cases*
Under 1	3	2	5	4	8	6	1
1	1	..	5	3	6	3	2
2	2	2	1	..	3	2	1
3	..	..	1	1	1	1	..
4	..	..	1	1	1	1	..
0– 4	6	4	13	9	19	13	4
5– 9	6	2	1	0	7	2	2
0– 9	12	6	14	9	26	15	6
10–19	2	2	3	3	5	5	1
20–29	..	..	1	0	1	0	..
30–39	..	..	..	0	..	0	..
40–49	..	..	1	1	1	1	..
50–59	4	3	1	1	5	4	1
Totals	18	11	20	14	38	. 25	8

No connection between cases, indicating contact infection, has been traced. Contact with horses has been only casual in many of the cases and no contact at all can be discovered in others. No epidemics among small animals have been observed in the vicinity of the households. Rhode Island Red chickens were found at, or in the vicinity of, many households but, since a large proportion of the cases lived in the more sparsely settled areas, this is probably to be expected. Practically every family had taken trips to nearby communities on motor rides, picnics, or visits to beaches.

Mosquitoes were unusually prevalent this summer because of heavy rains in July, and there is a universal history of mosquito bites. In a few cases, unusual reactions to such bites have been observed. This probably means that unusual varieties of mosquitoes were present this year since no local reactions due to the equine virus have as yet been described as occurring.

CLINICAL DESCRIPTION OF CASES *

The following summary gives the most common symptoms and signs which characterized the disease as seen at the Boston Children's Hospital and the Haynes Memorial Hospital. Cases occurring in other hospitals were similar in most details.

The onset in infants was sudden, with fever, irritability or drowsiness, cyanosis, and convulsions. In older children and in the one adult the symptoms were of slower onset, from 4 to 10 days. In 2 cases there was a definite remission of the symptoms lasting for 1 day. Headache, frontal in character, and dizziness were the first complaints in the older patients. In 2 infants diarrhea preceded the other symptoms, while vomiting occurred in half of the cases. All patients were semi-comatose to comatose on admission, and the majority showed continued tremors or muscular twitchings. Rigidity of the neck was a constant feature, as was a tense anterior fontanelle in the infants.

Evidences of an upper respiratory infection, *e.g.*, pharyngitis and otitis media simplex, were found in few of the cases. The suppression of the cutaneous reflexes was constant in the comatose patients, while the Kernig and kindred signs varied markedly. Facial palsies were seen in 3 cases, one of which had in addition a hemiplegia.

Outside of the fact that the pupils reacted sluggishly to light and one patient complained of photophobia, no abnormal eye findings were noted.

The temperature was invariably high, 102 to 104°, and in the fatal cases continued to rise. Where recovery took place the fever fell by lysis, becoming normal in 4 or 5 days.

The spinal fluid showed increased pressure, average 240 mm., hazy to ground-glass in appearance; the cell count varied from 200 to 2,000, of which 60–90 per cent were polys. Total protein was high, 95–185 mg.; sugar normal or slightly increased. Smears and cultures showed no organisms.

The blood showed the same polymorphonuclear response. The white count varied from 14,600 to 65,900, the percentage of polys from 75 to 90. The counts above 35,000 were in children who also had whooping cough.

When the patient lived over 2 or 3 days, there was a drop in both the spinal fluid and white blood counts, with a change to the mononuclear type of cell.

Convulsions and muscular twitchings marked the course of the disease. In the infants a peculiar edema developed about the eyes and in the upper extremities. Cyanosis was marked in all cases.

Deep coma from which the majority

* This summary was obtained from Dr. Charles F. McKhann and Dr. E. C. Smith.

of patients never aroused developed shortly after admission. When a patient survived the acute stage, coma and more or less rigidity of the muscles persisted for many days. An occasional patient showed gradual but slow improvement, returning apparently to normal.

Some cases suspected of being due to the virus have made complete recoveries, but it appears that certain other cases will show paralyses, mental changes, and other permanent residuals.

GROSS AND MICROSCOPIC PATHOLOGY *

Severe edema and congestion of the brain and cord, flattening of the convolutions and the formation of pressure cones in the cerebellum were conspicuous gross findings. On microscopic examination all parts of the brain showed some degree of involvement, with maximum changes in the brain stem. The lower cord was rarely involved except for edema and congestion. The anterior horn cells were spared.

The microscopic changes may be divided into several groups: (1) perivascular accumulations of large numbers of polymorphonuclear and large mononuclear cells; (2) diffuse slight infiltration of the meninges by the same types of cells; (3) numerous scattered focal areas of nerve cell destruction with infiltration by polymorphonuclear and microglial cells; and (4) small thrombi in vessels which often exhibited intramural degeneration and fibrin deposition.

The predominant type cell in the exudative response changed to the large mononuclear cell as the acute reaction subsided in cases where 6 to 20 days passed between the onset of important symptoms and death. After the longer duration of the disease, the perivascular infiltration and meningeal reaction almost disappeared, the areas of neuronophagia were less prominent, and the main picture became one of removal of debris and repair.

No bacteria were found by cultural methods or by histologic examination of the brain with the aid of appropriate stains in one patient who died 48 hours after the onset of symptoms.

Widespread congestion was present in the viscera. Numerous small thrombi were found on microscopic examination in many organs of the body. No bacteria could be demonstrated in relation to these thrombi. Severe pulmonary edema and congestion, probably secondary to the inflammatory process in the brain stem, were present in patients in whom no secondary bacterial infection could be demonstrated.

In summary, examination of the central nervous system demonstrated a severe, diffuse acute meningo-encephalitis, characterized chiefly by an intense polymorphonuclear and mononuclear cell infiltration in the perivascular spaces and to a minor degree in the meninges, and by widespread destruction of nerve cells.

DISCUSSION

As early as 1931, Meyer [5] suggested the possibility of humans contracting the equine disease. He noted in 3 individuals illnesses suspected of being due to the virus. The brief account of symptoms and findings in the fatal case is consistent with the clinical picture seen in the Massachusetts cases, particularly the finding of polymorphonuclears in the spinal fluid. The 8 cases in Massachusetts, however, are the first human infections definitely proved to be due to the equine virus. An entirely new public health problem has been opened up and the equine disease assumes an added importance.

The disease in the severer form is sufficiently different from the usual varieties of encephalitis to be recognized clinically. If some of the milder cases under investigation prove to be

* This summary was obtained from Dr. Sidney Farber.

due to the same virus, and particularly if the existence of subclinical infections can be established, the recognition of all cases will be difficult unless laboratory means of verifying the diagnosis can be found. A routine test within the scope of the public health laboratory would be invaluable. Whether the neutralization test or some similar procedure will be the solution is yet to be demonstrated.

A number of other problems in regard to the disease await elucidation. We need to know if other reservoirs beside the horse are important. In fact, Ten Broeck [12] and his coworkers suggest that the horse may not be the primary host, both because the disease is so highly fatal and because the virus disappears from the blood so early. Fothergill [13] has just isolated the eastern virus from a dead pigeon from an area where many pigeons have been dying this summer. It yet remains to be satisfactorily demonstrated that the mosquito transmits the natural infection among horses. The importance of other insects, especially the recently incriminated tick, as vectors of the disease awaits investigation.

The need of having all cases of encephalitis reported to health departments is emphasized by the presence of the equine infections in humans. The Massachusetts Department of Public Health has now made all cases of "Infectious Encephalitis" reportable instead of the former designation of "Encephalitis Lethargica."

SUMMARY

1. Eight cases of human encephalitis have been proved to be due to the eastern virus of equine encephalomyelitis.

2. The clinical picture and pathological findings in these cases appear to be sufficiently characteristic to make recognition of the disease possible.

3. While young children seem to be particularly vulnerable, adults are occasionally affected.

4. The case fatality appears to be high; 25 of the 38 cases under investigation died.

5. The attack rate among horses was low (3.5 per cent) but the case fatality was high (over 90 per cent).

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NOTE: Articles have been chosen partly because of detailed bibliographies.