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Psychosomatic therapy in cardiovascular disease

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EPIDEMIC ENCEPHALITIS

by

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HISTORY

Epidemic encephalitis is a general infectious disease which was first described as a triad of symptoms, somnolence, ophthalmoplegia, and profound asthenia by von Economo in Vienna in 1917. Gwyn (1921) states that the epidemiology of encephalitis is inextricably bound up with that of poliomyelitis and with that of cerebro-spinal meningitis and of all in turn has it been said that they preceded, accompanied or followed some more or less generalized febrile epidemic, influenza-like in its symptoms and character. An undoubted epidemiological relationship does exist, however, and in four hundred years of records of medical history there are to be found many interesting accounts of epidemic paralyses, stupors, and vague nervous disorder, occurring in more or less close connection with generalized waves of infections which are considered to have been influenza.

Realizing these points it seems better to come quietly down through the ages, to admit the many interesting associations of the many obscure affections of the nervous system with each other and with other epidemic disorders, but to reserve one's critical analysis for the age of more accurate observation.

One of the earliest writings on epidemic nervous disease was by Hippocrates. According to Crookshank (1920) he said, (quoting from Clifford's translation):

"During this state of the weather, in the winter, Paraplegias began and attacked many, some of whom dy'd in a short time, for the disease was epidemical." Wright (1927), however, states: "It is evident, however, to us that neither Hippocrates nor his French translator was familiar with the epidemic disease which has confronted us."

Riley (1930) writes that a similar syndrome was observed by Aretaeus and Galen and described under the title of phrenitis or causus. According to Wright (1927) lethargy arose from phlegm the same for Galen as it did for Hippocrates. If the disease was present in the Roman empire as a new disease, Galen failed to recognize it, and his works fail to describe it.

From this period up to the beginning of the sixteenth century very little was written about medicine. This period being known in history as the Dark Ages.

Beginning in the sixteen century or to be exact in 1529, the Germans ascribed some of the maleficent forms of the sudor Anglicus to the eating of fish; and in 1820, Justin Knerner, of Weinsberg, attributed outbreaks clinically identical with polioencephalitis to the eating of Swabian sausages; there by laying the myth of botulism. It was also the custom at this time in Germany to incriminate ergot or rye as the cause of

certain acute epidemic, and generally febrile maladies, exhibiting as their cardinal symptoms delirium or stupor, paralysis or convulsions or tremors, and interference with the special senses. At this same time the English were afflicted with a malady called the sweats. Stupor was a prominent symptom of the grave cases. Dr. Hamer has clearly shown the epidemiological features to be those of influenza. This disease was not confined to England, for each sweat in England there was a similar disease in every other European country. These can be demonstrated to be either influenza or encephalitis or both.

Schiller and others in Germany in 1529 gave contemporary accounts. The disease was of an extremely variable character, assuming different guises in different places; and it was of all grades of malignancy. Fever, convulsions, cranial nerve palsies, headache, and stupor were among the symptoms. In those people who escaped with their life, paralytic consequences of various kinds were noted (Crookshank 1920).

Crookshank (1920) states that there was a stuporous epidemic in Piedmont and Savoy described by Sander and by Ambroise Pare. Gwyn (1921) says that the epidemic stupor of 1543-6 and the head pain in Germany are put forward by some writers as encephalitic manifestations,

these conditions may have been almost anything. They seem at least to have existed apart from other epidemics; to call a disorder of 1557 an "avantcoureur" of the great influenza of 1580, is a kindness to history, it does service, however, in showing again that even if, "during the winter and at the beginning of spring there was a quantity innumerable of paralyses," that at least they seemed to have an independent existence.

The great influenza of 1580 was in some places so sudoral that many declared it the English sweat come back again. The next year, 1581, however, was marked at Luneburg in north Germany by an epidemic of palsies in the head and limbs.

1595 saw the "Krielblekrankheit" co-existing in Germany with epidemic catarrh (Gwyn 1921).

There is after 1600, a long, almost silent period in the history both of influenza and of all forms of encephalomyelitis. Then in the autumn of 1657-58 a strange fever appeared "whereby men were grievously affected in their brains and nervous stocks." An epidemic of lethargy was also present in Copenhagen at the same time (Crookshank 1920).

The European influenzas of 1674-75 were preceded or accompanied by epidemic psychoses in Sweden (1673) and the comatose fever of Sydenham (1673-75).

Shirley W. Wynne (1921) writes that there was in 1712 a well-defined outbreak of sleeping sickness in Germany, which was attributed to the eating of poisonous foods, and it is interesting to note that food poisoning was again advanced in the 1918 epidemic as the cause of the disease. Zueler (1920) stated that in an influenza epidemic at that time, profound sleep was so frequent and pronounced a symptom that in Tubingen the disease was called Schlafkrankheit. Camerarius spoke of it as "Somnolence with ophthalmoplegia."

Other epidemics occurred in 1729-33, 1741, and 1754. No large epidemics are recorded until the nineteenth century.

Chardel, of Paris, described cerebral fever, or primary inflammation of the brain as a definite entity. 1799 and 1800 was an influenza season. The world wide influenzal prevalences of 1800-03 was noted in Russia as extraordinarily cerebral. The same observation were made in Scandinavia and Italy. It was also reported in Hindostan by Crookshank (1920).

In 1824-26 epidemic influenza was severe in the United States. Phrenitis was diagnosed in a certain prison.

In Scandinavia and Russia, Raphania and epidemic psychoses prevailed throughout these years, while the

influenzas in the United States during 1842-42 had been preceded by an outbreak of infantile paralysis. Dunglinson noted the great increase of encephalitis everywhere at home and abroad (Crookshank 1920).

The last decade of the nineteenth century produced pandemic influenza. This was preceded by outbreaks of infantile paralysis in Sweden. It was also scattered diffusely in the mediterranean basin. It spread to Hungary, Germany, and France but not to America. Lonquet (1892) described the disease as "Nona." Minor waves of influenza followed the pandemic of 1889-90. These were accompanied by encephalitis throughout the world until 1895. Gordon (1919) reported that historical investigations show that in 1892, Henry of Switzerland, and Lonquet of France, described a comatose form of grippe which in every detail corresponded to encephalitis lethargica.

Epidemic Encephalitis was recognized, described, and named by von Economo in Vienna in the winterof 1916 (Boyd 1920). The disease seemed to develop simultaneously in France and Austria in 1916, although the war had interrupted all communication between them. The first case noted in England occurred in February, 1918 and during the following months about two hundred and thirty cases were reported in London and the provinces

(Hall 1918). In the United States the first cases were reported by Bassoe in the Journal of the American Medical Association of March 1, 1919. During that year localized epidemics of small proportions occurred in the larger centers, but in no case did the disease assume pandemic proportions. The first appearance of the disease in Winnepeg in the last week of October and during the succeeding weeks cases presented themselves almost every day (Boyd 1920).

In the late summer and early fall of 1924 there appeared an epidemic disese which differed clinically and epidemiologically from that seen in the United States and Europe. Its mortality was about sixty percent and was called Type B encephalitis. This type was limited to Japan and Formosa and was characterized by hyperkinesis rather than lethargy . Also there was a rarity of the postencephalitic Parkinsonian syndrome (Kaneko and Aoki 1929). Again in 1926 and 1929 similar epidemics took place (Matheson Commission, 1929).

There was also an outbreak of lethargic encephalitis in England, particularly around Sheffield, in the late summer months of 1924 (Wynne, 1926).

In the Summer of 1933, there occurred an acute epidemic disease with mental symptoms. In this disease

the patients either died rapidly or became well in a short time with no sequelae. This disease started in St. Louis and Kansas City, Missouri (Bredeck, 1933).

ETIOLOGY

The earliest cases of the disease were described in England by Dr. Arthur J. Hall (1918) and by Dr. Wilfred Harris (1918). Dr. Harris called attention to certain points of similarity in his cases to the clinical picture of "botulism." In consequence of this the Medical Research Committee (quoted in the Matheson Report, 1929) undertook at once a complete bacteriological investigation, in cooperation with medical practitioners and medical officers of health. The study included not only a consideration of "botulism"; it also covered the question infection or poisoning from food stuffs--including the absence from the food of some essential element--or toxic agents, such as benzene used in the manufacture of oleomargarine and solanine in undue concentration in potatoes; also researches upon lathyrism, as well as upon pellagra, beriberi and other deficiency diseases.

The results of the inquiry are summarized as follows: "First, on the bacteriological side, Dr. McIntosh, of the London Hospital, who was appointed to carry out the on behalf of the medical Research Committee, failed entirely to recover the Bacillus botulinus from tissues and fluids of fatal cases and from articles of food which had been regarded with suspicion; he failed also to obtain evidence that serum from recovered patients agglutinated this bacillus or protected mice from the

effects of its toxin; and he found microscopical evidence of changes in the nervous system which pointed to an acute infective disease, rather than to an intoxication. Secondly, on the epidemiological side the enquiries by Drs. Hancock and Pearse showed that among the 58 cases investigated up to May 7th there was no instance of more than one case in a household; that many of the patients had not eaten any food which might reasonably be regarded with suspicion; that in instances in which patients had eaten such foods it was almost invariably without ill effect; and finally, that in at least two cases the patients attacked were infants exclusively breast-fed.

The spread of the disease to so many nations with such varying dietary habits speaks strongly against such a theory.

Veillard in 1929 (quoting from Matheson's Commission 1932) still maintains that epidemic encephalitis is due to an alimentary intoxication caused by beans, corn, or peas. He states that these foods produce phenol-acetone and hydrocyanic acid. The action of the "radicicola bacillus" is considered to play a part in the evolution of these poisons.

The relationship of encephalitis to influenza is still an unsettled question. Neal (1919) found a history of an attack of influenza in 27 of 40 of her patients.

Crookshank (1920) traced many instances of encephalitis, most of them following shortly after major "influenzal epidemics" and concluded: "Epidemic meningo-encephalo-myelitis represents an intensified and specialized reaction that has the same epidemiological relation to pandemic influenza as have the prevalences and epidemics of septic pneumonia, of gastro-intestinal illness, and of other maladies described as occurring before and after the wide diffusions generally referred to as pandemic influenza.

Boyd (1920) states that, "the geographical distribution and general epidemic behavior of this disease are baffling to a degree. In distinction to influenza which swept across Europe with express trains, crossing the Atlantic with fast liners, and wandered through Asia with camel caravans, epidemic encephalitis appears now here, now there, descending on the startled community like a bolt from the blue. In this it bears a close resemblance to poliomyelitis. The explanation in both cases is probably the same, namely, that the abortive cases and carriers greatly exceed in number the typical examples of the disease, so that the infection is much more widely distributed than might be suspected." He also says, "that the champions of the theory, that there is a direct relationship between the incidence of influenza and that

of epidemic encephalitis, can marshal an array of facts in support of their contention which at first sight are very convincing. They use historical argument. Previous outbreaks of what has been called sleeping sickness have usually followed or accompanied epidemics of influenza. The outbreak of sleeping sickness which occurred in Tubingen in 1712 was associated with an influenzal epidemic at the same time. The mysterious condition called nona, characterized by profound lethargy and drowsiness followed on the great flu epidemic of 1890. The recent outbreaks in Austria, France, England, and America were all associated more or less closely with the influenza epidemic. Further many cases of influenza are marked by great lethargy."

"These spacious arguments fall to the ground, however, on closer inspection. Darwin's warning that analogy is a deceitful guide is necessary now as on the day he uttered it. To say that the present epidemic has followed the influenzal epidemic has about as much value from the point of view of proof as to say that they followed the Great War. The prolonged sleep occasionally associated with influenza is very different from the condition of encephalitis lethargica. In none of these cases has the characteristic lesion in the brain been demonstrated. The present outbreak is a year since influenza visited

the city, and not one of the cases had had a recent attack. Indeed in a majority of the cases there was no history at all of influenza."

Alamasio (1921) gives charts which show the flaring up in Turin of an epidemic of influenza and the nearly parallel curve of epidemic encephalitis, a total of 138 cases of the latter and 1,058 of influenza.

Hurst (1934) states that the Public Health study shows a disparity between influenza and epidemic encephalitis as regards the age groups attacked. In epidemic encephalitis the percentage of the cases in the age-group 10-39 years is below the percentage of the total population in these age periods whereas in influenza the percentage of cases is above the population in these age-groups. In 1929 there was 44,000 cases weekly of influenza and 18 of encephalitis. In 1928 there was 85,000 cases of influenza and 30 of encephalitis.

An early theory was that encephalitis lethargica was caused by the same organism that caused the disease poliomyelitis. An investigation of this was undertaken by the Ministry of Health (quoted in Matheson's Commission Report, 1929). Professor G. Marinesco made a histological study of specimens from fatal cases, and Dr. McIntosh carried out both histological studies and inoculation of animals. They both agree that their

research supported the clinical and epidemiological evidence that the two diseases were not identical.

Tilney and Howe (1920) say that the greatest difference between the two diseases is in the nature of the action of the virus on the nerve elements. "In poliomyelitis there is a sudden, sharp attack which develops rapidly and in a few days attains the maximum of severity, quickly producing the greatest extent of destruction. In epidemic encephalitis the onset is frequently very gradual and the progress of the disease slow, in some instances requiring several months to reach its greatest severity, and even then the findings have a tendency to variability, being subject to exacerbations and remissions."

Amoss (1921) made a most important point in demonstrating that serum from convalescent cases of epidemic encephalitis had no immunizing power for poliomyelitis virus.

Levaditi (1929) found that his herpeticoencephalitis virus did not actively immunize monkeys against poliomyelitis virus and vice versa. Furthermore, poliomyelitis virus while virulent for the monkey, rarely infects the rabbit; the encephalitis virus is very pathogenic for the rabbit.

Boyd (1920) points out that the resemblance be-

tween poliomyelitis and lethargic encephalitis are many and close. Poliomyelitis is a disease which in its typical form attacks the gray matter of the anterior horns of the cord, while in lethargic encephalitis the brunt of the attack falls on the gray matter of the brain stem, especially the nuclei of the third, fourth, and sixth nerves. Both diseases are acute in onset, febrile in nature and motor in their manifestations. A closer scrutiny reveals points of similarity of even greater importance. Very similar changes may be found in the brain in both diseases. There is also an encephalitic type of poliomyelitis. This may occur with spinal paralysis or may occur alone. Facial paralysis occurs eight out of twelve times and ocular palsies were present in four cases. Four cases were extremely lethargic. In a series of four hundred cases Batten found that 12 percent showed evidence of encephalitis involving the medulla, pons, or mid brain. Following are some of the arguments against the relationship of poliomyelitis to lethargic encephalitis:

1. Epidemics of poliomyelitis occur with remarkable constancy in the summer time, the outbreaks of encephalitis have occurred during the winter months.

2. Poliomyelitis is a disease par excellence of children; encephalitis is much more common among adults.

3. The onset of paralysis of poliomyelitis is sudden, the effects are lasting, and there is usually muscular atrophy; in encephalitis the palsies often come gradually, are characteristically fleeting, and there is no muscular atrophy.

4. Although the virus of poliomyelitis in introduced intracerebrally in monkeys, the lesions produced are always spinal, never cerebral.

5. Leukocytosis is sometimes as high as 30,000 per cubic millimeter in poliomyelitis while in encephalitis it is usually normal or only slightly raised.

Webster, Fite, Clow and Muench (1935) and Brodie (1934) by crossprotection test against the poliomyelitis virus have shown the St. Louis type of encephalitis virus to be immunologically distinct.

Bacterial Etiology

Von Wiesner in 1917 (quoting from the Matheson's Commission Report, 1929) reported that he had found in the brains of fatal cases of epidemic encephalitis a diplostreptococcus, which both he and von Economo believed for a time to be the cause of epidemic encephalitis. An emulsion of the brain injected intracerebrally in a monkey produced symptoms in a few hours and death in forty-six hours. This was Gram positive, grew well in bouillon containing glucose and later, on agar with no hemolysis

Von economo agreed with von Wiesner in 1920 but in 1923 he stated that he no longer believed that the diplostreptococcus was the cause of epidemic encephalitis.

Van Boeckel, Bessemans and Nelis in 1923 found the same organism in the brains of normal rabbits, especially when the material was not entirely fresh, and concluded that it was a secondary invader.

Stafford (1919) found in two spinal fluids from a case of epidemic encephalitis a diplostreptococcus which did not hemolyze blood or produce a greenish zone.

Maggiore and Sindoni (1921) isolated from the blood and spinal fluid of five patients with different types of epidemic encephalitis a gram negative coccus with which they reproduced the disease in rabbits by intracranial injection of a patient's spinal fluid or intravenous injection of a culture of the coccus. Repeated passages through animals reproduced invariably the same clinical picture and pathologic findings.

Rosenow (1924) isolated streptococci from the nasal secretion of patients having epidemic encephalitis. These he believed to be the primary agents in the production of encephalitis.

Evans and Freeman (1926) succeeded in isolating a pleomorphic streptococcus which they found to be highly virulent when injected intracerebrally in rabbits.

This organism was obtained from nasal washings, heart blood, and from emulsions of the mesencephalon of one fatal case of epidemic encephalitis. It could be isolated and grown only in a special beef infusion medium containing ground meat particles, used under anaerobic conditions. In its diplococcus form it corresponded morphologically with the streptococci obtained by von Wiesner, Rosenow and several others.

Oblitsky and Long (1928) found that they could recover streptococci not only from the brains of animals inoculated with the herpetic viruses but also from the brains of control animals receiving noninfectious material intracerebrally. They concluded that the streptococci were not visible forms of the herpes virus.

Rosenow (1924) stated that bacteria obtained from lethargic patients, produced lethargic rabbits; those from maniacal patients produced maniacal rabbits. The organisms were recoverable in pure culture from the brains of these animals. He claimed that not only the symptomatology but also the localization of the lesions in the brain varied with the strain of the organism, the basal ganglia being most frequently involved with strains from Parkinsonian patients; the cortical and subcortical regions with strains from myoclonic encephalitis; and the anterior part of the medulla with strains from

cases of respiratory arrhythmias.

In 1933 Rosenow reported the isolation from material from cases of encephalitis in the St. Louis epidemic, of a streptococcus similar to those strains previously isolated and virulent for rabbits. He says that in 100 percent of human cases, heat-killed streptococci cultured from the spinal fluids of active cases, produced a strongly positive skin test.

McKinley (1930) reported the isolation from the tonsils and nasopharynx of healthy persons, who had not contacted cases of encephalitis, a green-producing streptococcus, positively agglutinated by Rosenow's antiserum for encephalitis and producing in rabbits exactly the same clinical and pathological picture as obtained by Rosenow.

Rosenow (1942) found that he could isolate streptococci from the spinal fluid of encephalitic patients in North Dakota and Minnesota. These could be grown consistently on brain media. On intracerebral injection with highly diluted serum from 1:10,000 to 1:1,000,000 the characteristic symptoms could be elicited. A specific precipitation reaction was consistently obtained between cleared extracts of nasopharyngeal swabbings and human and equine antistreptococcic sera and three commercial preparations of antiserum produced with the

western strain of equine encephalomyelitis virus. These same organisms were isolated from the blood and nares of horse, brains of sheep, a dog, a hog, a chicken, a goose and a pheasant which were ill or had died of symptoms of encephalitis in the epidemic zone. It was isolated from the brains and spinal fluid of wild ducks and fish. Also found consistently from flies and mosquitoes, from milk, from water of wells, and from the air of rooms occupied by persons or stalls occupied by horses ill with this disease.

Rosenow's work, however, by no means receives general acceptance. Especially is his claim of successful treatment of patients with hyperimmune serum, prepared by inoculation horses with his streptococci, discounted.

Filtrable virus

Bradford (1919) was one of the earliest investigators who published an article describing a minute, filter passing organism, cultured in Noguchi's tissue media, from the blood, spinal fluid, central nervous system and lymphatic glands of patients with encephalitis, and also from the brain of monkeys inoculated intracerebrally with an emulsion of the human brain. The organism remained viable for some months in 50 percent glycerin. Strauss, Hirshfeld and Loewe of New York (1919) inoculated an emulsion of the brain of patients dying

from epidemic encephalitis into the brain of a monkey. These produced the typical lesion of encephalitis in the monkey brain. A filtrable virus from the nasopharyngeal washing also when injected intracerebrally caused the characteristic lesions in the brain of the monkey.

McIntosh and Turnbull (1920) isolated a virus from the brain of a fatal case of epidemic encephalitis which produced the disease in a monkey when injected intracerebrally.

Strauss, and Loewe (1920) obtained cultures with 50 percent of spinal fluids; and with 66 percent of Berkefeld filtrates of nasopharyngeal washings; in seven out of ten instances with Berkefeld filtrates of nasopharyngeal mucous membrane from fatal cases. Positive cultures were obtained in 85 percent and 66 percent respectively from the brains of monkeys and rabbits that had been successfully inoculated.

Many investigators have described viruses which display the ability not only to produce encephalitis in animals, but also to give typical herpetic lesions on inoculation into the skin or cornea. These viruses, grouped together as the herpetico-encephalitis group; all are related immunologically not only to each other but also to the herpes virus, are of great importance in relation to the question of the etiology of epidemic

encephalitis (Matheson Commission, 1929).

The true herpes virus, present in the fluid from typical herpetic lesions of the skin, has been demonstrated to be filtrable, sterile in culture, infective for most of the small laboratory animals, whether inoculated intradermally or intracerebrally, producing in the first case typical herpetic lesions, and in the second an encephalitis with symptoms and lesions very like those produced by the encephalitis virus. They report no neutralization of the herpes virus by human encephalitis convalescent serum. Flexner and Amoss (1929) considers this virus separate from that causing human epidemic encephalitis because they were unable to neutralize either the herpes virus or the herpetico-encephalitis strain with human convalescent serum, although they isolated from a fresh lesion of herpes febrilis, a virus which displayed a remarkable degree of neurotropism.

Gay and Holden (1929) say that lethargic encephalitis may well be caused by a neurotropic strain of the virus of herpes simplex. Their studies are based on examination of a very strongly neurotropic herpes virus, the Le Fevre virus. It is without demonstrable dermotropic properties. They find the ideal method of producing active immunity in rabbits and guinea-pigs lies in provoking an herpetic eruption with a less neurotropic

but dermotrophic virus. A virucidal antibody is produced which can be easily demonstrated in the serum of the animal; it gives generalized immunity against both the dermotropic virus and also against the strongly neurotropic virus.

Perdrau (1925) showed that in rabbits immunologically identical strains of herpes virus vary in their relative dermotropism and neurotropism. The virus of herpes simplex produces in rabbits brain and skin lesions which resemble brain and skin lesion of encephalitis and herpes in man.

Zinsser (1929) produced a disease in the Cebus monkeys which resembled the human disease of acute lethargic encephalitis by introducing the virus of herpes simplex intracerebrally. He concludes that encephalitis might be due to the development of neurotropism by a number of different filtrable agents including herpes as "occasionally responsible."

Gay and Holden (1933) give their argument in favor of the herpetic origin of encephalitis as: (1) The virus of herpes simplex produces in many animals skin and brain infections which respectively compare to herpes and epidemic encephalitis in man. (2) A subacute disease clinically human encephalitis has been produced in the Cebus monkey by Zinnser. (3) Pathologically the lesions are similar.

(4) There is evidence that the naturally occurring antibodies active against the herpes virus and present in human beings suffer fluctuation both in herpes and in encephalitis in man that suggest a causal relationship of both diseases to herpes virus. (5) Both herpes simplex and epidemic encephalitis belong to the exceptional group of virus diseases (approximately 10 percent in which recovery does not give lasting protection).

Against the herpetic origin of encephalitis: (1) The herpes virus has rarely been isolated from cases of epidemic encephalitis. (2) Herpes is a common infection whereas encephalitis is rare. (3) Herpes accompanies epidemic encephalitis less frequently than does many other diseases.

Webster and Fite (1933) disclosed a virus from the intracerebral inoculation of special mice with brain tissue from fatal cases of encephalitis occurring in Kansas City and St. Louis during August and September 1933. The mice employed had been previously proven to be susceptible to an infectious encephalitis of sheep. The brains from the dead mice were removed and cultured and found sterile. Injected into two white face and two Swiss mice. In each case the mice remained well for three days and were dead by the fifth day. This procedure was kept up for fifteen passages. They also

showed that when the mouse brain virus was instilled intranasally in 0.03 cc. quantities, fatal signs developed practically 100 percent of the time.

Webster and Fite (1933) injected 1cc. of mouse brain culture into the Macacus Rhesus monkey intracerebrally. They showed significant elevations of temperature in seven to nine days. Apathy or hyperirritability followed. This condition was induced regularly for four monkey passages. Blood and spinal fluid drawn from the monkeys during the febrile period and injected intranasally into mice had no effect.

The characteristics of the virus was described by Muckenfuss, Armstrong, and Webster in the Journal of the American Medical Association in 1934. These were: (1) Usually active on intracranial inoculation of 1:1,000,000 into the mouse brain. (2) Readily filtrable. (3) Size 22-33 millimicrons. (4) Virus neutralized by serum of individuals convalescent from encephalitis in the 1933 outbreak and is not neutralized by the serum of normal individuals from uninfected areas. (5) Mice inoculated subcutaneously or intraperitoneally do not develop encephalitis but become immune.

Webster and Clow (1936) reported that virus dropped in the nose is demonstrated in the olfactory bulbs in 24 hours, in piriform lobes in 24-48 hours, and in the

remainder of the brain in 3 days, and in the spinal cord in 4 days. The virus was not found in the blood, but was present in the spleen in 48 hours.

Webster (1938) states the St. Louis encephalitis virus is immunological distinct from the Japanese B encephalitis virus. They are not neutralizedby the others convalescent serum. Japanese encephalitis virus produced reaction in animal species readily distinguished from those produced by the St. Louis type. It prove innocuous in rabbits and guinea pigs but induced a fatal encephalitis in mice, monkeys, and sheep.

EPIDEMIOLOGY

Season: The classical epidemic encephalitis of von Economo is a disease of the winter months. The highest incidence was found in February and March (League of Nations Report, 1936).

Iimura in 1936 (quoting from the Matheson Commission's Report 1939) states that the outbreaks of Japanese B encephalitis are usually sharply limited to late summer and fall. The peak was always in August or September.

In the later epidemics as found in St. Louis, Australia, and Japan the seasonal incidence has become less marked. These are most common in the late summer and early fall months. This is also the most common season for poliomyelitis.

Distribution: This disease is found most commonly in the temperate zones. There are, however rare sporadic cases in tropical countries. Also there has been eighty-one cases reported in Iceland in the last ten years. Japanese B encephalitis is confined to Japan and Formosa.

Age: Epidemic encephalitis may occur at any age; however it is most common between the age groups of twenty and fifty (Wechsler 1921)

	Below 5	6-10	11-20	21-30	31-40	41-50	51-60	61-70	Over 70	Total
No.	13	37	136	222	215	140	72	23	6	864
%	1.5	4	15.7	25.7	25	16.2	8.3	2.8	0.7	100

Cases have been found in children four weeks old.

Boyd (1920) reports the age incidence between twelve weeks and fifty years in the Winnepeg epidemic.

In the St. Louis epidemic the age incidence was much the same.

Age Incidence (1931-37) in New York City

Age group	1931	1932	1933	1934	1935	1936	1937	Total
Under 1	0	2	1	1	0	1	1	6
1-4	11	3	5	5	4	4	5	37
5-9	14	7	10	3	15	2	10	61
10-14	12	6	9	5	5	4	7	48
15-19	9	1	5	5	7	4	6	37
20-24	5	5	4	5	4	1	5	29
25-44	21	19	33	17	18	9	17	134
45-64	22	10	18	9	9	10	3	81
65 & over	3	4	1	1	1	7	2	19
Total	95	57	86	51	69	37	55	452

From the State of New York, Department of Health
Matheson Commission Report 1939

The League of Nations Epidemiological Report (1934) shows that in the epidemic of 1933-34 the maximum morbidity was found in the age group between five and ten years. There was a high morbidity in the ten to forty year age group. There is a decrease in morbidity after this time. The death rate is just reversed being the highest is from forty on and the lowest around five years.

Age Group	Cases per 100,000	Deaths per 100,000	Case fatality
0 - 9 yrs.	54	4	8%
10-19 "	64	3	5%
20-29 "	68	3	4%
30-39 "	73	6	8%
40-49 "	119	14	12%
50-59 "	169	36	21%
60-69 "	285	109	36%
70-79 "	364	204	56%
80-89 "	419	335	80%

Leake, Musson, Chope 1934

This table prepared by Leake, Musson, and Chope shows a striking increase in incidence with age, and an even more notable increase in the fatality with age.

Kaneko and Aoki in 1928 (quoting from the Matheson Commission Report 1929) commented on the increase in incidence with age. This has been a prominent feature in all epidemics in Japan. The morbidity is markedly higher in subjects over fifty years of age.

Sex: The majority of the reports of epidemic encephalitis show that more males are affected than females. Wechsler (1921) states that of 864 cases in the United States and Canada 522 were males while 342 were females giving a ratio of three to two. Neal (1919) reports

that thirty-three out of forty cases were males. She also reports that Tucker had nine males in eleven cases.

In the Sheffield Epidemic in 1924 of 301 cases 176 or 58.4 percent were males while 125 or 41.6 percent were females. Here the mortality was 14.77 percent for males and 15.08 percent for females.

Iimura in 1936 ascertained the sex in 10,952 cases reported from 1924 to 1933 in Japan. Of this number 55.6 percent were males and 44.4 percent were females.

In the St. Louis epidemic Leake, Musson and Chope (1934) report that the incidence in both males and females were about equal. The percentage for males was 50.9 percent and 49.1 percent for females, however, between 1931 to 1937 the number was much closer being 235 males and 217 females.

Race: There are no reports on epidemic encephalitis in 1918 about racial characteristics, however in St. Louis in 1933 it was found that a greater percentage of whites were affected than negroes. In Tucker's cases in Illinois 2 percent were in negroes although they constituted 4.3 percent of the population. Also the incidence of encephalitis seemed to be markedly higher in the Jews in Poland and Russia than in other people. They also showed a higher mortality rate because of the larger groups of

children and aged people (Matheson Commission 1939).

Occupation: The occupation or social status must not have mattered much in the epidemic of 1918 because no mention was made of it.

Houston in 1932 (quoting from Matheson Commission's Report 1939) states that neither economic status nor occupation is a factor in the St Louis type of encephalitis. Wechler (1929) showed that in 864 cases the incidence was about eighteen times as high among physicians as among the average population. This is for the number of physicians as compared to the number of people. He explained this because of their exposure. He also showed that 55 percent of the people were foreign born. The native population greatly exceeds the foreign born. This would indicate that foreign born in the United States are more susceptible than native Americans.

Inada in 1938 (quoting from Matheson Commission's Report 1939) says that all social classes are equally affected.

Communicability: "The rarity of any evidence of contagion has been noted in every country in which the disease had occurred,"(Hall 1924). Roger (1921) estimated that there has been 10,000 cases in France, yet nowhere has there been a true epidemic; the cases occur in distant quarters, withoutit being possible, usually,

to distinguish any link between the persons affected. In only 174 cases could direct contagion be determined.

Claude and de Laulerie in 1921 (quoting from Matheson Commission Report 1929) report the case of a man in the hospital for seven months who developed epidemic encephalitis,unmistakably a case of hospital infection. There had been five cases in the hospital but the last one had been seven months before the man developed his symptoms. They also tell of a girl of seventeen who developed encephalitis a month after she entered. In this same article Halle reported the death of an infant with symptoms suggesting possible epidemic encephalitis ten days after the mother had presented the same.

Mac Nalty (1925) reports three brothers who developed the disease, one after the other, over a period of three weeks. The incubation period in these cases of familial incidence varied from ten days to several months.

Godfrey and Gwyn (1922) reported the case of a nurse who contracted the disease five days after she started nursing a patient with epidemic encephalitis.

Wechsler (1929) could find only five instances in 864 cases. This gives only a little over 0.5 percent in which the disease occurred in two member of one family.

In 1931 a case is recorded of a newborn infant with onset of symptoms on 5 th day and death on the 11 th day. Autopsy showed true congenital epidemic encephalitis. The mother had had a severe case of influenza three days before delivery.

Stewart (1934) writes of a group of seven children with character defects typical of post encephalitic behavior disorders. The symptoms apparently existed from time of birth. Six had organic signs of epidemic encephalitis sequelae. All the mothers had had influenza in the latter months of pregnancy. No mother had symptoms of encephalitis.

Leake, Musson, and Chope (1934) reported that in St. Louis epidemic there was a noticeable freedom of multiple cases in the same family or from obvious contagion between cases. It seemed that the disease picked on the weakest people, even those out of contact with the outside. They also report that there was no instance of two attacks in the same individual and people who had had an attack of poliomyelitis, even within the last two years were not spared the disease.

Lepine in 1921 (quoting from the Matheson commission's Report 1929) observed that in all of his fifty cases a predisposing factor could be distinguished. Excessive physical or emotional strain, a constitutional nervous

or mental taint, a tendency to migraine, or the onset or conclusion of the genital phase of a women's life. A peculiar predisposition to the disease was found in pregnancy.

Incubation period: The incubation period of the disease was determined by Godfrey and Gwyn (1922) as around five days. They cite the case of a nurse who became infected five days after she had started taking care of a patient with epidemic encephalitis. Mac Nalty (1925) states that in his experience the incubation period varied from ten days to several months.

Leake, Musson, and Chope (1934) in determining the incubation period found that people who entered the St. Louis area uninfected developed the symptoms usually between twelve and twenty-one days. People who left the area and then developed the disease had usually been gone from four to fourteen days. From the above figures they state that the incubation period was from nine to fourteen days.

Bashford (1919) injected two monkeys with a drop of emulsion of brain in saline, and the other with a fourteen days growth of a subculture prepared from the brain. Eleven days later the first monkey developed symptoms and thirteen days later the second monkey developed symptoms of lethargic encephalitis. He con-

cluded that the incubation period was probably between eleven and thirteen days.

Kling, Davide, and Liljenquist (1922) though the incubation period was fairly long. They injected rabbits with brain substance from encephalitic patients and with nasopharyngeal secretions and it took from one to three months for symptoms to develop.

Webster and Fite (1923) found that mice, inoculated with brain tissue from a fatal case of St. Louis encephalitis, developed symptoms and died in six to nine days. Also the virus was instilled intranasally and fatal signs developed one hundred percent of the time in ten days. Symptoms began about the fifth to sixth day.

Transmission: Bredeck (1933) says that in the first place water was excluded because there were two separate water supplies in St. Louis County, both of which areas were equally involved in the epidemic.

Leake (1933) stated much the same opinion as Bredeck but added the Kirkwood cases. These were investigated and found to have a water supply entirely different from both St. Louis City and County, and here the incidence of the disease was even slightly higher than in the remainder of the county.

Bredeck (1933) writes that milk and food transmission

are ruled out by the fact that on home investigation there was no common sources of food and milk.

The occurrence of the 1918 epidemic ruled out the possibility of insect vectors such as flies and mosquitoes; however in the St. Louis epidemic occurred during the warm season of the year and insect vectors could not be ruled out so easily.

In the Journal of the American Medical Association (April 23, 1921) the remark is made that the resistance of the virus is demonstrated by the long duration of the disease, the frequency of relapses and the evidence that certain persons may transmit the disease several months or years after its first onset, and that healthy people may be carriers. The secretions of the mouth and nose seem to be the vehicle of contagion which suggests the possibility of infection by clothing, etc.

Leake (1934) states that everything except the mosquito was ruled out because an insect with an especially long range of light was needed for the rapid spread of the disease. All tests were negative by the United States Public Health Service at this time on monkeys, mice and state convicts.

Webster, Clow, and Bauer (1935) make these statements that viruses injected directly into the blood stream are relatively harmless. Mosquitoes fed directly on human

cases ill with encephalitis and then allowed to bite humans failed to transmit the disease. They found that samples of mosquitoes tested within four hours of feeding on infected mice contained demonstrable virus. Two to fifteen days later these mosquitoes show less virus than in the first sample. Samples tested in twenty-five days showed virus present in amounts approximately equal to but not exceeding the titre of the original sample. They also found that mosquitoes which had fed on infected mice and then allowed to feed on normal mice and monkeys at various intervals failed to transmit the disease or develop an immunity or serum neutralizing substance against the virus.

Direct transmission by human agents is about ruled out by the lack of obvious contagion between cases and the infrequency of the occurrence of more than one case in a family.

Leake (1934) states that between communities the spread was obviously by human contagion, chiefly through the medium of healthy carriers. It was felt again in 1937 that this was the method of spread.

As regards to type of spread, several investigators though it through the respiratory system. Rosenow (1922) caused the disease by inoculating the nasopharyngeal washing of a patient ill with epidemic encephalitis into

a monkey. Later Webster (1938) and many others including McCordock, Smith, and Moore got the same results.

Immunity: There was not much said about immunity in the lethargic encephalitic epidemic of 1918. There were no cases mentioned, however, which had contracted the disease twice, and as rare as it was for multiple infections in a family it makes one think that maybe there is an immunity built up by exposure to the disease. People knew that it was possible to protect mice from a lethal dose of encephalitic virus by first building up their antibody titre by small injections of the virus.

In the Japanese B encephalitic epidemic having the disease did not absolutely protect the individual from a second attack. There are a few cases on record in which the individual had the disease twice (Matheson Commission 1939).

In the St. Louis epidemic there are no cases on record of the person having the disease twice.

Webster and Fite(1934) found that susceptible mice when given intraperitoneally or subcutaneously injection of 1,000 lethal doses of virus remained well. Within seven days, however, they were found to have developed a high grade immunity, so that they resisted 1,000 intranasal or 1,000,000 intracerebral doses. Webster also found that these susceptible mice when

immunized by these methods only kept the immunity for four to eight weeks. After this it gradually decreased until by twelve weeks it had practically disappeared. He also found that more than 1,000 intracerebral doses of virus given as a vaccine do not materially increase the amount or duration immunity. Less than 1,000 doses give little or no immunity. The test virus injected intracerebrally into immunized mice induces few lesions and is rapidly destroyed; instilled intranasally, it rarely reaches the olfactory lobes or the brain. While immunity is maximum, circulating antibodies are not detectable. Moreover, the immunity is not affected by endothelial cell blockade, or by splenectomy. It was found that a few moments after the immunizing virus is given, it can be recovered from the blood in relatively high concentration. After twenty-four hours the blood no longer contains demonstrable virus nor do any of the organs except the spleen. The spleen, however, becomes enlarged and harbors the virus for as long as thirty days.

Webster and Fite(1933) found that the virus was neutralized by serum of an individual convalescent from encephalitis and is not nertralized by serum of normal individuals from uninfected areas. Wooley and Armstrong (1934) reports that of 129 sera from patients with a clinical diagnosis of "encphalitic epidemica," pre-

sumably of the St. Louis type, positive protection test were obtained in 85 cases or 65.8 percent.

Webster, Fite, and Clow (1934) carried out a series of protective tests. Those who had had the disease showed 82.5 percent protective qualities while 66 percent of the sera from other tested people though had the disease likewise had protective power.

The conclusion has been drawn by Muckenfuss, Smadel and Moor (1938) that protective antibodies against the St. Louis virus, as demonstrated by the nertralization tests, are highly specific and result from exposure to the virus.

Wooley and Armstrong (1934) examined sera from fifty-six normal encephalitic contacts in St. Louis. Of these twenty or 35.7 percent had serum with protective antibodies in contrast to eleven or 9.7 percent of 113 cases with no history of contact.

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