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Epidemic encephalitis: etiology and new epidemics

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EPIDEMIC ENCEPHALITIS

ETIOLOGY AND NEW EPIDEMICS

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HISTORY OF ENCEPHALITIS

There are few diseases that are new; rather, there are diseases newly recognized. Whether encephalitis began in 1917 in Vienna or has been present for centuries may never be known. However there has been epidemic and sporadic examples in the past of a disease or diseases with symptoms very characteristic of our present day epidemic disease. But how can we say that the epidemics with cerebral symptoms of the past are identical with those of the present when we are uncertain about the close relationship of the present epidemics?

Medical historians give interesting evidence of diseases with symptoms not much unlike the epidemic disease of today. Crookshank (1920) gives this quotation from Hippocrates "During this state of the weather, in the winter, paraplegias began and attacked many, some of whom died in a short time, for the disease was very epidemical. In other respects they were well". Wright (1927) on the other hand says that "it is evident to us that neither Hippocrates nor his French translator was familiar with the epidemic which has confronted us". However Wright believes that Galen must have seen cases like our encephalitis lethargica. Galen and his contemporaries observed combinations of lethargy and "phrenitis" (characterized by delerium and positive motor symptoms). This combination is quite common especially in cases within the last decade (Boyd 1924).

Wright gives some curious sentences from Caelius Aurelianus, a contemporary of Galen. "Lethargy is more serious than phrenitis". "Phrenetics frequently lapse into lethargy - - no more infrequent that lethargy is converted into phrenitis." "But this is not sleep, it is an obeyance, an impediment to all natural functions, it is an oppression which in no

way refreshes the patient, but rather depresses him." Caelius Aurelianus describes many symptoms very characteristic of our own presnet cases.

Crookshank (1920) believes that the disease has prevailed for centuries. "In great part these occurrences have been noted as incidental to major prevalences known historically as the sweating sicknesses, the epidemic catarrhs, or influenzas and the like".

Riley (1930) mentions Aretaeus and Galen as describing a syndrome similar to epidemic encephalitis. Riley follows the history up to the present. In 1521 there was described a similar syndrome under the name of mendorr or mordorillo by De Sousa in Lisbon; In 1561 the "pestilence soporeuse by Amatus in Italy; in 1695 lethargy with ocular palsies by Albrecht in Germany; in 1912 "Somnolence with ophthalmoplegia" by Camerarius of Tubingen; in 1768 "coma somnolentum" by Lepecq dela Cloture in France; in 1835 cases of catarrhal fever with somnolence reported by Ozanam who also reported cases as having occurred in Germany in 1745, in Lyon in 1800, in Milan 1802; in 1892 an epidemic in Italy, Swetzerland, Dalmatia and Hungary described under the title of "nona" or "malattia de la nona" by Longuet also by Leichtenstern and later referred to by von Economo.

In 1917 von Economa described cases under the name encephalitis lethargica. Sonn cases became recognized in France and England, described in France by Cruchet and in England by Hall and Wilson. (Hall 1918, 1923)

By the fall of 1918 reports of cases in the United States appeared. Between September, 1918 and May, 1919 Smith (1921) collected 178 cases of epidemic encephalitis from nine states.

Neal (1933) who is secretary of the Matheson commission finds the first cases of epidemic encephalitis occurring in the spring of 1915 in Bucarest, Rumania and described as hemorrhagic encephalitis.

GENERAL ETIOLOGIC FACTORS

Because of the epidemic nature of this disease the causative agent is gamerally assumed to be a living virus or organism. There is no evidence to support an old theory of food poisoning such as botulism being the etiologic factor. (Hall 1923)

Although the disease is usually seen in epidemic form it is very difficult to trace the source of infection. This is probably due to the existence of many carriers (Zinsser 1928). Bernard and Renault say that from January to May 1920 although there were more than 400 cases in France there was not one case of direct contagion. Smith (1921) finds no secondary cases in immediate families of 181 cases reported estimating about 900 thus exposed. The Sheffield report (Medical Research Council 1926) showed a notable absence of outbreaks in schools etc. Hall (1923) states that evidences of contagion are rare, but says evidence for contagion may be marked at times as (1) in institutions--he gives three definite examples of outbreaks in schools for girls--(2) in new born babes infected by mothers having the disease, and (3) in more than one case in one household and nurses attending cases.

The Sheffield report finds no evidence of any relation between the disease and social conditions such as overcrowding, poverty, or unsanitary conditions, and no evidence of any association with topographical considerations ar with the supply of water, milk or any other form of food.

The season is winter and early spring. The outbreaks usually begin in November or December and reach their maximum in February or March disappearing rapidly in April and May (Hall 1923).

In regard to age and sex the Sheffield report concludes that there is increased susceptibility to infection in males and increased

liability to death in females. There is increased susceptibility to infection between the ages of 15 and 30 years. Smith (1921) finds the incidence between 30 and 45 a little higher than between 15 and 30. However the important fact that both figures show is that the disease occurrs very largely in the young adult and adult where as in anterior poliomyelitis the disease is predominately in children, especially under 10 years of age.

The reports by year of encephalitis in England and Wales shows the peaks of incidence in 1921 and in 1924. Riley (1930) gives cases reported from 14 countries showing the peaks to be in 1921 and in 1924.

Riley's figures are as follows:

1920	1921	1922	1923	1924	1925	1926	1927	- year
7,739	4,735	1,468	3,597	9,393	6,470	5,774	3,832	- cases

RELATIONSHIP TO INFLUENZA, POLIOMYELITIS, AND OTHER DISEASES

The epidemics of encephalitis or something similar to encephalitis that are mentioned under history have been largely associated with epidemics of catarrhal fever or influenza. Smith (1921) cites Ozamann in 1835 as mentioning epidemics of catarrhal fever with "soporosite" as having occurred in 1745, 1800, and 1802. In 1918 in France and England cases of epidemic encephalitis followed in the wake of the pandemic of influenza. Late in 1918 and early in 1919 the disease appeared in the United States following the appearance of influenza in this country. The outbreak reported by von Economo in Vienna in 1917 is generally said not to have been associated with influenza. Crookshank (1919) however states that grippe was prevalent in Vienna at that time but was not diagnosed influenza because the Pfeiffer bacillus was not found.

In regard to the epidemic of influenza in 1890 in the United States there is evidence that there were many cases of encephalitis associated with this epidemic. Here the cases were thought of as part of the influenza and the cases were not given the distinction of a separate disease.

In Smith's series of cases about 46 percent give a definite history of influenza, which was considerably higher than in the general population.

Crookshank (1926) believes that the relation between encephalitis and influenza is very close. "Cases and epidemics of encephalitis appear sometimes as autonomous cases and epidemics but always in close relation in time and space to cases and epidemics of influenza. Cases and epidemics of encephalitis occur in persons and in places that have recently suffured from influenza. Cases and epidemics that appear to be cases and epidemics of influenza may rapidly and without break of continuity

become cases and epidemics of encephalitis."

Flexner (1923) and more recently Jordon according to Zinsser (1928) come to the conclusion that influenza may be a contributing factor, but the encephalitic process is a separate pathologically distinct entity. "This is strengthened by the fact that it is not only influenza which is apparently associated with encephalitis but also measles, varicella, vaccination and smallpox, pneumonia, and whooping cough." -Zinsser. However as will be discussed later the postvaccinal and related encephalitides are not the same especially pathologically as epedemic encephalitis.

As mentioned above the age incidence of poliomyelitis is much different from encephalitis. But Crookshank (1926) says "No clear line of demarcation other than topographical can be maintained between epidemic encephalitis and epidemic poliomyelitis".

Besides the gross location of lesions in the central nervous system the microscopic pathology is quite different in the two diseases. In Polioencephalitis the pia-arachnoid shows as a rule considerable involvement not true of epidemic encephalitis; the polymorphonuclear leucocytes predominate in cellular infiltration, while plasma cells predominate in encephalitis; hemorrhages are common and relatively large, but absent or microscopic in encephalitis; vascular changes about the small arteries, but infiltration about venules in encephalitis; cellular degeneration and neuronophagia active in poliomyelitis, relatively slight if present at all in encephalitis. (Tilney and Howe 1920)

Borman (1929) believes that anterior poliomyelitis may have epidemic encephalitis superimposed on it. He reports a case.

Epidemic hiccough according to Boyd (1924) prevailed in Winnepeg at the time of the first Winnepeg epidemic of encephalitis in the winter of 1919-1920, and in fact was more extensive than the latter. The two diseases were rarely associated in the same individual suggesting that the one may immunize against the other disease.

From a study of epidemic mumps in the last 100 years in Norway, Gundersen (1927) concludes that there is reason to look on this infection as the origin of lethargic encephalitis. He finds a marked monthly and yearly parallelism.

POSTVACCINAL ENCEPHALITIS

A type of encephalitis somewhat similar to the epidemic type but probably quite a different thing is the postvaccinal type. Encephalitis following measles, small-pox, varicella, whooping cough and mumps are often classed with the postvaccinal type. On a pathological classification these encephalitides may well be grouped together opposed to the epidemic type (Armstrong 1929). The postvaccinal type etc. is that of a toxic-degenerative rather than an inflammatory process(Ford 1928). There is perivascular destruction of myelin with collection of lipoid waste products in phagocytes, the perivascular zone of softening described first by Turnbull and McIntosh (1926). In postvaccinal forms there is a wide demyelinization of the nerve tissue so that lesions resemble those of acute disseminated sclerosis (Flexner 1929). Epidemic encephalitis on the other hand is characterized by diffuse inflammatory reaction associated with exudation of blood cells. Zinsser (1928) is inclined to the view that the pathology of postvaccinal encephalitis is not so different from the epidemic type. He sites Luchsch and Bastiaanse and says that even Turnbull and McIntosh admit considerable similarity between the histological pictures of the two diseases.

Post-vaccinal encephalitis was observed as early as 1912 by Turnbull and McIntosh but was not published until 1926, after the epidemic encephalitis was recognized. The most thoroughly studied cases were in Holland reported by Bastiaanse (Zinsser 1928).

Armstrong(1929) gives reports in England 100 cases, Holland 150, and Germany 34 cases up to 1929. In Germany the figures indicate 1 case in 700,000 vaccination, in England 1case in 48,000 and in Holland 1 case in 4,000 vaccinations. In Holland vaccination has been supervized by the government, and the results were more carefully studied and reported.

Reports of postvaccinal encephalitis in America are rare compared with in Europe. No cases have been reported in Canada up to 1929 according to Defries and McKinnon (1929).

Dr. George Blummer, discussing Flexner's paper (1929) reports two cases of encephalitis out of 40,000 vaccinations in Bridgeport Conn. The cases appeared at the time of the year of epidemic encephalitis. He states "These may have been typical epidemic encephalitis cases occurring coincidentally after the use of vaccine". No report of the pathological findings are given to substantiate this belief.

The Holland studies showed that the serum used in cases developing postvaccinal encephalitis was not at fault as many different types and brands were used, brought from several different countries.

The symptoms of postvaccinal encephalitis usually appear suddenly when the local reaction at the site of vaccination is at its height, about 10 to 13 days after the inoculation. "Prodromata include headache vomiting and hyperpyrexia with alarming nervous symptoms soon supervening. These three prodromata plus paralysis are the cardinal symptomes". (Flexner 1929) According to Armstrong's studies stupor is always present in fatal cases and symptoms of meningeal irritation usually present in conscious cases but absent in others. The Babinsky reflex is usually positive a point of diagnostic importance.

The course is hyperacute and the fatality high, ranging from 35 to 50%. Recovery is usually rapid and complete in contradistinction to epedemic encephalitis. Death or amelioration of symptoms occurs in ten days to two weeks.

The age of patients is usually 3 to 13 years. La Page (1933) believes that this indicates that vaccination should take place in infancy and at as early an age as possible.

Theories of the cause of postvaccinal encephalitis are given by Armstrong (1929). (1) Result of activation some unknown agent in the virus or more likely in the vaccinated individual--supported by most European authorities. (2) Vaccine virus itself--Luchsch, Leiner, McIntosh. (3) Some state of local anaphylaxis.

Berger in 1921 (Matheson commission 1929) tested the above theories but failed to get any positive evidence for any one of the three theories. He used rabbits. To test the first theory he used rabbits previously inoculated on the cornea with herpes virus. Bijl in 1927 failed to produce the disease in animals by intracerebral injection by use of spinal fluid or brain of cases of postvaccinal encephalitis. Vaccine itself however produced the disease. Demme in 1924 brought out the point that the lesions in animal brains were not at all characteristic of the human postvaccinal encephalitis.

The presence of vaccine virus in the brain has been shown in only a few cases (Zinsser 1928). Turnbull and McIntosh report 7 cases. Zinsser says that after any vaccination the virus can be found for a short time in all the organs of the body and he believes this is probably the case when virus has been found in the brain. "It is definite that vaccination is at least a contributary cause but the immediate cause is probably some distinct agent." Zinsser puts vaccination in with measles, small-pox, mumps, whooping cough, pneumonia, and influenza as predisposing causes of encephalitis.

AUSTRALIAN "X DISEASE"

There was in the late summer and early autumn of 1917 and 1918 in New South Wales, Australia an outbreak of acute encephalomyelitis. The disease was of definitely epidemic character, but the districts which suffered were remote from each other and only connected indirectly by long radiating roads to Sydney, the metropolis. The regions were in the "outback" districts, about 200 miles from Sydney, where the climate is hot and dry in contrast to the muggier climate of Sydney and the coast.

The outbreaks in the two regions began simultaneously and since there was no cases in Sydney the carrier theory would hardly explain the original dissemination (Cleland 1919). Since the disease was proved to be communicable to sheep, horses and calves, there was the bare possibility that these animals might be carriers. There was no evidence that flies, mosquitoes, lice, etc. were etiologic factors.

During the outbreaks of "X disease" there were remarkably few cases of cerebrospinal meningitis and infantile paralysis, both notifiable, and the State was free from influenza.

The disease was often abrupt in onset with a mortality of 70%. Four and one-half days was the average duration of illness.

Children chiefly were affected but adults did not escape. General signs of cerebro-spinal irritation, namely, convulsions, rigidity, increased reflex excitability and loss of consciousness, accompanied by high fever were the dominent bedside features.

Paralysis of voluntary muscles was usually absent (Cleland 1919). The symptoms in no way suggested poliomyelitis, nor did the appearance of mental disorders and Parkinsonism as residuae in a few cases (Neal 1933). Neal is of the opinion that this outbreak "may very well have been epidemic encephalitis".

The pathological lesion resembles acute poliomyelitis, but differs inasmuch as the lesions were always widspread and changes in the brain were always as great if not greater than in the cord. Cleland and Campbell (1920) say that histologically the outstanding feature was distension of the perivenous sheaths by cells of lymphocytic appearance. The lesions were scattered throughout the brain and spinal cord. The corpus striatum, pons, and medulla were the parts most intensely affected.

Flexner (1923) compares the Austrian "X disease" with poliomyelitis and encephalitis. "The infiltrative character of lesions about the blood vessels, the foci within the tissues and the degeneration and phagocytosis, neuronophagia of the nerve cells, in the spinal cord and basal ganglia hardly differ in kind from those found in these structures in poliomyelitis. Moreover the relative escape of cortical structures is similar in these instances." "The pathological histology seems to definitely distinguish the Australian disease from encephalitis because of the great involvement of the cord." Flexner suggests that the disease may be an exhalted form of poliomyelitis.

However as Flexner states it differs from poliomyelitis in that it may be transfered to sheep, horse and calf as well as monkey and man. Poliomyelitis has never been successfully transmitted to any animal other than man and monkey.

Neal (1933) believes that there is not enough difference to base a diagnosis of epidemic encephalitis and "X disease" on pathological grounds alone.

Crookshank (1918) states that Dr. Breinl has confirmed that the virus of this disease is identical with that of poliomyelitis. "Otherwise we might now be hearing of Encephalitis convulsiva var Australiatica."

BACTERIAL CAUSATION

The first researches on the etiology of epidemic encephalitis by Wiesner and by Bernard attribute this disease to the organism of influenza, especially the polymorphous diplostreptococcus. Zinsser (1928) in mentioning Wiesner's theory of the diplostreptococcus says that the results of inoculation with this organism were too good. The animal died in two days.

Rosenow in 1924 isolated streptococci from the nasal secretion of patients having epidemic encephalitis. These he believed to be the primary agent in the production of encephalitis. His latest studies (1933) link encephalitis and influenza. He compares the cataphoretic velocities of the streptococci isolated from atria of infection of persons suffering from encephalitis with the velocities of streptococci from patients recovering from influenza. The streptococci from encephalitis shifted toward the slow velocity of streptococci from influenza. "The marked neurotropic type of velocity of streptococci found during convalescence from influenza suggests, perhaps, why encephalitis and other diseases of the nervous system such as epidemic hiccough, polio-encephalomyelitis, radiculitis and neuritis are so prone to occur following attacks of influenza or epidemics of influenza."

"Prolonged use of vaccines containing streptococci having chiefly neurotropic velocity as isolated especially from animals given injections of material derived from patients having encephalitis and other diseases of the nervous system, has been followed by improvement in symptoms and concomitant disappearance of neurotropic streptococci from nasopharynx in some cases." (Rosenow 1933)

Freeman (1927) finds a large percentage of individuals carry in the nasopharynx an organism indistinguishable from organisms isolated in

certain cases from the brain of patients daying of encephalitis. He argues that a certain degree of immunity is carried by the healthy individual. He sites patients benifited by blood transfusions. Freeman and Evans isolated a neurotropic streptococcus in 1926 which is identical with the organism isolated by Rosenow.

According to Zinsser (1928) this streptococcus although it has been observed histologically, usually assumes a filtrable form in the human brain and in the rabbit brain and in cultures. This strain has been found by Zinsser to be identical with strains of herpes virus. Yet he does not accept the possibility of a mutation of an organism into a filtrable virus. Evans (1927) studied bacteriologically six strains of so-called viruses. Four of these strains were originally from vesicles in cases of herpes, one was from the cerebrospinal fluid in a case of syphilis and one was from the brain in a case of epidemic encephalitis. Cultures of virulent streptococci and cultures of spore-producing rods were obtained from all six strains.

Goodpasture (1929) believes that bacteria such as streptococci prepare the tissue for inoculation with the filtrable virus, but are not the primary factor. Zinsser rejects the bacterial causation of this disease on the following grounds: (1) The clinical symptoms and speed of death of inoculated animals is different from the human disease. (2) The pathologic changes in encephalitis in man are fundamentally different from those produced by any known forms of bacteria. (3) The nature of immunity as far as is known in encephalitis and certainly in filtrable virus diseases generally is different both biologically and serologically from that in streptococcic infections. (4) All who have claimed bacterial etiology for this disease have assumed an interrelationship between the bacteria and a filtrable stage, in which case it would be necessary to stretch this

mutation not only into one of form and and infectious properties but into one affecting all the basic biologic attributes of the agent; for unlike bacteria the filtrable virus can be preserved in glycering indefinitely, degenerates easily in salt solution and is much less resistant to heat, chemicals, and most other deleterious agencies than are bacteria.

VIRUS CAUSATION AND HERPES ENCEPHALITIS

The preceding arguements against bacterial causation introduces the theory of filtrable virus as the responsible agent for this disease.

Some of the first experiments indicating a virus of this nature as being the etiologic factor were by Strauss, Hirshfeld and Loewe of New York (1919) who inoculated emulsions of human brain of patients dying of epidemic encephalitis and produced in monkey lesions characteristic of lesions found in epidemic encephalitis. Also a filtrable virus, obtained from the nucous membrane and washings of the nasopharynx in a fatal case of epidemic encephalitis produced encephalitis in the monkey. This virus was carried through a second generation.

This experiment should be observed in the light of knowledge of the herpes virus. As early as 1913 herpes was known to have been caused by a living infectious agent from the work of Truter. In 1920 Doerr and Voechting discovered that herpes virus from man could become neurotropic and give rise to encephalitis in rabbits (Zinsser 1928). "When herpes virus was isolated from the spinal fluids and brains of several patients with encephalitis, it was natural that an association between herpes and encephalitis should be considered."

Effort to bring encephalitis in man into relationship with herpes virus encephalitis in rabbits and monkeys has been mainly by the Pasteur Institute at Paris under the influence of Levaditi. In 1920 taking material from 16 clinical cases inoculated 19 rabbits, 13 monkeys and 8 guinea pigs and produced two positive results. Doerr in 1921 taking material from 11 cases produced the disease experimentally only once. Szymanowski and Zylberblast-Zand (1923) obtained 18 positive results in 55 inoculations or 33%. They employed cerebro-spinal fluid, discharge from

the nasopharynx and emulsions of the brains of patients dying with the disease. Their results were obtained on rabbits. They believe their results to be due to an encephalitis virus which is identical with the herpes virus but more neurotropic. They say that their encephalitis virus produced the same clinical symptoms and the identiadl pathologic changes in rabbits as does the virus of herpes.

The latter authors do not state the number of patients of encephalitis from whom material for positive animal inoculation was taken. It was probably a very small number. In fact among all experimentation along this line the number of human cases carrying a virus neurotropic for rabbits is extraordinarily rare. Rose and Walthard recently according to Flexner (1929) thought from their experiments with the guinea pig that this was due to the virus acting for a brief period damaging and inflaming the brain and dissappearing. Flexner however repeated the guinea pig experiments with a strong herpes virus and found the virus not destroyed in the course of the inflammatory reaction but multiplying in the infected and inflamed brain and capable of unbroken, indefinite guinea pig passage. Whatever the explanation, the fact stands that a virus has been isolated from cases of human encephalitis very few times, probably only in 10 instances (Gay and Holden 1933). Dawson(1933) says it is at least an unusual occurrence. "The association of herpetic virus with human encephalitis seems on the basis of available evidence, adventitious."

Flexner has done considerable experimentation on the nature of herpes virus (Flexner and Amos 1925 I, 1925 II, Flexner 1928, 1929). He considers this virus separate from that causing human epidemic encephalitis. Concerning the attempts to identify encephalitis in the human with virus encephalitis in the rabbit, Flexner (1929) says "This undertaking disregards all criteria which make epidemic encephalitis in man a so-called clinical

entity". "There is striking absence of essential conformity between these rapidly fatal infections and the whole complex train of symptoms and consequences which characterize epidemic encephalitis in man." MacCallum (1926) also believes herpes and encephalitis are not identical.

Zinsser (1929) produced a condition in Cebus monkeys simulating with considerable accuracy the human disease of acute encephalitis in symptoms, in course, and in pathological changes by means of the herpes virus, using more resistent individual monkeys. (The ordinary Cebus monkey quickly succumbs to the herpes virus intracerebrally.) Zinsser believes encephalitis might be due to the development of neurotropism by a number of different filtrable agents including herpes as "occasionally responsible".

In New York City, Gay and Holden (1929) support a similar hypothesis. "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 strongly neurotropic virus and also against the dermotrophic virus. They do not say how long the immunity may continue.

Gay and Holden (1933) report that they have found a new strain of herpes simplex virus recovered from the brain and cord of a human case of acutely fatal epidemic encephalitis. This virus is extremely fatal to rabbits whether injected intradermally or intracerebrally. It acts on the Cebus and the Macacus rhesus monkey as does herpes, and cross immunity tests identified the two viruses as the same.

Demonstration of herpes virus in the brain of human cases of encephalitis has also been accomplished by Pedrau (1929). Three cases of encephalitis gave positive results by their technique.

The evidence against and in favor of the herpetic origin of epidemic encephalitis is discussed in detail by Gay and Holden (1933). The herpes virus has rarely been isolated from cases of epidemic encephalitis, but: There is some evidence that the disease is cyclic and the virus is not always present except in the acute stage, and relatively few cases have been studied in the acute stage; the virus is usually sought for in the cerebrospinal fluid rather than in the brain tissue where it is more likely to be present; the virus in human brains has been sought almost exclusively by intracerebral inoculation and yet such a fatal human virus although neurotropic for man might be strictly dermotrophic for animals. Herpes is a common infection whereas encephalitis is rare; this can be explained by a fairly competent defense mechanism in the normal central nervous system and by lack of neurotropism on the part of the usual virus of herpes. Herpes accompanies epidemic encephalitis less frequently than does many other diseases but: At times the sequence of herpes and encephalitis is striking and suggestive; herpes may actually serve to protect against encephalitis as at least it does regularly in experimental infections.

They give their arguement in favor of the herpetic origin as: (1) The virus of herpes simplex produces in many animals skin and brain infections which resemble respectively herpes and epidemic encephalitis in man. (2) A subacute disease clinically human encephalitis has been produced in Cebus monkeys by Zinsser and by McKinley and Douglass. (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 fluctuations both in herpes and in encephalitis in man that suggests 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%) in which recovery does not give rise to lasting protection.

To continue the subject of virus causation of encephalitis some mention might be made of the general nature of the so-called filtrable viruses. The name implies that it is living. But none of the filtrable viruses have been cultivated (Zinsser 1929). Some think that the virus is a lytic principle, not living. This theory links the filtrable virus with bacteriophage.

Zinsser explains this possibility "Once a bacteriophage for a given culture has been started, usually in the intestine or in glycerinated vaccine pulp or under other conditions in which the bacteria are in contact with the autolyzing cells, something is produced which initiates lysis of similar bacteria; and these bacteria in turn while undergoing lysis, reproduce the lytic principle. This principle is filtrable and in a great many important attributes is analogous to filtrable virus agents in general. Could one conceive a cytophage which would initiate a similar autolytic process in cells of the nervous system, not only would the injuries produced by such an agent account for the pathologic conditions and lesions but they would explain experimental transmission from animal to animal, since such a cytophage would in complete analogy with bacteriophage be produced by the specific cells which degenerated because of its action"

"While the idea is consistent with almost all the clinical and experimental observations that have been made on herpes and on encephalitis, it is impossible to harmonize it with observations on spontaneous transmission from patient to contacts or attendants."

In regard to the possibility of the virus remaining infective or virulent for long periods of time, Holden (1932) finds that herpes virus in desiccated brain can be kept virulent in the dried state for at least 18 months. While herpes virus in moist brain in glycerine at icebox temperature conserved its virulence for only six months. The same degree of infectivity is present whether the virus is moist or dry. "This conservation of herpes virus is analogous to the survival of pneumococci in dried animal tissues for a period of several years."

This may be of interest in the discussion of the St. Louis epidemic which occurred in exceedingly dry weather as also the Australian "X disease". Conservation and propagation in dust might be considered. The weather in these epidemics was not only dry but very hot. "Dried herpes virus withstood 90° C." Somewhat analagous results were found with the pneumococci.

The question of the tissue localization of the virus in the nervous system and possible modes of passage of the virus has been contributed to largely by Goodpasture and Teague. Their experiments demonstrated that in ocular herpes the virus does enter the brain invariably by way of the sensory fifth nerve. Goodpasture (1929) demonstrated in suitable experiments (intramuscular inoculation) herpetic changes within the motor ganglion cells deep in the pons before lesions could be found within the nerve or elsewhere. It was concluded that the myelin sheaths seem to insulate the virus in its passage up the axon for the cells of the sheath of Schwann surrounding the axis cylinders are susceptible to herpetic virus, and when they become affected an acute neuritis manifest itself. Goodpasture believes that the virus may be harbored in an inactive state within the nerve

cells and axons. Flexner (1925) believes that the virus attacks the nerve cells directly "affecting them quantitatively in such ways as at one time to produce stimulation and at another time paralysis."

Inclusion bodies particularly within the nucleus are coming to be regarded as a criterion of the presence of virus in a lesions of unknown etiology according to Goodpasture (1927). Trachoma and rabies produce inclusion bodies in the cytoplasm alone. Varriola and vaccinia produce changes within both cytoplasm and nucleus. Varicella, herpes zoster, herpes simplex and possibly verruca vulgaris involve specifically the nucleus.

These inclusion bodies have the appearance of being a new substance originating within the cell. Da Fano (1920) was one of the first to describe inclusion bodies in nerve cells in cases of epidemic encephalitis. He found similar bodies in salivary gland cells in an acute case of encephalitis. Dawson (1933) says that Da Fano described vague intracellular bodies not at all typical of virus inclusions. He believes no one has demonstrated in human cases inclusions characteristic of herpetic infection. He describes a case in which they are present and two fatal cases in which they are not present. From his studies he concludes that epidemic encephalitis may not be a distinct entity, his first case being due to a definite"cytotropic virus"and the other two being of a somewhat different nature.

Before leaving the subject of filtrable viruses as the causation of epidemic encephalitis attention might be called to an encephalo-myelitis of horses, sheep, and cattle called "Borna" (Galloway 1929). This is caused by a virus of the same catagory as poliomyelitis and herpetic

encephalitis, and thereby, possibly epidemic encephalitis. It resembles poliomyelitis in confering immunity after one attack and in this same feature differs from encephalitis of man. The pathology resembles encephalitis very closely as far as microscopic changes are concerned. It differs in that the spinal ganglia show very intense lesions in all cases. It resembles herpetic encephalitis in that inclusions bodies are found within the nuclei of the nerve cells. Galloway suggest that inclusion bodies are barriers to the destructive action of the virus, i.e. a defensive mechanism on the part of the nerve cell.

Nicolau and Galloway in 1929 showed that the virus when inoculated intracerebrally disseminated in a similar way to the virus of rabies, poliomyelitis, and herpes i.e. centrifugally by the nerve tracts. In "Borna" lesions may be found in the peripheral nerves.

In discussing Galloway's paper J.G. Greenfield emphasized a point; "The extreme rapidity with which neurotropic viruses can disseminate themselves through the nervous system certainly suggests something of the same nature as the transmission of an impulse through a nerve or the passage of ignition along a gunpowder trail."

CLINICAL FEATURES OF EPIDEMIC ENCEPHALITIS

In this paper only the important symptoms will be mentioned. Stress should be laid on the change of some of the major symptoms from the time the disease was described in 1917 until the present.

There is information that as epidemics have decreased the clinical features have changed. The earlier cases of encephalitis, occurring in 1917, 1918, and 1919 were chiefly epidemic with ophthalmic symptoms and lethargy very prominent. In 1922 and 1923 according to Stallybrass (1923) the epidemic gave way to one in which there was extreme restlessness, prolonged sleeplessness, often delirium with terror, and other positive motor symptoms. At the same time the mortality also increased rising by steps in England from 12% in 1920 to about 40% in 1923. Boyd (1924) sites similar change of symptoms in the Winnepeg outbreaks, but the mortality is reduced in the later epidemic.

Smith (1921) gives a good summary of the characteristics of the earlier cases. "The clinical course of the disease may be divided into three stages; (1) a prodromal period with fatigue, lethargy, headache, giddiness, and disturbances of vision; (2) the stage of acute manifestations, with vomiting, fever, paralysis of certain cranial nerves, changes in tendon reflexes, alteration in speech, marked general weakness, and in the majority of cases coma of varying intensity; and (3) the period of convalescence which varies. In some cases recovery is complete within ten days to two weeks after subsidence of the acute symptoms. In other cases however convalescence is prolonged and is accompanied by changes in the mental state, definite loss of function of certain muscles and obstinate palsies of the cranial nerves.

The case fatality was 60% in cases of sudden onset and 22% in

cases of gradual onset, or 29% in a series of 159 cases according to Smith. Tilney and Howe (1920) in a report of 20 cases give the fatality as 25%, 15% complete recovery, 20% improving slowly, 35% stationary or worse. Someone has said that 25% die, 25% recover and 50% are left with some residuae.

Different types of the earlier form are described by Tilney and Howe (1920): (1) The lethargic type is characterized by a condition of modified stupor in which it is possible to rouse the patient for a time, gaining his intellegent cooperation, after which he lapses into deep sleep again. This condition usually is accompanied by cranial nerve palsies, especially oculomotor. (2) The cataleptic type, in which the patient is able to understand questions but is unable to make the slightest response. (3) The paralysis agitans type--Parkinsonian syndrome--extremities stiff and trembling, facial expression fixed, movements slowed down, monotony in speech, and shuffling gait. In this type there is "supression of automatic associated movements, slowness in somatic movement, a characteristic attitude and facies, and agitans tremor.

(4) Polioencephalic type, characterized by cranial nerve palsies with other nervous symptoms not prominent. This is an abortive type of encephalitis. (5) Acute anterior poliomyelitic type is rare. It combines symptoms of encephalitis (as lethargy and eye signs) with symptoms of anterior poliomyelitis. Possibly this is not a true epidemic encephalitis. (6) Posterior poliomyelitic type is also rare. In it there is affection of the dorsal root ganglia causing pain and burning in the distribution of the nerve, the fifth nerve for example. (7) A type in which the sleep ratio is inverted is the epilepto-maniacal type, characterized by lethargy in the day-time and insomnia, delerium, hallucinations and violent and destructive actions at night. The patient may die in epileptiform convulsions. (8) The psychotic type shows hallucination illusions, depression, apathy and

delirium. (9) The meningitic type is characterized by headache, rigid neck, delirium, positive Kernig sign etc.

Other types that may be distinguished are polyneuritic, cerebellar ataxic, hemiplegic, monoplegic, diplegic, and bulbar type.

General symptoms include fever, increased perspiration, loss of appetite, loss of weight, vertigo, vomiting and catarrhal symptoms. Fever is present in a big majority of cases. Fever may be present and escape detection. In the lethargic types a temperature of 102° is the rule. The fever is more marked in acute psychotic and epilepto-maniacal types.

The course may be acute, subacute, or chronic. Tilney and Howe give the average duration as eight weeks. However the infection may involve the bulbar nuclei early with death in a few days. Psychotic, apoplectic and fulminating cases are generally rapid and often fatal. Paralysis agitans and other sequelae may follow from the first or develop several months later.

Parkinsonism, according to the Sheffield report (Medical Research Council 1926) develops in 22% of the cases. If not present in the primary attack it often develops 6 to 12 months later. Its symptoms differ from paralysis agitans of the aged mainly in the tremor being courser and not so markedly intensional in type. The site of the lesions often differs being more in the substantia nigra, whereas the lesion of paralysis agitans of the aged is confined to the basal ganglia (Wechsler 1928).

Moral changes may be marked in children and young people. The most common features are destructiveness, uncontrolled attacks of temper, quarrelsomeness, interference with others, lying and thieving.

Mental changes to some degree is a very common after-effect. "It would probably be not far from the truth to say that few cases are

mentally the same as before." (Medical Research Council 1926)

Other sequelae include tics and spasma, hyperkinesias, pupilary abnormality as irregular, unequal pupils, fixed pupils, ocular palsies--less common, nystagmus, inversion of the sleep mechanism and diabetes insipidus (Wechsler 1928).

Returning to the change of clinical feature from one epidemic to another consideration is given to the Winnepeg outbreaks Boyd 1924). The first outbreak occurred in the winter of 1919-20 with 159 cases in all of the Province of Mantoba, mortality 39%. The second outbreak occurred in winter of 1922-23, 165 cases, mortality 25%

Boyd says the first epidemic was characterized by stupor; the second by a state of constant activity. However lethargy developed in more than one-half of the cases of the second epidemic sooner or later, and cranial nerve disturbances, present in almost 100% in the first epidemic, were still present to a very great degree 82% in the second epidemic.

The second epidemic was characterized especially by a different type of onset. This epidemic showed two main types of onset. The sensory type began with neuralgic pains, which Boyd thinks is due to lesions in the nerve root. The second type of onset was a motor onset with muscular spasms, and choreiform movements of various types and degrees.

The pathological lesions were the same except for calcification of vessels seen in many of the cases of the second epidemic. Boyd makes particular note of these changes observing them not to be presenile changes as many of the specimens showing this change were from young adults.

The spinal fluid in epedemic encephalitis often shows no changes whatsoever. The cell count and pressure may be slightly increased, rarely very marked. In cases in which there is an increase in pressure and in cells and presence of symptoms of meningeal irritation differentiation from infective menigitis by the amount of sugar in the spinal fluid is of diagnostic value. According to Coope (1921) the normal sugar is 50to 80 mg. per 100 cc. In epidemic encephalitis the sugar is normal or higher. Low sugar especially one below 40 mg. is strongly in favor of an infective meningitis.

The blood count usually shows a moderate leucocytosis. Heagey (1921) finds an average of 10,000 with the highest 22,000 in a series of 15 cases of epidemic encephalitis.

THE JAPANESE EPIDEMICS "SUMMER ENCEPHALITIS"

In the late summer of 1924 and in 1929 there occurred endemics of encephalitis in a certain region of Japan, the Inland Sea area. The symptoms of this epidemic from the account given by Kaneka (1925) resemble in many respects the epidemic encephalitis of Europe and America.

The onset is characterized by fever, headaches, and general malaise and finally disturbance of consciousness. The lethargy, which appears sooner or later may be typical of lethargic encephalitis but usually develops into a comatose condition more severe than is seen in the epidemic encephalitis.

The fever approaches 104 to 107° and bears no relation to the disturbance of consciousness.

It is to be noted that these epidemics were very fatal the percentage begin close to 60% and the age incidence mainly in the older adult and aged.

Meningitis-like symptoms were usually present in the acute cases but mild or absent in other cases. Spinal fluid cell count was usually above 20 p.c.m. The severe cases did not necessarily have cloudy fluids. The pressure was only slightly increased, possibly 11 to 18 mm. of Hg.

Eye symptoms were rarely observed in this epidemic, and when present were not palsies but were more of the nature of spasticity or rigidity of movement and fixity of gaze.

Myoclonus, choreiform movements, resistence to passive movement of the extremities were sometimes seen.

The course of the disease was very rapid, death sometimes occuring in 24 hours. The majority would die in 4 or 5 days to 2 weeks. In milder cases recovery was very rapid, 5 to 10 days. Kaneko reports that there were known only 28 cases with sequelae in 2000 reported cases of the disease. Parkinsonism was very seldom seen.

Because of the severity of this epidemic in Japan, the time of the year and the absence of certain signs such as ocular and cranial nerve palsies, many doubt the identity of the disease with the epidemic encephalitis in Europe and America (Futaki 1924). Aoki, Kondo and Tazawa report the discovery of spirocheta-like organisms in the blood, cerebrum, cerebral fluid, and other organs in fatal cases. This has not been substantiated to my knowledge.

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In China between 1923 and 1925 Pfister (1929) observed 100 cases of encephalitis typical of that in Europe and America. Clinical symptoms were the same and the Parkinsonian sequel was common. He observed the disease to be more endemic and less epidemic in China.

In the dry season, August, he observed a secondary incidence of the disease. Whether these cases were in any way different from the cases observed in the winter season he does not state.

THE ST. LOUIS EPIDEMIC

This epidemic occurred in the summer of 1933. The climatic conditions were very unusual in the area involved. The rainfall in the St. Louis area was the lowest since 1837 when the first official records began.

The first information giving evidence of an epidemic reached the St. Louis Health Division August 8. There were 16 cases of an unusual type of encephalitis in the Isolation Hospital at that time. Later past cases were analyzed and it was found that the first cases in St. Louis county were on July 7 and in St. Louis proper on July 30 (Bredeck 1933). A table of cases by the week shows the cases in St. Louis County as more numerous early in the epidemic and reaching the peak earlier than in St. Louis City (Leake 1933). The total in each division of the area was nearly the same, 522 in the County and 533 in the City through the week ending October 14. It is evident that the epidemic began in the County and was more intense there, the population of the City being 3½ times that of the County. By November 15th the total cases reached 1,104, deaths 216, a mortality of about 20%.

Milk, water, and food were early excluded as factors. The drainage and sewage problem in St. Louis was favorable to the breeding of unusually large number of mosquitoes. With such a prevalence of mosquitoes along with an infection so widely spread, the possibility of transmission of the disease by mosquitoes was studied thoroughly with no evidence of a positive nature forthcoming as yet.

This epidemic affected chiefly older adults. The age group under 15 years comprises 23% of the population of St. Louis area and had 13% of the cases, the group 15 to 34 years old had 36% of the population and 23% of the

cases; the group 35 to 54 had 28% of the population and 29% of the cases; the group 55 and over had 13% of the population and 35% of the cases. The age group above 55years was then the most severely affected, differing greatly from the age group affected in poliomyelitis, the Australian "X disease, both prevalent in young children, and also the winter epidemics of encephalitis in this country and in Europe, which is found usually in young and middle aged adults. In regard to age this epidemic resembles the Japanese epidemics. Leake (1933) says an even greater preponderance in the aged characterized the two Japanese epidemics. According to him there were in Japan in 1912 and 1919 epidemics with a similar tendency as to age in the same areas as the 1924 and 1929 epidemics.

The distribution of cases in the St. Louis area is interesting but not satisfactorily explained. The heavy incidence was around rather than in the middle of the most densely populated area. This was also the case in Kansas City and in other cities (Leake 1933). This same characteristic however has been found in regard to poliomyelitis. The rate in the New York City epidemic of poliomyelitis of 1916 was nearly tripled in the less thickly settled boroughs of Richmond and Queens as compared with Manhattan and the Bronx.

Cases in epidemic intensity occurred this year in the Kansas City area, in St. Joseph, Mo, and in Louisville, Ky.

Bassoe (1933) describes the clinical course of the cases in the St. Louis epidemic. The onset is usually sudden, high fever, and pronounced meningeal symptoms, recovery ordinarily rapid, eye symptoms and sequelae were rare. The most common cases are characterized by abrupt onset, headache, high fever, nausea, stiff neck and positive Kernig. Convulsions might occur. Mental confusion, aphasia, and tremor of hands,

tongue and lips were common. Drowsiness might be supplanted by hyperexcitation, but noisy delirium was rare. Pains in back and limbs were rather frequent and occasionally some hyperesthesia occurred.

Any ocular disturbances were of the slightest nature and transient. Hempelmann (1933) observed no cases showing ptosis in the large number of cases which he saw.

Drowsiness was common, but coma was rarely so deep that the patient could not be roused.

The lumbar puncture in practically all cases showed a marked increase in cell count, often surprisingly high. Hempelmann (1933) observed that at times the first count revealed a normal number of cells, but, when repeated a day or two later the typical increase was noted. The cells were predominately lymphocytes. The spinal fluid sugar was normal or slightly elevated.

The neurological examination showed in most cases absence of abdominal reflexes in the acute stage. Kernig was positive in the majority of cases. Pupils were usually quite small but reacted to light and accomodation.

The temperature curve was rather characteristic, being highest at the onset, approaching 104- 105°, and falling step by step untill normal was reached in about 6 to 10 days. Deaths usually occurred from complications, broncho-pneumonia, nephritis or both.

The recovery after such a severe illness was very rapid, "little short of amazing". In cases of marked severity, in some instances, would return to normal in 10 days to two seeks.

The pathological lesions according to Mc Cordock (Neal 1933) were characterized by intense vascular congestion, cellular infiltration

and toxic degeneration in the nerve cells. The cellular infiltration consisted in perivascular cuffs of round cells, and focal collections of similar cells scattered through the brain without relation to the blood vessels. Small petechial hemorrhages in the brain tissue simialr to those seen in poliomyelitis are occassionally encountered. Usually, however, the hemorrhage is confined to the perivascular lymphatic space.

The nuclei of the cranial nerves were not especially involved in the degenerative changes. "The brunt of the attack appears to be borne by the nerve cells in the mid-brain and basal nuclei." "A study of many cases gives one the impression that the process in the brain is not one that starts in the mid-brain or basal ganglia and spreads from there to the rest of the brain; but that it is a diffuse process which apparently begins simultaneously in many regions of the brain."

Intramuclear inclusion bodies in the kidney were found in one-fourth of the cases examined.

Experiments on the etiology are most interesting. Muckenfuss, Armstrong and McCordock in Public Health reports of Nov. 1933 report that from 7 out of 15 fatal cases successful inoculations of brain emulsions have been made into Macacus rhesus monkeys. Three strains have now been carried through 5 passages in monkeys. "Only about 40% of the inoculated monkeys developed symptoms although the acuteness of the illness in animals coming down during the fourth and fifthe transfers suggests that the virulence may be increasing." None of the monkeys died if left alone. The pathologic picture is consistent with that seen in the human cases. The virus persists in 50% glycerine for at least one week.

Webster and Fite (1933) have disclosed a virus from cases of the St. Louis encephalitis by intracerebral inoculation of special mice.

This has been proven to be the same as the virus of Muckenfuss, Armstrong, and McCordock. The mice remained well and active for four days and usually died by the 6th or 10th day. When the mouse brain virus is instilled intranasally fatal signs also develop, in practically 100% of the mice. Stock mice and specially bread virus-resistant mice show negative results.

Brain tissue preserved in glycerol from two fatal cases of encephalitis in Kansas City in September 1933 produced similar symptoms of encephalitis, convulsions, etc, and died on the 9th day. This Kansas City virus has proved identical with the St. Louis strains. It does not appear to be related to the louping ill virus of sheep because sera protecting mice against 100 lethal doses of this virus have no effect upon the present one.

The virus appears unrelated to herpes virus, since rabbits show no effects following intracerebral, corneal, and intradermal injections.

Macacus rhesus monkeys given 1cc. of mouse brain vurus intracerebrally show significant elevation of temperature and symptoms, such as course tremors, drowsiness, etc. in from 7 to 9 days. As in case of the mice pathological lesions of the brain are similar to that found in the fatal human case.

This virus is neutralized by serum of encephalitis convalescents of the St. Louis epidemic. Monkeys injected with the virus develop in their sera protective properties similar to that produced in human patients.

Webster and Fite in a second report show that patients serum does not show protective properties until at least 7 days after the onset of symptoms. Sera from two cases of miningoencephalopathy in Indianapolis did not protect. Sera of 13 cases of acute encephalitis from New York did not protect. Sera of cases diagnosed chronic epidemic encephalitis with Parkinsonian sequelae did not protect.

However sera from cases from outbreak of encephalitis in paris Ill. in summer of 1932 did show protective properties as did sera from a case in New York of September 1933.

Sera from 8 normal adults in New York tested twice show no protective qualities.

Webster and Fite (1934) have been able to obtain sera from cases of encephalitis in Japan from 3 persons with a history of encephalitis in the summer of 1924 and from 9 persons with a similar history in August and September of 1933. None of these sera showed any protective action against the virus of the St. Louis epidemic.

These experimenters have gone further and have been able to produce immunity in their mice without producing any symptoms. Active brain virus given to mice intranasally in doses as small as 10^{-5} gms. or intracerebrally in 10^{-8} gms. causes death, while the same virus injected intraperitoneally or subcutaneously in 10^{-2} gms with $\frac{1}{2}$cc. of diluent (which is a million intracerebral and a thousand intranasal lethal doses) rarely proves fatal. Still smaller amounts 10^{-3} to 10^{-6} gm. when inoculated subcutaneously induce no symptoms but render them immune to a million intracerebral and a thousand intranasal doses. This induced active immunity has persisted unchanged for 3 weeks and doubtless endures longer (Webster and Fite 1934).

CONCLUSIONS

(1) Epidemics of encephalitis, whether or not identical with any of our present day epidemics, have occurred for centuries.

(2) Epidemic encephalitis is contagious; although the evidence for is rare. Most individuals are probably immune.

(3) Epidemic encephalitis follows in the wake of influenza epidemics. Influenza is probably a very definite contributing factor. Relationship to influenza is not noticeable, however, in the summer type of encephalitis.

(4) Although poliomyelitis and encephalitis are in parallel relationship, they are in all probability distinct entities.

(5) Postvaccinal encephalitis is very rare especially in America. The explanation for this encephalitis very likely awaits knowledge of the interaction of viruses.

(6) Australian "X disease" is a debatable problem. It may be a virulent form of poliomyelitis or a new form of epidemic encephalitis.

(7) The neurotropic streptococcus of Rosenow, although not the primary factor in encephalitis, may be a very important preliminary invader, preparing the nervous tissue for inoculation with the virus of encephalitis.

(8) There is little doubt but that epidemic encephalitis is caused by a filtrable virus. There is some evidence that the virus is identical with a neurotropic strain of herpes virus. Flexner believes the two are not identical.

(9) The symptoms of ordinary epidemic encephalitis have changed somewhat since 1917. Onset with lethargy and ocular palsies, although still present in most of the cases, is giving way to onset with positive motor symptoms and positive sensory signs. Insomnia and a state of constant

activity is chacteristic of many of the cases.

(10) The Japanese and the St. Louis epidemics resemble each other and differ from ordinary encephalitis in season, age incidence and symptomatology. The cases occurred in the summer, prevailed in older adults, showed no ocular palsies, had a very rapid course and few sequalae. The Japanese epidemics had a much higher mortality.

(11) Most striking are the results on the etiology of the St. Louis epidemic. A filtrable virus was readily obtained, which produced symptoms in monkeys and in special strains of mice.

This virus is not identical with the virus of herpes as shown by rabbit inoculation.

Sera from patients with ordinary epidemic encephalitis does not neutralize this virus.

The experimenters have been able to actively immunize their mice against a million intracerebral lethal doses of the virus.

SUMMARY

Knowledge of the causative agent of epidemic encephalitis is still very much in the experimental stage with the possible exception of studies of the virus readily obtained from cases of the late St. Louis epidemic.

Possibly two or more forms of encephalitis distinct from the ordinary epidemic encephalitis have appeared in the world in recent years.

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