Epidemic encephalitis etiology and sequelae

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EPIDEMIC ENCEPHALITIS

ETIOLOGY and SEQUELAE

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SENIOR THESIS

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INTRODUCTION

Perhaps no other primary infection of the central nervous system has attracted such widespread attention and extensive study within the last few years as has the disease syndrome known since 1917 as epidemic, or lethargic, encephalitis. Jelliffe (86) very aptly puts the position that epidemic encephalitis has come to occupy in the study of neurology when he says:

"In the monumental strides made by neuropsychiatry during the past ten years, no single advance has approached in importance that made through the study of epidemic encephalitis. No individual group of diseased reactions has been as widely reported upon, as intensely studied, nor as far reaching in modifying the entire foundations of neuropsychiatry in general. "While, as yet, the etiological factors, the constitutional or dispositional backgrounds which permit infection, and the epidemiology, are far from being completely grasped, the advances made in our understanding of cerebral mechanisms have, in truth, been enormous. The entire symptomatology of affections of the striatum, interbrain, and midbrain structures has been greatly clarified, a much greater insight gained into the problems of structure and function of these parts, and above all, the synthesis of the working parts of the body as a whole, physical, chemical, biological, psychological, and sociological, has progressed, through the medium of this disease process, into a pragmatic and comprehensible whole of great significance to neurology and psychiatry alike."
"An entirely new orientation has been made imperative. An orientation towards certain conceptions of disease, grasped for centuries by a favored few, has been made the property of the many, and the future is filled with promise that some of the darkest chapters in the understanding of the emotional and mental life of the individual will be greatly clarified by this "borderland" process which has reached, on the one hand, into the deepest recesses of the vegetative organization of the bodily organs, and, on the other hand, carved out, as it were, cameos of behavioristic reactions, the further scrutiny of which will resolve many a heretofore uncomprehended subtle mental condensation product. Thus complex vegetative processes all too ill understood in current physiology, have been most intricately dismembered into their simpler component parts, and the equally if not more involved mental syntheses also cut into and partly fragmented into simpler fundamental integers. It is due either to the chronicity of the process or the psychological factor of regression that a continuous series of observations have been made possible."

Since the etiology is one of the most carefully studied and yet most controversial phases of this disease, while, as pointed out by Jelliffe, the study of the chronic stage has been of very great importance in unraveling many of the problems in the physiology and psychology of the central nervous system, we shall confine this paper, for the most part, to a discussion of these two phases of epidemic encephalitis.
In 1917, von Economo (35) published his classic report on what appeared to many observers to be a new disease. However, "a search of the medical literature of the past soon demonstrates that this is not a new disease, but one to which attention has been dramatically directed by the enormous number of its victims," Riley (139). Although it had not been described in its typical syndrome, as it revealed itself during the 1917-1924 epidemic, careful investigation has resulted in the unearthing of reports of various kinds going further and further into the archives of medical history, and the interpretation of these descriptions by several investigators (Crookshank, Wright) as examples of epidemic encephalitis apparently gives this disease ancient lineage.

There is some dispute as to whether Hippocrates knew of the disease. Wright (192) in reviewing the works of Hippocrates, says: "It is evident, however, to us that neither Hippocrates not his French translator was familiar with the epidemic disease which has confronted us." On the other hand, Crookshank (28) points out that Hippocrates in writing on epidemic diseases, says that in Thasus (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 very epidemical."

In classic times, a similar syndromes was, according to Riley (139), described by Aretaeus and Galen under the title of phrenitis or causus. Wright (192), however, states, "For Galen lethargy arose from phlegm as it did for Hippocrates. If the
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disease was present in the Roman empire as a new disease, he failed to recognize it, and his works fail to describe it."

Wright considers that the first man to describe the disease was Caelius Aurelianus, a Numidian, probably a contemporary of Galen. Caelius Aurelianus, in his books, "De Morbis Acutis" in the first chapter, "De Lethargo," gives a description of lethargy in a "disease (which) has arisen in many."

"First there comes a doubtful depression and pressure (Meaning unknown. May indicate profound sleep) similar to sleep but out of which the patient can be easily aroused when called; not promptly but after a little he will respond." He further mentions weakness, dysphagia, sialorrhea, sweating, and finally respiratory paralysis and death. It may be seen that in many of its features this disease resembled epidemic encephalitis, although by no means presenting a classical picture.

The Dark Ages, in which scientific medicine came to a standstill, gives us little with regard to this scourge. Crookshank (28) found reference in the Frankfort Chronicles to a disease known as Hauptkrankheit, which in 1481-1482 swept over Germany. It was characterized by various nervous manifestations, including lethargy.

However, in the early years of the Renaissance can again be found descriptions exceedingly suggestive of this disease appearing from clinicians, such as de Sousa of Lisbon, who wrote of mendorra or mordorillo in 1521, the "pestilence soporeuse" by
Amatus in Italy in 1561. This was soon followed by the first "sweats" in England (influenzas of malignant and nervous type in some years and places--Hamer). In 1581 at Luneburg in North Germany there appeared epidemics of palsy in the head and limbs (Described by Ronsseur). The patients, often slumberous, lay with "half-closed eyes, open mouth, filled with ropy mucus, and tongue affected as if paralyzed." (Crookshank).

Lethargy with ocular palsy was described by Johann Peter Albrecht of Hildesheim as, "De febre lethargica in strabismus utrisque oculi desiventi." He speaks of "a continued fever, characterized by acute headache, dryness of the mouth, and other symptoms which are customarily observed in acute diseases of this kind, the chief of these symptoms centering around this, namely, it consisted of a great inclination toward sleep, which took on greater and greater force in proportion as the pain in the head relaxed, with the result that as many times as she (the patient) was aroused from sleep, so many times did she sink back into that most profound slumber." After apparent recovery, "a distortion of her eyes of such a kind that it forced the pupil in each eye up toward the upper eyelids with the lower part of the eyeballs showing white for more than halfway up," appeared. This description is very suggestive of a case of epidemic encephalitis showing residual oculogyric crises.

In 1712, an outbreak of so-called "sleeping sickness", centering about Tübingen in Germany, made its appearance. Zueler (180) stated that in an epidemic of influenza at that time, profound sleep was so frequent and pronounced a symptoms that in Tübingen
the disease was called Schlafkrankheit. Camerarius spoke of it as "Somnolence with ophthalmoplegia."

In 1768, Lepecq de la Cloture recorded the appearance of a syndrome which he called "coma somnolentum," and Ozanan in 1835 described cases of catarrhal fever associated with somnolence. In 1875, Gayet of Lyon made note of a disease characterized by ophthalmoplegia of subacute onset, accompanied by apathy and somnolence.

The last few years of the nineteenth century contributed rather extensive reports of an epidemic which appeared in northern Italy, spreading to Hungary, Germany, and France but not to America. Longuet (175) described the disease under the title of "Nona" or "Malattia de la nona" in 1892, calling attention to the presence of lethargy, ptosis, pupillary changes, patchy anesthesia, absence of reflexes, and weakness. Mauthner (Longuet) regarded the disease as an acute hemorrhagic polioencephalitis superior. Although this outbreak is frequently cited as evidence of the epidemic nature of encephalitis prior to 1917, it did not at the time attract much professional attention even from the medical authorities in Rome. Indeed, "an occasional correspondent" writes in the British Medical Journal for 1890 (200) that the rumors of an epidemic disease with cerebral manifestations are unfounded. Finkler in discussing encephalitis (in Stedman's Twentieth Century Practice of Medicine) in 1898 speaks of a widespread disease of cerebral character which definitely followed outbreaks of influenza in 1890-1892 and also of a few cases of
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a type of encephalitis not related to influenza and designated by Leichtenstern as a "primary acute encephalitis," in which involvement of the basal ganglia was marked.

In the United States, no cases suggestive of epidemic encephalitis seem to have been observed before 1900 (Archibald Church). However, within the next fifteen or sixteen years a few sporadic cases were described. Dr. W. G. Spiller (17) in a personal communication to Dr. W. Browning states that in 1910 he observed a case of cerebral disease with lesions and symptoms closely resembling those that he (Spiller) had observed since 1918. Dr. Browning (17) reports a case of the hyperkinetic type of encephalitis, seen in December, 1906. This patient later developed a typical parkinsonism. Similar instances have been noted by Raymond and Claude in 1909 and by G.W. Watson in 1912 (Matheson Commission).

The first recorded cases of the great epidemic of 1917-1918 had their onset in April and May, 1915 in Bucarest, Rumania, and were reported in 1916 by Obregia, Urechia, and Carnic1 (107) as "Encephalite hemorrhagique avec un diplocoque encapsulé." Still other cases were studied in the French military hospitals and occurred at Commercy, Verdun, and Bar-le-duc in 1915 and 1916. These cases were designated by Cruchet, Moutier, and Calmettes (107) as "Encephalo-myelite subaiguë." From central Europe the disease spread to England, the first cases there being reported early in 1918 by Harris (71) and Hall (69), and to the United states in the fall of that year. The first case of epidemic encephalitis in this country on which any data are available
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occurred in the City of New York on September 4, 1918, (Hurst). The disease spread rapidly, and by May, 1919, cases had been reported from twenty states. Subsequently cases were reported from all parts of the world.

It is very difficult to get any accurate conception of the total morbidity and mortality in this widespread outbreak of epidemic encephalitis because in many countries, especially in France, Germany, and Spain where the disease first appeared and undoubtedly was extensive, no statistics are available, since the disease was not reportable. The Matheson Commission (D7) reports 42,988 cases as the number noted between 1917 and 1927 (which includes the Japanese epidemic). Assuming that only one-fourth of the actual cases were reported (Riley), the tremendous proportions of this epidemic may readily be seen.

Three extensively studied and yet unclassified epidemics of encephalitis, very similar to and yet showing more or less difference from the Economo type, have appeared in widely separated localities since the great epidemic of 1917-1923.

In the late summer and early autumn of 1917 and 1918 there appeared in New South Wales, Australia, an outbreak of a disease characterized by general signs of cerebro-spinal irritation, namely, convulsions, rigidity, hyperactive reflexes, unconsciousness, accompanied by a high fever. In its lack of paralytic residua, as well as in certain other features which will be discussed more fully later on, it differed from poliomyelitis, while its high mortality (70%), high incidence among children under five (50%-Cleland and Campbell), lack of ocular palsies, and
failure to show residua made identification with true epidemic encephalitis impossible. The cases occurred in widely separated communities between which no communication existed, except via routes radiating from Sidney, in which no cases of poliomyelitis, meningococcic meningitis, or influenza were reported during the epidemic of "X-disease". Therefore, it seems unlikely that there were human carriers. Experiments of Cleland and Campbell (26) suggest that some domestic animal (sheep or horse) might have served as a reservoir. Indeed, there is a well recognized form of acute encephalomyelitis in horses, known as Borna's disease, although no definite relationship between it and human encephalitis has been established.

In the late summer and early fall of 1924 there occurred in Japan an epidemic outbreak of a disease which clinically and epidemiologically differed somewhat from the usual form observed in Europe and the United States. Kaneko and Aoki (107) designate this as an epidemic of Type B encephalitis, which because of its high mortality (60%), its high incidence in people above fifty, the marked meningeal manifestations and tendency to hyperkinesis rather than lethargy, and the rarity of the Parkinsonian syndrome is to be distinguished, in their opinion, from Type A encephalitis, which in its seasonal incidence (winter), greater incidence in the 10-30 year period of life, and moderate mortality rate closely resembles the European and American type of epidemic encephalitis. However, pathological changes (Flexner) appear to be the same in the Japanese and
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European types. The Matheson Commission finds that there are no satisfactory grounds for making a differentiation "either between these two types in Japan, or between the Japanese and the European or American form of the disease." Again in 1926 (1,012 cases) and in 1929 (2,000 cases) encephalitis appeared in Japan. In both the mortality was high, and in other respects these outbreaks resembled the 1924 epidemic, although neither was so extensive as the latter (6,551 cases). The possibility that an endemic focus of encephalitis exists in Japan has been suggested by the Matheson Commission (107).

Finally, in the summer of 1933, there appeared in St. Louis and Kansas City, Mo. a rapidly spreading disease, characterized by severe psychic manifestations. Coming on abruptly with high fever and other signs of general infection, marked symptoms of meningeal irritation, neck rigidity, positive Kernig, etc., appeared, and lethargy, very much like that seen in the classic epidemic encephalitis, soon followed. The patients either died within a few days or rapidly recovered with no sequelae persisting. Cranial nerve palsies were never associated with the symptomatology. The first cases had their onset late in July, and the epidemic was practically ended in October. 577 cases occurred in St. Louis city and 520 in the county, making an attack rate of approximately (Leake, Musson, and Chope) 100 cases per 100,000 population for the city and 212 per 100,000 for the county. The only approach to this incidence is that reported in Paris, Ill., in August, 1932 where in a short outbreak of a very
similar disease, an attack rate of 433 per 100,000 prevailed. The true epidemic encephalitis of 1917-1923 never was epidemic as compared with either of these outbreaks. In the 1933 epidemic both sexes were equally attacked, and the great majority of the patients fell within the age group above fifty years. No means of communication, insect, food and water, or human, could be demonstrated.
The agent causing this widespread disease still remains to be proven. In 1932 the Matheson Commission concluded its report with these words, "Again it is necessary to conclude that the question of the etiology of epidemic encephalitis is still unanswered."

The theories regarding etiology may be classified under five headings:

1. General Factors.
2. Relationship to Other Diseases.
3. Toxic Disturbances of Central Nervous System.
4. Cultivatable Bacteria.
5. Filtrable Viruses.

General Factors.

Season: Epidemic Encephalitis of the classical von Economo type is a disease of the winter months. The Matheson Commission gives figures which substantiate the predominantly fall and winter incidence of the disease in its 1918 to 1923 appearances. The total cases collected by this survey for the years 1919-1927 show that the highest incidence was in February and March.

The "mysterious disease" in Australia in 1917-1918, the Japanese epidemic of 1924, and the St. Louis outbreak in 1933, on the contrary, occurred in the late summer and early fall. Furthermore, the characteristic preference of the European and American form of the disease for the colder months
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has undergone a change during the last few years. The League of Nations Monthly Epidemiological Report for September, 1927 comments, "Seasonal fluctuations are becoming more and more uncertain."

**Age:** Epidemic Encephalitis may occur at any age. It has been reported in the newborn by several investigators (Harris, Parsons). At the other extreme, Netter is reported by the Matheson Commission (107) as having seen a patient of eighty-seven years. MacNalty (107) refers to the death of a woman of eighty-four years from this disease, and Leiner (97) speaks of age incidence "to 96 years."

However, with few exceptions, young adults are most susceptible to epidemic encephalitis. In 1,273 cases in England and Wales between 1919 and 1920, the highest incidence (25.6 percent) was in the age group, 10-20 years. In the Sheffield epidemic, the incidence in this age group was 30.9 percent. Strauss and Wechsler's (107) 864 collected cases showed a percentage of 25.7 in the age period of 21 to 30 years. Of 9,680 cases collected for the Matheson Commission survey from the literature reports of all countries, the age was stated in 7,584 cases. Of these the age group 20-30 years showed the highest incidence. 1,921 (25.3 percent) came within this period.

**Sex:** The majority of statistical reports show a higher incidence among males than among females. In the Sheffield epidemic in 1924, 186 males (59.3 percent) developed the disease to 131 females. Of 531 cases in New York City in 1926
and 1927, 55.45 percent occurred in males. Of 8,537 cases collected from the world literature, in which the sex was stated, the Matheson Commission found 4,935 (57.8 percent) were males, and 3,602 (42.2 percent) females.

**Occupation and Social Condition:** "There is no indication of any connection between occupation and liability to infection," Hall (107). James (84) found "among the adult male patients nearly as many occupations as there were cases of illness." Strauss and Vechaler's (107) study showed "every conceivable occupation represented." Professor Wynne's (193) study of the occupations involved and of the social status of the patients in the Sheffield epidemic, led him to conclude that there was no relation between the disease and social conditions; the occupations were affected in due proportion to the population. Sterling (107) also concluded that neither social nor economic conditions played a role in the development of the disease. He listed 34 occupations but found no one affected unduly.

Parsons, on the other hand, concluded "that the disease attacks chiefly those individuals who spend the greater part of the day indoors." On the contrary, Kaneko and Aoki (107) found the greatest incidence among the peasants or farmers, and attributed it to overwork and exposure to the sun. However, there is such a disparity in these reports and others which purport to find an occupational factor that the Matheson Commission, after a study of 7,000 cases, concluded, "It seems fair to conclude that neither occupation nor social condition bears any
relationship to the susceptibility to epidemic encephalitis."

**Race:** Very little comment has been made in the literature on racial incidence. The Matheson Commission states, "The incidence of epidemic encephalitis has undoubtedly been greatest among the nations of Europe and in the United States. Whether this is due to a greater susceptibility of the white race or to the conditions, as yet undetermined, that were responsible for the recent epidemic (1918-1924), is a question that cannot be answered."

**Communicability:** "The rarity of any evidence of contagion has been noted in every country in which the disease has occurred," (Hall). In spite of the mass of material (1,156 cases) studied at the Neurological Clinic in Vienna, Hoff (107) states that no case of definite contact infection could be established. Similar reports come from Germany and Japan.

Some writers find convincing evidence, however, of communicability, although the number of cases involved is small. Netter (134) determined, he believed, eight clear cases of contagion out of 174 cases studied (4.6%). In the Sheffield epidemic, Professor Wynne (193) also found "evidence of contact, more or less intimate in six instances, involving thirteen patients, or just over 4% of the total number of cases ascertained."

Instances in which the disease has been noted in more than one member of a family have been described by many writers.
in each country from which literature reports are obtainable. MacNalty (103) 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.

During 1919, twelve cases with five deaths developed among the inmates of a girl's home in Derby, England in less than two weeks (107). Similar instances have been reported by Hall, MacNalty, and Fyfe.

Several well defined instances of probable contact infection in hospital wards have been reported (Claude and de Laulerie, Duzar and Palo in the Matheson Commission report). However, as Hall (107) says, "....considering the large number of cases of encephalitis lethargica admitted to hospitals in all parts of the world, the fact that such instances (of ward infection) are thought worthy of record is the strongest testimony to their infrequency."

More numerous are the reports of instances in which a nurse caring for a patient with epidemic encephalitis has herself contracted the disease. Godfrey and Gwynn (62) observed a nurse who contracted the disease, after she had been nursing a patient with epidemic encephalitis for five days. Doyle (33) reports a similar instance but does not give the incubation period.

Transmission of epidemic encephalitis from mothers to newborn babies has been described (Hall, Harris). It is
probable that the infection was not by "placental transmission" as suggested by Hall (107), but by direct contagion at or before birth (Matheson Commission).

Zinsser (196) suggested that the difficulty in attempting to trace the course of the infection is probably due to the existence of many carriers. Whatever the reason, the fact remains that evidences of contagion are inadequate for definite conclusions as to incubation period and modes of transmission of the disease.

Relationship to Other Diseases.

The difficulties in diagnosing epidemic encephalitis, especially great before its establishment as a definite clinical entity, quite naturally led to its confusion at first with other diseases. Among the earliest theories proposed was that of Harris (71), who called attention to certain points of similarity in his cases to the clinical picture of botulism.

This theory was soon, however, effectively quashed by the Medical Research Committee of the Great Britain Local Government Board, London (107) which reported several findings furnishing conclusive evidence against such an origin of the epidemic: (1) Failure to recover the Bacillus Botulinus from the tissues and fluids of fatal cases or from articles of food which had been regarded with suspicion; (2) Serum from recovered patients failed to agglutinate this bacillus; (3) The changes in the central nervous system pointed to an acute infection rather
than to an intoxication; (4) There was never more than one in a family affected; (5) Many of the patients had not eaten any suspicious food; (6) Two instances of the disease in exclusively breast-fed infants.

The remarkable association of the disease with the prevalence of epidemic influenza, which has been noted in the historical review (Crookshank), has given rise to the belief among quite a few investigators that the two diseases may be causally related, epidemic encephalitis being the result of cerebral localization either of the influenza organism itself or of a peculiar modification of it. Crookshank (29) traced many instances of encephalitis, most of them following shortly after major "influenzal epidemics", and concluded: "Epidemic meningo-encephalomyelitis 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."

Symonds (175) notes that the so-called "Nona" of 1890 and the war time epidemic of encephalitis both coincided in their appearance with world-wide epidemics of influenza.

If, however, we examine closely the epidemiology of the early years of the war time outbreak, it is evident that the early cases of epidemic encephalitis preceded rather than followed the outbreak of epidemic influenza. The first recorded
cases of the great encephalitis epidemic, as mentioned previously, had their onset in April and May, 1915 in Bucarest, Rumania, and were followed by cases in the French military hospitals that same year. The epidemic of influenza which reached its peak in 1918-1919 was already on the march in Europe as early as 1917, but while some cases occurred in Vienna during that year, there was no epidemic then. Furthermore, while there was some overlapping in the occurrence of the two diseases in 1917-1919, once the pandemic of influenza had passed that of encephalitis still continued. The height of the wave of lethargic encephalitis came several years after that of influenza, in England, for example, in 1924-1925.

There is also a disparity as regards age groups attacked. Hurst (82) finds that the age period, 10-19 years, is the lowest of all periods for epidemic encephalitis but the highest of all ten year periods for influenza. As mentioned above, encephalitis attacks males more often than females, while influenza attacks both sexes equally. And finally, as Luger (89) points out, influenza is highly contagious, but there is almost complete absence of evidence for direct infection in influenza.

Therefore, with regard to epidemiologic evidence, we may conclude with Jordan, "It does not seem possible to identify surely the present pandemic of encephalitis with nervous disorders accompanying or following the historical pandemics of influenza."
Clinically post-influenzal encephalitis and so-called epidemic encephalitis are to be differentiated chiefly by the characteristic sequelae, such as parkinsonism and behavior difficulties, following the latter.

Similarly, experimental attempts to establish a relationship between the two diseases have, for the most part, given negative results. While Stewart and Evans (171) in 1930 reported finding in 100% of cases of encephalitis studied (114 patients) positive cultures for the Pfeiffer bacillus from the nasopharynx, and positive agglutination of the Hammet strain of this bacillus by the blood serum, this work remains unconfirmed. Volpino and Racchusia (184) failed to find the bacillus in the tissues of rabbits dying of encephalitis following inoculation with sputum from human influenza cases. Rosenow (150) and Tarorzi (107) likewise reported negative results in their search for the Pfeiffer bacillus in encephalitis patients. Furthermore, even granting the accuracy of Stewart and Evans' observations, it has not been conclusively shown that the Pfeiffer bacillus is the etiologic agent in influenza.

Histologically, influenza encephalitis and epidemic encephalitis differ considerably, the former presenting essentially an hemorrhagic encephalitis, the latter showing few and very minute red cell extravasations (Strumpell, Gross, MacNalty). Bassoe (9) points out that influenza encephalitis does not, as does epidemic encephalitis, show selective invasion of the basal ganglia.
While, therefore, the general consensus of opinion and the burden of the experimental work is against any direct relationship between epidemic encephalitis and influenza, there are still those who hold that an indirect relationship exists between the two diseases. Flexner (46) states, "Whether an attack of the first (influenza) predisposes to an attack of the second (encephalitis) in the manner of the predisposing effect of influenza on bacterial affections of the respiratory tract, is another question awaiting close study." Zinsser (196) reaches the same conclusion. Kramer (107) believes that influenza is one of the factors that are responsible for the epidemic spreading of the sporadic cases of encephalitis usually present in almost every country.

Another disease which was in the early studies linked with encephalitis, but is now generally considered to have no part in the etiology of that condition, is acute anterior poliomyelitis. Briefly, the evidence against any causal relationship between the two diseases is as follows:

1. Encephalitis is, for the most part, a disease of early adult life. Poliomyelitis, on the other hand, is found for the most part among children.

2. The geographical distribution of the epidemics of encephalitis have been far more widespread than any of poliomyelitis, but the former has not been so severe in any one small area as the latter often is.

3. The seasonal occurrence of the two diseases also
differs. Encephalitis in its classic form is most frequent in February and March. Poliomyelitis occurs most frequently in warm weather.

(4) Poliomyelitis shows an almost exclusively spinal localization with typical residual paralyses. The residua of encephalitis point to an almost exclusive involvement of the higher centers. In poliomyelitis degeneration of the nerve elements, large hemorrhagic areas, and polymorphonuclear infiltration are common, while in encephalitis, degenerative changes, if present, are slight, hemorrhages rare, and infiltration chiefly with lymphocytes and plasma cells. "In brief, the lesions are of a definitely infectious character in poliomyelitis, while the alterations result rather from a chronic process in encephalitis". (Levaditi).

(5) Experimentally no relationship has been shown. While Neustaedter, Hala, and Banzhaf (126) have reported in vitro neutralization of poliomyelitis virus with convalescent serum from encephalitis patients, no confirmation is reported in the literature. Amoss in 1921 (3) failed to obtain protection against poliomyelitic virus in monkeys with convalescent encephalitis serum, but procured complete protection against the same dose of virus with an equal amount of poliomyelitis convalescent serum. Levaditi (98) found that his herpetico-encephalitis virus did not actively immunize monkeys against poliomyelitis virus and visa versa. Furthermore poliomyelitis virus while virulent for the monkey, rarely infects the rabbit; the encephalitis virus is very pathogenic for the rabbit, only
weakly so for the monkey (Levaditi).

Toxic Disturbances of the Central Nervous System.

This theory is suggested by the very similar clinical and pathological pictures that may be produced by the action on the brain of certain toxins of bacterial origin, such as those of typhus and Bacillus botulinus, as well as by certain chemical poisons, such as lead. Furthermore, such an etiology would fit in well with the repeated failures to isolate a living causative agent.

Two lines of investigation have been followed in this connection: (1) Search for a focus of infection in which a neurotoxin might be elaborated; (2) Attempts to show a constant metabolic disturbance.

Along the first line of investigation several workers have reported finding a source of the intoxication in either the upper respiratory or gastro-intestinal tracts. Yates and Barnes (194), after careful examination of twenty-three cases of epidemic encephalitis, concluded that the infection is a symbiotic process, involving: (1) damage of the mucosa of the upper respiratory tract by one of the catarrhal group of organisms; (2) inhalation of the encephalitis virus and its passage through the damaged mucosa to reach the brain via the peri-neural lymphatics along branches of the first division of the trigeminal nerve or along the olfactory nerve. Salzman (161) indicted the gall bladder as the focus of infection. He suggested that the transient nature of many of the manifestations of encephalitis is due to a tempor-
ary edema "due to a selective action of toxin elaborated in some source of infection of the body," which clears up with the resolution of the infection. He reported six cases of epidemic encephalitis cured by cholecystectomy.

The work along the line of metabolic disturbances has been chiefly in the direction of changes in carbohydrate utilization, which some have attempted to relate to liver dysfunction. Buscaino (107) advanced the theory that post-encephalitis syndromes are degenerative lesions of the central nervous system due to the presence of special toxic substances, particularly aromatic amines, in the circulation, due to hepatic lesions. Runge and Hageman reported (127) finding pathological liver function in twenty cases, and suggested that liver lesions might allow penetration of toxins into the nervous system. However, the constant presence of liver lesions or liver deficiency has not been demonstrated (O'Flynn and Critchley).

In chronic epidemic encephalitis several reports indicate some defect in carbohydrate metabolism, manifested by alterations in the glucose tolerance curve. Kasanin and Grabfield (92) found in seventeen cases, both acute and chronic, flat or high blood sugar curves. McCowan, Harris, and Mann (112) reported that in the majority of cases of chronic encephalitis a hyperglycemia after glucose ingestion was manifest, markedly sustained in 50% of cases. They claimed that the benefit derived from hyoscine in cases of parkinsonism, is due to the lowering of the blood sugar curve by some direct or indirect action of the drug.
However, even though these reports indicate the presence of some metabolic deficiency, which may or may not be related to some endocrine upset, no one has been able to show that this condition is the cause and not, as is more likely, the result of epidemic encephalitis. The rather sudden appearance of epidemic encephalitis in its wartime outbreak, and its spread in recurring waves strongly suggests its relationship to other proved infections of the nervous system, such as poliomyelitis and meningococcic meningitis. Furthermore, it seems likely that a focus of infection elaborating toxins which so profoundly affect the central nervous system would give local signs in the infected area, and would, moreover, result in evidence of intoxication elsewhere than in the central nervous system. This theory has accordingly been dropped from consideration by most modern investigators.

Cultivatable Bacteria.

A great deal of conscientious, painstaking investigation has been expended in an attempt to isolate the specific organism of epidemic encephalitis, but no one has yet been able to advance irreproachable evidence of the cultivation of an organism that can be held responsible, according to the postulates of Koch, for the causation of the disease.

Many organisms have been described as the causative agent, chiefly of the streptococcus group. However, since most of the work has been done on rabbits, it is perhaps well to explain that a spontaneous meningo-encephalitis, having a pathol-
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...logical picture closely resembling that described by many investigators as the result of inoculation with their particular organism, occurs in a rather high percentage of animals. Flexner (46) reports 50% positives among a large series of supposedly normal stock animals. Clinically the animals are normal; no nervous or other symptoms betray the presence of the disease. Pathologically there are widespread inflammatory changes, chiefly in the cerebrum, but also in the basal ganglia, where lesions in human encephalitis are most pronounced (Oliver, Twort and Archer, Goodpasture). Levaditi, Nicolau, and Schoen (107) point out that late in the course of spontaneous rabbit encephalitis, granulomatous nodules with a central area of necrosis, in which they find a parasite, the "Encephalitozoon cuniculi," (considered by these workers to be the cause of this particular type of spontaneous rabbit encephalitis) appear throughout the areas of greatest damage. Of course, if these "encephalitis" nodules are present, this disease is easily separated from experimental encephalitis. However, Oliver (130) states that the majority of rabbits show only mild changes consisting of perivascular infiltration with lymphocytes and plasma cells, exactly simulating human pathology.

River and Stewart (141) describe another form of spontaneous rabbit encephalitis, caused by their filtrable virus III, not related immunologically to the herpes virus, but capable of producing changes in the central nervous system of rabbits, which resemble closely those produced by the latter virus. Clinically the two diseases are likewise similar.
It can readily be seen, therefore, that many reports of isolation of various cocci and viruses, which have been claimed to produce typical lesions in the rabbit must be discounted, especially since many of the investigators ran no control series of animals to find the percentage of spontaneous lesions in their particular stock of animals.

In 1917 von Wiesner (168) described a Gram-positive diplostreptococcus, which he claimed to have isolated from one of von Economo's cases, and with which he produced hemorrhagic encephalitis in apes by intracerebral inoculation. However, he could not demonstrate the same pathologic picture which was found in fatal cases of epidemic encephalitis. Similar organisms were reported to have been isolated from the brain and spinal fluid of patients with the disease by Stafford (1918), House (1920), and Maggiora and Sindoni (1921), but none of these investigators were able to reproduce the disease in animals. Pico (107) in 1921 described a diplostreptococcus, isolated from spinal fluid, which produced a fatal encephalitis, transmissible in series, in rabbits.

Loewe and Strauss in 1919 (102), working with filtrates from nasal and nasopharyngeal washings from encephalitis patients, reported the isolation of a filtrable virus, which they carried into the twelfth generation through successive inoculation and recovery from the brains of rabbits, dying with an encephalitis, showing quite typical brain lesions. Monkeys were also positively inoculated. Further studies and cultural investigations, us-
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ing Noguchi's ascitic-fluid, kidney-tissue medium under anaerobic conditions, resulted in the identification of minute, globular, refractile bodies, Gram ampholitic, and occurring singly, in chains, and in diploform; this organism was cultivated from spinal fluid, blood, nasopharyngeal washings, and brain substance.

These studies have never been confirmed except by Thalhimer (177, 178), a collaborator in the first work, who described a similar organism obtained from the brain and spinal fluid in human cases. Levaditi (99) and Flexner (46) believe that these investigators, however, were working with spontaneous rabbit encephalitis.

Evans and Freeman (40) in 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. The organism, Gram-ampholitic, slightly hemolyzing, varied from a filter-passing form to a "giant" coccus in size, and at times appeared in culture as a spore-forming rod, which produced minute filtrable, coccoid bodies, appearing as buds along its walls. In its diplococcus form it corresponded morphologically with the streptococci obtained by von Wiesner, Rosenow, and several others. Pure cultures of the
organisms were recoverable from the brains of inoculated rabbits and monkeys, showing a clinical picture closely resembling that of human cases. Intravenous injection of the organisms showed elective localization in the brain, especially in the mesencephalon where the lesion consisted chiefly of marked meningeal inflammation and perivascular infiltration with round cells.

In 1927, Evans (39) claimed to have isolated the same streptococcus from six strains of virulent herpetic virus sent to her by various investigators along that line—either directly from the material sent or from the brains of animals inoculated with this material.

Oblitsky and Long (128), on the other hand, 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 non-infectious material intracerebrally. Furthermore, using Evans and Freeman's technic for preparing the brain emulsion, they ground up meat with sterile sand, and obtained from cultures of this emulsion, streptococci, giant cocci, spore-forming rods, and other organisms. These streptococci corresponded culturally with those described by Evans and Freeman, and in rabbits produced a purulent meningoencephalitis. They concluded that the streptococci were not visible forms of the herpes virus.

Rosenow of the Mayo Clinic has probably contributed more than any other investigator to the literature of the bacteriology of epidemic encephalitis. The great majority of his
Experiments have been carried on by culturing and subculturing nasal, nasopharyngeal, dental, and tonsillar exudates from patients with epidemic encephalitis, isolating pure strains of streptococci and injecting them in almost every known manner, as well as packing the nose with gauze soaked in cultures, into laboratory animals, chiefly rabbits. His studies have led him to claim great specificity for the various strains of streptococci which he has isolated. He states (150) that bacteria obtained from lethargic patients, produced lethargic rabbits; those from maniacal patients produced maniacal rabbits; those from patients with persistent hiccups (143, 148, 152) produced in rabbits rhythmic, clonic spasms of the diaphragm; those from myoclonic patients and choreiform patients reproduced the same phenomena in 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.

All strains of the streptococci were found to be immunologically similar. All were pleomorphic, hemolyzing organisms, which with successive animal passage tended to lose their specificity and to produce more uniformly the more ordinary manifestations of experimental encephalitis in rabbits, such as
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lethargy accompanied by general tremors and other nervous symptoms. Since he was able to produce a similar picture by injecting filtrates not only of human material but also of his cultures, he concluded that the specific localizing power of the organisms depended on "a chemical substance produced either by the streptococcus or during the reaction incited in the host."

In 1933 he reported (155, 156) 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 also claimed that in 100% of human cases, heat-killed streptococci cultured from the spinal fluids of active cases, produced a strongly positive skin test. In 1935 (157) he described the production of encephalitis in monkeys with cultures and filtrates of cultures of this organism.

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 of horses with his streptococci, discounted.

McKinley in 1930 (115) reported the isolation from the tonsils and nasopharynges 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.

Again in 1933, McKinley and Verder (117) were unable to culture organisms from and to obtain positive animal inoculation
with brain emulsions from cases of the St. Louis type of encephalitis.

Zinsser in 1928 (19) surveyed the bacteriological data that had been obtained up to that time, and concluded as follows: "If one assumes the possibility of a mutation of an organism into a filtrable virus form, and together with that, a modification in pathogenic properties during the course of the mutation, one could accept as a solution of the problem, not only the work of Evans and Freeman, but that of others who have cultivated bacteria. It is still a far cry experimentally to such a premise, however, and logic forces one at the present time to reject the bacterial causation of this disease." He stated his belief that a filtrable virus of some type is the most logical conclusion with regard to etiology. Since these conclusions, little in the way of demonstration definitely of a bacterial causation has been done. Therefore, we must consider the filtrable viruses in some detail.

Filtrable Viruses.

At the present time the theory of virus causation of epidemic encephalitis meets with most general approval (Grinker). McIntosh and Turnbull (114) isolated the first virus from the brain of a human case and produced a disease in monkeys resembling the human encephalitis by intraberebral injection of brain emulsions. The virus was not cultivatable and has never been classified.
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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 herpetic-co-encephalitis group (Levaditi), all 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). The following table (reproduced from the Matheson Commission Report, 1929) shows the viruses belonging to this group which have been most extensively studied. The only virus of importance which has been reported since 1929 and belonging to this group (Gay and Holden) has been added to the table.

HERPES-LIKE VIRUSES ISOLATED FROM MATERIAL FROM CASES OF EPIDEMIC ENCEPHALITIS

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Date</th>
<th>Name of Virus</th>
<th>Material Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levaditi and Harvier</td>
<td>1920</td>
<td>C</td>
<td>Brain</td>
</tr>
<tr>
<td>Levaditi and Harvier</td>
<td>1921</td>
<td>CH</td>
<td>Nasopharynx</td>
</tr>
<tr>
<td>Doerr and Schnable</td>
<td>1921</td>
<td>Bâle I</td>
<td>Spinal Fluid</td>
</tr>
<tr>
<td>Doerr and Berger</td>
<td>1922</td>
<td>Bâle II</td>
<td>Brain</td>
</tr>
<tr>
<td>Berger</td>
<td>1922</td>
<td>Bâle III</td>
<td>Brain</td>
</tr>
<tr>
<td>Schnabel</td>
<td>1923</td>
<td>Berlin</td>
<td>Spinal Fluid</td>
</tr>
<tr>
<td>Doerr and Zdansky</td>
<td>1923</td>
<td>Hogander</td>
<td>Brain</td>
</tr>
<tr>
<td>Luger and Lauda</td>
<td>1924</td>
<td>Wien</td>
<td>Spinal Fluid</td>
</tr>
<tr>
<td>Perdrau</td>
<td>1925</td>
<td>E.L. I</td>
<td>Brain</td>
</tr>
<tr>
<td>Gay and Holden</td>
<td>1933</td>
<td>W</td>
<td>Brain &amp; Cord</td>
</tr>
</tbody>
</table>

Levaditi and Harvier first reported a virus belonging to this group (98), the so-called virus "C", isolated from the brain of an encephalitis patient also suffering from facial...
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herpes. It could be passaged through rabbits, producing in them typical clinical manifestations and pathological changes of encephalitis. Later the virus "CH", from the nasopharynx of a patient, was found to produce in rabbits a kerato-conjunctivitis, which in one instance progressed to a fatal encephalitis, which could be transmitted in series.

Meanwhile in 1920, Doerr and Vochting (107) reported that certain of their rabbits in which an herpetic keratitis had been produced, also developed symptoms pointing to a lesion of the central nervous system. This production of encephalitis in rabbits by the herpes virus has been confirmed by Blanc (107) and Doerr and Schnabel (107).

Levaditi concluded that the viruses of herpes and encephalitis differ only in relative virulence for the skin and cerebrum, both being strains of an herpetico-encephalitis virus with relative cutaneous and cerebral affinities as expressed by the following formula:

\[
\begin{align*}
\text{Cutaneous Affinity} & \quad \text{Cerebral Affinity} \\
\text{Virus of encephalitis} & \quad + \quad ++++ \\
\text{Virus of Herpes} & \quad ++++ \quad ++
\end{align*}
\]

Otherwise they are identical since: (1) they are equally filtrable, equally well preserved in glycerine; (2) they produce the same symptoms in rabbits inoculated either by the ocular or cerebral route; (3) the histo-pathological changes produced by each are identical; (4) they show cross immunity. This conclusion is the basic principle underlying this theory of the causation of epidemic encephalitis. All the other viruses men-
tioned above have been shown to have immunological reactions similar to Levaditi's virus, and to possess both keratogenous and encephalitogenous powers. All are highly virulent for the rabbit but rarely produce disease in the monkey, a fact, which together with certain immunologic differences, distinguishes them from the virus of acute anterior poliomyelitis.

The true herpes virus, present in the fluid from typical herpetic lesions of the skin, has been demonstrated by Blanc and Caminopetros (107) 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 (in the rabbit especially) an encephalitis with symptoms and lesions very like those produced by the encephalitic virus isolated by Levaditi, Doerr and Schnabel, etc. Monkeys are resistant to it just as they are to the encephalitic viruses. The above investigators reported no neutralization of the herpes virus by human encephalitis convalescent serum. However, neither was Levaditi (98) able to neutralize his encephalitic virus with human convalescent serum. Flexner and Amoss (51,52,53) in 1925-1928 likewise reported negative results in attempts to neutralize either the herpes virus or the herpético-encephalitis strain with human convalescent serum, although they isolated from a fresh lesion of herpes febrilis, a virus which displayed a remarkable degree of neutropism as well as dermatropism. Corneal, cutaneous, even testicular inoculation produced an encephalitis.
Perdrau (136) concluded that the herpes virus has two strains, one present in the brains of inoculated animals, which is more neurotropic, and another recoverable from the cutaneous vesicles, which is more dermotropic. Zinsser and Tang (138) after finding that animals partially immunized with the herpes virus developed a clinical syndrome very like that of human encephalitis following intracerebral injection of the (herpes) virus, whereas non-immune animals developed a very acute encephalitis unlike that in human beings, concluded:

"Human beings by repeated skin infections attain a not inconsiderable partial immunity to herpes virus, which would explain the nature of the clinical course (as in our partial immunity rabbits) as well as the innocuousness of direct injections of herpetic virus into man, as reported by Bastai and Busacca, and the finding of herpes virus in human beings not suffering from lethargic encephalitis."

Proof of invasion of the central nervous system by the herpes virus is lacking. Most investigators (Schnabel, Doerr, Zdansky) have failed to isolate the virus from the brains, blood or spinal fluids of patients with herpes. As mentioned above, Bastai and Busacca (10) found inoculation of man with herpes virus without general effects; even intraspinal injection of brain emulsion from rabbits dying of herpetic encephalitis only occasionally gave mild nerve root pains, never encephalitis. "The weight of the evidence is definitely against the invasion of the central nervous system by the (herpes) virus except as a rare occurrence," Matheson Commission.
The problem of the relation of the herpes virus or a neurotropic strain of this virus to the etiology of epidemic encephalitis is still unsettled. The evidence for and against such a relationship may be summarized as follows:

Against the herpetic origin of encephalitis:

1. In only a few cases (perhaps ten, according to Gay and Holden) has the herpes virus been isolated from encephalitis patients. Perdrau (136) points out, however, that if, as he claims, the antibody and the virus in human brains studied degenerate at different rates, the former more rapidly than the latter, the amount of virus in each brain will vary greatly. Therefore, many negative results will be obtained, especially as the duration of the disease before death is so variable. He also suggests that failures may be due to the difficulty in infecting one species of animal with a strain of virus adapted to another species. Levaditi (98) postulates the theory that the marked defense reaction aroused in the nervous tissue with which the virus comes in contact, in addition to destroying the virus (autosterilization), is incompatible with life. Therefore, the brains of many fatal cases will not show the virus, the latter having been destroyed in the reaction which resulted in the fatality.

Gay and Holden (58) give as other reasons for the rarity with which the herpes virus is found in encephalitis patients: (1) true epidemic encephalitis is probably often confused with similar infections (e.g. post-vaccinal encephalitis) which are in all probability due to other organisms or viruses;
(2) relatively few cases of encephalitis have been studied in the acute phase when the virus is most probably present; (3) when present, the virus is probably in small amounts; (4) the human virus, although neurotropic for man, may be strictly dermotropic for animals, and consequently not demonstrable by intracerebral inoculation of human material, the method most used in attempts to isolate the virus.

2. Herpes virus, when found in human brains is merely a contaminent; but control cases also show the virus rarely (Gay and Holden).

3. At least two viruses displaying both encephalitogenous and keratogenous powers, have been isolated from patients with neurophilis, giving no history of encephalitis. Joltrain and Hutinel (87) as well as Flexner (51) isolated such viruses, capable of producing encephalitis in rabbits, and immunologically related to the herpes virus from the spinal fluid in cases of neurphilis. Perdrau (136) says that in these instances the dermotropic strain of the virus, so commonly present on skin surface, merely showed its characteristic preference to graft itself on a pre-existing lesion of the central nervous system.

4. Herpes is a common infection whereas encephalitis is rare, but: (a) most human beings are probably immune to the encephalitis (Matheson Commission); (b) the usual virus of herpes lacks neurotropism (Gay and Holden).

5. Herpes accompanies epidemic encephalitis less fre-
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quently than it does other diseases, but experimental results (Perdrau, Gay and Holden) suggest that herpes may actually serve to protect against encephalitis.

For the herpetic origin of encephalitis:

1. The virus of herpes simplex produces in many animals, especially rabbits, skin and brain infections which resemble, respectively, herpes and epidemic encephalitis in man. Perdrau (134) has shown that in rabbits immunologically identical strains of herpes virus vary in their relative dermotropism and neurotropism.

2. A subacute disease clinically resembling human encephalitis has been reproduced in Cebus monkeys with the herpes virus (Zinsser, McKinley and Douglas).

3. Herpes virus produces in animals lesions, which while variable, yet correspond with various stages in the human epidemic encephalitis (Gay and Holden, Stern and Dawson).

4. Evidence that the naturally occurring antibodies against the herpes virus fluctuate both in herpes and in encephalitis in man, suggests a causal relationship of both the diseases to the herpes virus (Gay and Holden).

Before closing this discussion of the filtrable viruses mention should be made of three major outbreaks of encephalitis, in each of which unclassified viruses, apparently unrelated to each other, to the virus of herpes simplex, or to the herpeticoencephalitis strains, have been reported.

The so-called Australian "X-disease" has been variously
classified as an atypical poliomyelitis or an aberrant form of epidemic encephalitis, but its true nature remains a mystery.

Flexner (45) claimed that the pathology resembled that of poliomyelitis much more closely than that of epidemic encephalitis (This is denied by Cleland and Campbell). However, certain points speak against its being a form of poliomyelitis, namely: (1) adults were much more often affected than is common in poliomyelitis; (2) mortality was higher; (3) out of forty survivors (in Cleland and Campbell's series), only three had residual paralyses, but there were two cases of residual mental disorder; (4) lethargy or varying degrees of unconsciousness occurred in the majority of cases (Cleland and Campbell); (5) the spinal fluid showed very slight increase in the number of cells, with no predominating type; (6) during its outbreak, there were reported very few cases of poliomyelitis elsewhere in Australia; (7) the anterior horn cells of the spinal cord were usually in fairly good condition, (Cleland and Campbell).

On the other hand, while the presence of lethargy, slight changes in the spinal fluid, and cases of mental residua suggest epidemic encephalitis, the very small number of residua, especially the total absence of parkinsonism, the lack of ocular palsies, and the very high mortality, are all against such a conclusion.

Cleland and Campbell (26) isolated from the brains of rapidly fatal cases a non-cultivatable, filtrable virus, capable of producing in monkeys, sheep, even calves and horses, as well
as in many small laboratory animals, a disease characterized by symptoms (violent, irregular movements, with little or no paralysis) and lesions very similar to those in human cases. Breinl (107) obtained from the spinal fluid of cases a virus which produced a fatal paralytic disease in animals. No attempt was made to identify either of these viruses with the herpetico-encephalitis group. Since the definite relationship of either virus to the disease has not been demonstrated, the etiology is still in the dark.

The conclusions with regard to the Japanese epidemics of 1924 and 1929 are similarly indefinite. Kaneko and Aoki (91) divided the cases of encephalitis in Japan into two types in 1924: (1) Type A, the same as that occurring in the western hemisphere; (2) Type B, more or less endemic in Japan, but sometimes, as in 1924, reaching serious epidemic proportions. However, Flexner (45) concluded after study of material from these cases that the lesions closely resembled the European and American type of the epidemic encephalitis.

Several viruses have been isolated in connection with the 1924 epidemic, but none have been proven to be the etiologic agent. Among the most extensively studied of these were six strains reported by Takagi (176) in 1925, as virulent for animals, and entirely unrelated immunologically to the herpetico-encephalitis viruses. He called them strains of the virus of encephalitis japonica, which he considered entirely different from the European and American type. Similar confusion exists
in connection with the 1929 epidemic; no very well substantiated claims have been made for any one virus in connection with this outbreak.

Within the last two years a great deal of work has been done in connection with the St. Louis epidemic of 1933. It is considered doubtful by most workers that this was an outbreak of the Economo type of epidemic encephalitis, because: (1) once started the disease spread rapidly within a relatively small area, not gradually over a wide area as is the usual experience with the von Economo type; (2) the highest incidence came in the age groups over fifty; (3) it attacked both sexes equally; (4) it had a very short course, with a high fever which fell rapidly after three or four days; (5) recovery was rapid and complete; (6) the spinal fluid showed a typical mononucleosis; (7) there were marked meningeal signs, but only transient ocular manifestations; (8) the pathology differed in showing more intensive meningeal inflammation, more degenerative changes in the nerve cells, more widespread inflammatory foci, rarely degenerative changes in the cranial nerve nuclei, not even in the third, so commonly affected in Economo's disease, and more extensive involvement of the spinal cord (McCordock, Collier, and Gray). However, Neal (122) maintains that these cases did not differ materially from the meningeal type of epidemic encephalitis which she saw in New York City in 1918.

Neither was this disease similar to poliomyelitis because of: (1) its non-paralytic character; (2) it predominant
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incidence in the older age groups; (3) its marked mental symp-
toms, including affection of the speech, confusional states, etc.
Furthermore, polioencephalitis, due to an attack on the brain by
the virus of acute anterior poliomyelitis, is very rare (Neal).
And finally, there were several instances of patients who had
once had poliomyelitis, even within a few years, who contracted
this type of encephalitis, (Neal).

However, it is almost impossible to differentiate it
from the Japanese Type B encephalitis, and from a small outbreak
that occurred in Paris, Ill. in August, 1932, which is generally
considered a prototype of the St. Louis epidemic. In all three
the incidence above fifty years of age was the highest; all had
an acute onset and an acute course, ending either in death or
rapid recovery which was complete; all appeared and spread rapid-
ly; few, if any, ocular signs were present in any case. However,
Webster and Fite (187) found no serologic similarity between the
Japanese type and the St. Louis type.

As already mentioned, Rosenow (155,156) claims to
have isolated a diplostreptococcus responsible for this disease,
although McKinley (115) was unable to confirm this finding. Arm-
strong, Muckenfuss; and Webster (120) failed to demonstrate bac-
teria in brain sections, and found only a few bacteria in 50% of
cases on culture of brain emulsion. The organisms were of such
variety that no one could be held responsible.

There seems, however, to have been a very definite
virus isolated in this disease. This virus, which is considered
by many to be the etiologic agent, was isolated from the brains of fatal cases almost simultaneously by Muckenfuss, Armstrong, and McCordock (120) using rhesus monkeys, and by Webster and Fite (185) using a special strain of white mice, particularly susceptible to neurotropic viruses. These two strains have been found to be immunologically similar, and both are neutralized by convalescent serum from patients with the St. Louis type of encephalitis. The symptoms and lesion in the mouse resemble those in man. The virus is described by Webster and Fite (188) as filterable, capable of retaining its virulence 32 days in 50% glycerine, and "probably different from any hitherto known."

This opinion is substantiated by the failure to obtain neutralization of the virus by convalescent serum from suffers from true lethargic encephalitis (1-10 years after the initial attack), poliomyelitis, Japanese encephalitis, and Australian X-disease (Webster and Fite). Similarly neutralization experiments with serum from animals with experimental poliomyelitis and from patients with herpes simplex were negative. Webster and Fite consider the ability of the virus to pass filters with an average pore diameter of 66 milli-μ differentiated it from most known viruses, including those of the diseases mentioned above. Furthermore, it failed to provoke a response in rabbits, as do the viruses of herpes, vaccinia, and Japanese encephalitis. Since both strains are immunologically and pathogenically similar even though carried in different animal hosts, the virus is probably not related to any spontaneous disease in the animals used.
From all the evidence presented it would seem that the most logical and the best supported experimentally conclusion as regards the etiologic agent of true lethargic encephalitis as well as of the closely related forms of epidemic encephalitis is that a filtrable virus, probably some form of herpes virus in the case of the von Economo type of encephalitis, and apparently specific, independent viruses in the case of the related types. This is the view held by Zinsser, Grinker (66) and many other investigators.

Perhaps a word should be appended regarding the method of spread of the virus within the body and its localization in the tissues. Goodpasture and Teague (64) have done considerable work along this line. They have demonstrated that in ocular herpes, the virus does not enter the brain invariably by way of the sensory fifth nerve. Goodpasture in 1929 (65) showed following intramuscular injection of the virus in animals, changes in the motor ganglion cells deep in the pons before lesions could be demonstrated in the fifth nerve or elsewhere. He concluded that the myelin sheaths seem to insulate the virus in its passage upon an axon, for the cells of the sheath of Schwann surrounding the axis cylinders are susceptible to herpetic virus, and when they become affected, and acute neuritis manifests itself, Goodpasture believes that the virus may be harbored in an inactive state within the nerve cells and their axons. Flexner in 1925 (47), however, stated that the virus attacks the nerve cells directly, "affecting them quanti-
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Epidemic Encephalitis tentatively in such ways as at one time to produce stimulation and at another time paralysis."

Webster and Fite (125) and Brodie (16) have made extensive studies on the mode of dissemination of the virus from the St. Louis encephalitis. Repeated attempts to infect mice via the gastro-intestinal tract have always proven negative. However, the virus could be transmitted serially by instillation of the virus into the nasal cavity for 28 passages. Attempts were made to trace the further course of the virus by intracerebral and intraperitoneal injections of blood and emulsions of parenchymatous and cerebro-spinal tissue taken at various stages of the incubation period and of the disease. Rarely was the virus demonstrable in the blood and only occasionally in the parenchymatous tissues. However, it was present in the olfactory bulbs as early as two hours after inoculation and next in the lobus pyriformis; late in the incubation period or early in the disease, but before the appearance of lesions, the virus had spread throughout the whole central nervous system. Brodie concludes: "The virus then appears to travel along the nerve fibers of the olfactory nerve to the bulb, and then to the lobus pyriformis, after which it spreads to all parts of the central nervous system."

However, since the mode of transmission and the portal of entry of the virus of epidemic encephalitis have not been demonstrated, any conclusions as to the manner of spread of the virus in the body must be purely tentative. As previously noted
the inability to demonstrate definite contagion in epidemic encephalitis, makes it impossible to be sure of man to man infection. No insect vectors have been demonstrated although careful search, especially in the St. Louis epidemic, has been made for them. Furthermore failure to find the virus in the blood, and failure to produce the disease in humans by intracutaneous inoculations with various of the viruses (Bastai and Busacca, Brodie) speak against an insect vector. Careful check on the food, water, and milk supplies during the St. Louis epidemic failed to indict any of these as the agent of dissemination of the infection.

Nevertheless, despite failure to find a portal of entry, the numerous reports of isolation of viruses from the spinal fluid or from the nervous tissue itself suggests that at an early period in the course of the disease the virus has reached and spread widely in the nervous system, perhaps along the nerves, especially the cranial nerves (Goodpasture, Brodie), but evidently not in the blood stream (Brodie).
Despite the large amount of work expended in the so-far indecisive attempts to ferret out the etiology of epidemic encephalitis, attention has been within the last few years increasingly drawn to the clinical conditions following the acute phase, which have shown this disease to rank with syphilis in the protean nature of its manifestations. These signs and symptoms have been labeled and analyzed in many exhaustive contributions under the title of post-encephalitic types of sequelae.

However, from time to time a certain amount of dissatisfaction has been evinced over this title with its connotation of a completed, burned out picture, characterized by a static condition, and the implication of a final conclusion. Not only has the so-called chronic stage of the disease in some patients apparently grown directly out of the acute stage but also supposedly completely recovered cases have, after an interval of from six to twenty-four months of apparent good health, begun slowly to develop progressive syndromes like those of the first group. Furthermore, these syndromes, either growing out of acute manifestations or coming on after apparent recovery, do not tend to remain stationary, as sequelae due to parenchymatous damage in an acute disease should. Many examples continue to manifest a slow, relentless progression, which successively destroys one function after another, until death brings the tragedy to a close. And finally, patients who apparently showed no acute symptoms at any time previously, developed, de novo, the chronic form.

Consequently the recent considerations of this phase
have turned more to the conception of a continuing process, one which in many instances may produce an apparently definitive form, but in many others takes on itself a mutational aspect, first bearing one and then another imprint. Schaller and Oliver (162) in 1922 reported a case as chronic epidemic encephalitis, which lasted fourteen months. At autopsy examination instead of showing the usual pathologic appearance of a degenerative encephalopathy, the nervous system presented the picture of an inflammatory reaction in all stages and grades of tissue activity. Areas were found which presented the picture of a healed process with dense masses of gliogenous tissue, mostly of glia fibers. In other parts of the brain there were areas of acute inflammatory reaction with hemorrhage, perivascular infiltration with round cells, the larger cells (plasma cells, "endothelial leucocytes") containing much fat. Adventitial proliferative changes were also present, and occasionally Nissl's acute type of degeneration with nuclear eccentricity and chromatolysis was found. Neuronphagia was frequently seen. Von Economo (140) reported similar observations, as did Globus and Strauss, (61) who described the condition as a subacute form presenting lesions of mixed acute and chronic pathologic character. Apparently this disease is never a completed story, but "retains the possibility of flaring after the passage of months or even years into renewed activity, not as fresh attacks but rather as regional resurgence into an active destructive process," Riley (140).

The frequent history of clinical cases with, as Free-
man pointed out (55), latent periods, remissions, exacerbations, and progressive involvement of one system after another points to a persistence of the causative agent, long after the subsidence of the acute infection, in many instances manifesting an increasing disablement and eventuating in death. He believed that the marked evidences of destruction, the widespread scattering of pigment, the appearance of wandering glia cells, the overgrowth by a gliogenous feltwork, and the presence of fat in the scavenger cells years after the active onset of the disease show that the activating agent is still producing pathologic and clinical evidence of persistence. The sequelae result from a continuing process not from a slow degeneration following the initial destructive activity. Freeman also cited several cases from the literature in which persons apparently contracted this disease through close association with patients who were suffering from a chronic form of the disease, or who were in an acute exacerbation.

Hohman (76) commented on the universal discovery in his cases of evidence of persistent acute and subacute inflammatory reactions, even after months and years of the disease. Abrahamson (1) believes that permanent defects in the nervous, vascular, and glandular structures of the body may result from the acute process, which although themselves invariable, may be followed by progressive functional deterioration to which the term chronic may be applied; or organisms may survive in sheltered sites, where, acting with greatly reduced virulence, they may in-
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sidiously produce progressive lesions. Functional recovery of cells not vitally damaged accounts for, in his opinion, disappearance of some of the physiologic alterations in this disease; or the physiologic consequence of a permanent lesion may be compensated and the functional defect disappear. Alteration of one unit of, for example, the endocrine system of glands may so derange the whole system that indirectly a progressively increasing defect develops. He attributed great influence to heredity, environment, and age in determining the development, persistence, or disappearance of sequelae. "The factors in the chronicity of the disturbance in lethargic encephalitis are thus not merely the disease agent and the resistance of the person to this organismal invasion, but also the general functional integrity of the individual and the nature of his environment."

As in the acute stage itself, the symptoms and signs of the sequelae of epidemic encephalitis can be classified as mental or physical. Usually there is not a clear relation between these groups, and it will be more convenient to consider them separately, and to describe under the physical conditions any mental disturbances closely associated with them. The mental sequelae are, therefore, to be considered first.

Mental Sequelae.

It seems reasonably certain, as outlined above, that as a result of the activity of the infective agent or its toxin within the body, a varying degree of temporary or permanent
damage to the nervous tissues takes place. It is not strange then that so many psychic disturbances, which Kirby and Davis (94) classify in the realm of the organic, more specifically the toxic-infectious mental reaction types, arise in the course of the disease. Usually the psychic alterations are without definite intellectual disturbances (Gordon). Gordon (66) states that while some cases may simulate a demented state, actually there is no genuine dementia, only a generalized akinesia involving the entire psychomotor sphere.

The lack of any intellectual defect and certain other characteristics of these patients have aroused doubts in the minds of many investigators as to the definite organic background for these psychic manifestations. Contrary to the opinion of Kirby and Davis (94) is that of Clarke (24), who finds no evidence that any lesion left in the wake of this disease has any direct bearing on the conduct, as such, observed in chronic encephalitis. He states, "We must look upon the lesion here as one that singularly wounds the psyche and personality of its victim, not in the somatic and physiologic sense, but in a psychological one." The failure of neuro-pathologists to find any constant or severe lesion in the cortex to account for the psychic manifestations, and to explain why one patient, having suffered the same acute manifestations, should react differently than another, bears out this viewpoint.

The more generally accepted position with regard to this question is a middle one, which accepts an organic change.
as the background for the psychic symptoms but recognizes that the individual picture is dependent upon the modifying influences of heredity and environment on the organic syndrome. As Hohman (76) puts it, "With diffuse organic change (in the higher nerve centers), the personality or constitution of the patient is apt to rupture at its point of greatest vulnerability." In support of this theory are the observations of Still, (172) Strecker and Ebaugh (173) that the mere presence of a brain lesion, such as trauma, tumor, etc. may be sufficient to produce behavior disorders very similar to those seen in epidemic encephalitis.

In general the psychiatric picture of chronic epidemic encephalitis presents nothing very characteristic. The symptoms vary from minor defects, such as impairment of memory and alteration of sleep rhythm, to much more severe conditions, such as neuroses, mental deficiency, and psychoses. Duncan reports (34) 72% and Grossman 57% of his patients (chronic encephalitics) as having mental sequelae. Other investigators report 40% to as high as 70% (Paterson and Spence) of patients who have recovered from the acute phase as presenting some degree of mental alteration. The higher figures are for the most part obtained in series including only, or to the largest extent, patients under twenty years of age. Duncan finds the highest incidence of mental sequelae in this group. Sex apparently has no influence on the incidence of these residua.

Since the residual mental states of epidemic encephalitis are similar to and indeed in not a few cases apparently
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grow out of acute psychic syndromes, we shall follow Riley's (140) classification, in so far as it is applicable to the chronic phase, of the psychiatric disorders in this disease.

He divides the syndromes into the:

1. Somneic- including lethargy, hypersomnia, hyposomnia, and inverted sleep.
2. Delirious-confusional.
3. Manic-depressive. In this group we may also include other postencephalitic syndromes which resemble the true psychoses.
4. Amnesic-confabulatory. This group includes all disorders of memory.
5. Mixed trends- including the phobic, compulsive, paranoid, emotional, and degenerative states.

We may perhaps add a seventh group, that including the mentally arrested cases, which are observed only in young children.

In following the above classification we shall from time to time modify it in order to limit the discussion to the chronic phase of the picture only.

1. Somneic: In only a few cases does prolonged somnolence persist beyond the acute phase of the disease. Abrahamson, however, states (1) that if the disease has been very acute, especially if meningo-encephalitic signs occurred, the patient may remain as if stunned for months. Spiller (138) reports three cases of narcolepsy. Abnormal drowsiness, rather than actual somnolence, however, is a fairly frequent symptom
among patients in whom lethargy was a marked feature of the acute stage. Nocturnal wakefulness is commonly associated with this diurnal hypersomnia.

On the other hand, hyposomnia is not infrequently found as a residua (in 49% of Grossman's patients). In the majority of cases the insomnia develops in the later rather than in the earlier stages of the disease (Kirby and Davis). In this condition also nocturnal hyposomnia may be associated with diurnal hypersomnia, often expressed as a gripping lethargy; more often is this condition seen in children (Kirby and Davis).

Various theories have been proposed to explain these sleep disturbances, chiefly attempts to show some damage to a "sleep center", in the hypothalamus, the presence of which has not been definitely shown, but none are satisfactory. Progulski and Grübel (43) maintain that an organic lesion, just where they do not designate, is responsible, while Franchioni (54) points to a neurotropic predisposition as the chief factor in the development of these sleep disturbances.

(2) Delerious-confusional: This manifestation rarely persists into the chronic stage. Courtney (23) states that we may look, as a rule for complete disappearance of the delusion states which not infrequently mark the acute phase of epidemic encephalitis.

(3) Manic-depressive and other psychoses: In the acute stage, as a result of the infection and the reaction to it, there is often (Jones and Raphael) evidence strongly suggestive
of infectious, toxic delirium, or toxic-organic psychosis, which in some cases appears to simulate strikingly certain other common, non-infectious psychoses. The possibility of the existence, however, of a definite or characteristic psychosis is deprecated by Wechsler (88), who feels that findings suggestive of such a state are but manifestations of an underlying infection or toxic delirium syndrome. Several other investigators, including Tilney and Howe (180) and Wilson (88), bear out this point of view. Cases reported by Hammes and McKinley (88) as showing delusions, hallucinations, and temporary disorientation, and by Cruchet (30) as presenting disorientation and paraphasic features may be construed on the same basis. Nevertheless, as pointed out by Jones and Raphael (88), there is no reason to suppose that a true latent psychosis may not be precipitated as a result of the infection, as has been determined in the case of other infectious processes, notably epidemic influenza.

Leiner (88) mentions two apparently frank cases of manic-depressive psychosis, one of the cyclothymic type. Clemenko (88) speaks of a characteristic euphoria which he claims to have found to frequently precede the acute phase of the disease, and which, as the disease progresses, tends to become a hypomania, and this in turn may become a truely manic condition. He mentions that in some patients an excited-depression instead of a hypomania may develop. Bond and Partridge (12) state that definite psychoses in the chronic stage are rare, most of them among adults, and usually they take the form of some phase of a
manic-depressive psychosis, or a profound bradyphrenia, precoxlke reaction, which may present the features of deterioration and dementia.

While in some cases affectivity may appear to be so seriously involved as to give the impression of a true psychosis, such as dementia precox, Gordon (66) points out that the fact that these patients are keenly aware of their behavior difficulty, often much grieved over it, differentiates the true psychotic from the postencephalitic patient. Furthermore, this affective disturbance is often only transient or periodical, being amenable to amelioration or even to recovery within a comparatively short time. Duncan (34) reports several cases of manic-depressive syndrome and also encountered depression and melancholia, either constant or periodic, and often related to some physical disability, such as parkinsonism.

(4) Amnesic-confabulatory: Abrahamson (1) finds that frequently amnesia exists during part of or the whole period of the disease. Duncan (34) and Grossman (68) report not amnesia but frequently defective memory among their patients. While Grossman notes that memory defects are chiefly for recent events, Duncan finds memory defective equally for recent and remote events. Some patients confabulate to fill memory defects, especially those who develop a confusional psychosis of the Korsakoff type.

Occasionally, although not usually (Duncan), the memory defect is severe enough to interfere with the normal occupation of the patient; probably it is not infrequently the cause of
backwardness in some patients of school age. Defective memory is often associated with difficulty in fixing the attention, which may also occur without forgetfulness (Duncan).

(5) **Mixed Trends:** Among the mixed types of mental disturbances, the phobias, compulsions, and paranoid states are confined almost entirely to the acute phase of the disease, usually in the initial stage of this phase (Jones and Raphael).

However, emotional instability tends to persist beyond the acute phase and is found in many patients, both adults and children. It is mostly manifested by marked depression, these cases showing a close relation to those presenting the manic-depressive syndrome. Sometimes, however, euphoria amounting almost to a hypomania may be seen (Climenko, Grossman). Kirby and Davis (94) found that emotional states were most apt to persist in patients in whom the acute stage had been marked by delirium and stupor.

The essential characteristics of the postencephalitic sequelae in the emotional sphere are as follows: aggressiveness, hostility, impulsive outbursts of excitement or anger, easily provoked or occurring without the least external stimulation; restlessness, discontent, a tendency to misrepresent or frankly to lie without any specific motive, and a tendency to misappropriate or steal; excessive eroticism accompanied or not by self abuse.

In general what characterizes this group of symptoms may be termed, "psychomotor instability," (Gordon). They do not
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occur periodically or at more or less regular intervals as do those observed in maniacal or hypomaniacal states, but present continuous states without intervallary periods, analogous to the purely motor manifestations of epidemic encephalitis, in which the symptoms exist for a long time without modification. The group of symptoms outlined above cannot, therefore, be considered parallel to the clinical pictures observed in the classical psychoses. While individually they may be encountered in several types of psychoses, nevertheless collectively they cannot be identified with the latter. They constitute a clinical entity apart because they involve almost exclusively the domain of emotional forces, the intellectual forces being almost always intact in such cases (Gordon). Consequently, these cases are characterized by a dissociation between the psychomotor instability, which is so strikingly exhibited in most of the cases described, and the intellectual integrity, strictly speaking.

Of the various theories proposed to account for this emotional instability, most of them (Hill, Gordon, Gibbs, etc.) attempt to connect it with lesions involving the thalamus and causing a release of primitive and instinctive tendencies with an increase in their affective accompaniment. This theory is in accord with the opinion held by several neurologists (Gibbs) that "the thalamus is the seat of affective life." However, such a relationship has not been conclusively demonstrated, and the question may not be considered as solved.

We may include in this group also certain neuroses
and psychoneuroses, which Duncan (34) states are not infrequently found as sequelae. These may include hysteria, periods of dissociation, etc., occurring in both adults and children.

In summarizing then, the postencephalitic syndromes may resemble the psychoses and psychoneuroses encountered in non-encephalitis, but are usually differentiable because of their confinement almost entirely to the affective sphere, the intellect being intact, and their transient and changing character, which often yield rather rapidly to psychotherapy. However, it must be borne in mind that a true psychosis may be precipitated in a constitutionally predisposed person.

(6) **Behaovir Disorders:** Besides the purely psychotic phenomena analogous to the classical psychoses, there is another set of manifestations which are more frequently observed, especially in children and young adults up to the age of eighteen, (Price, Bond and Partridge). These are alterations in disposition, character, and behavior, which may vary from a slightly altered mannerism to a complete change in the patient, mentally and physically. Bond and Partridge (12) state that this behavior reaction cannot be oriented definitely in any clinical picture, or identified with any particular degree of severity of the acute attack, or correlated with precision with a localization of lesion or course of a chronic process. In these patients intellectual impairment seems to be the rare exception (Gordon, Bond and Partridge).

The onset of changes in behavior may come within a
few days, weeks, or months after the acute attack, or may not reveal itself for several years (Molitch). There may or may not have been psychopathic tendencies in the child prior to the acute attack. Sherman and Beverly (164) found previous delinquency in only two out of twenty cases, while Anders (119) reported that 30% of his cases had hereditary taints and had come in contact with the law before their encephalitis. Bond (12) states that there are "many cases in which pre-existing psychoneurotic or psychopathic tendencies are brought out by the disease."

These patients do not usually have very severe neurological residuals, although Bond finds them generally hyperkinetic. However, he finds no evidence in them of progressive deterioration, nor "in general any evidence of an active chronic process affecting either the intellect or behavior."

The types of behavior exhibited by these children are so varied that they include almost every overt act to which an human being can fall heir. The most common observation of the parents, Stevenson (170) found, was that the child had "completely changed his nature." Leahy and Sands (95) state that "their mental status" is characterized by purposeless, impulsive motor acts, marked irritability, definite attention disorders, distractibility and changing mood, inadequate and inconstant emotional reactions, precocious sexual feelings, and intense eroticism.

Hall (7) classifies these children into the following clinical types:

(1) The "Apache" group: This, a severe disorder, seen
for the most part among boys, is characterized by a complete change of character. The child quarrels with his fellows, wanders abroad, is dirty in his habits, shows sexual tendencies, and may even be homicidal or suicidal.

(2) The "Difficult Child" group: By far the greatest number of cases reported in the literature may be classed under this heading. These patients too are excitable, irritable, and quarrelsome. Most of them show marked nocturnal restlessness and insomnia, but can sleep well toward morning. In their waking hours they are surprisingly alert and active, "constantly on the move," as the parents say. They are difficult to control, bad-tempered, lacking in respect. Mental efforts soon tire them, for they cannot maintain concentration on any one subject for any length of time. "It is as if the mind like the body partook of the general restlessness," Smith (165).

These postencephalitic behavior patients closely resemble in their clinical manifestations the constitutional psychopath, especially in the later phases of the encephalitic behavior disorder where the organic process seems to be clearing up, but with some emotional instability persisting. The diagnosis in such cases must rest on the history of a preceding acute attack of encephalitis, or if such is lacking, some cases may be differentiated by the late appearance of parkinsonism, choreiform movements, or other physical sequelae of epidemic encephalitis.

Many theories as to the mechanism underlying the change in behavior have been proposed and fall under two lines
of reasoning, attempting to correlate the behavior changes with:
(1) the direct or indirect effect of localized lesions; (2) psychic and social factors.

The purely neurological theory of the behavior reaction would account for these changes as due not to some general effect upon personality, but to definite physical changes, localized for the most part in the basal ganglia, thereby relating the behavior to motor disturbances (Leahy and Sands). Several investigators hold that the structures involved are motor, inhibitory, or tonus producing or regulating. Gerstman and Kaunders (12), for example, believe that there is a more or less primitive letting loose of the motor mechanism in response to environment, due to inhibition of parts of the strio-pallidal system. Wimmer (190) also relates the emotional incontinence to striatal deficiency, but points out that some of the general symptoms may be referred to the cortex. Some (Gibbs), however, deny that the behavior disorder, which, they point out, is much more emotional than motor, is to be correlated with disturbances in the extra-pyramidal motor apparatus, and suggest a disorder of a specific center of emotional control in the thalamus or elsewhere.

Bond and Partridge (12) believe that environmental factors combine with an organic factor to produce these behavior reactions. In the hyperkinetic type at least there is probably an organic background. It seems possible that lesions in the globus pallidus, putamen, and caudate nucleus may be responsible for the increased muscle tonus and abnormal movements associated
with these behavior states.

Collin and Requin (22) suggest that a brain lesion in individuals whose nervous system is not fully mature may so arrest development that the preponderance of the higher centers over the lowers ones is not fully established, with resultant inability of the former to inhibit the excitation of the latter so that there are impulsive automatic acts, predominance of bad instincts, and infantilism.

Many of these unfortunate children are uncontrollable at home, and in schools they prove to be disruptive elements. They do not thrive in the ordinary placement situation, and are not suited for care in many institutions. They are menaces to their own community, and as individuals, they are out of line of social remedial endeavors. Treatment in the hands of some has yielded variable degrees of amelioration of the condition. Most agree that institutionalization with individual psycho and occupational therapy is the best means of approach (Hall, Clark, Bond and Partridge).

Finally we come to a consideration of the group of patients who show variable degrees of mental deficiency following an attack of acute epidemic encephalitis. These cases occur not infrequently, for the most part among young children. Patterson and Spense (132) noted that the younger the child at the time of the acute illness, the greater was the degree of mental deficiency apt to be. Hall (70) states that the worst examples of this sequel (the so-called "idiot group") are practically always
found in children from infancy up to five years. Most investigators believe that the mental deficiency in these young children is due to arrested development of the encephalon and its connections by the severe reaction in the nervous tissue to the causative agent (Bramwell and Shrubsall, Dawson and Conn, Collin and Requin). The permanency of the mental defect (Hall) bears out this belief that there is actual arrest in the brain's development.

In some children with severe behavior disorders, the apparently poor judgement, poor attention, and memory defect may lead one to suspect a lowered mental level. However, as previously noted, several investigators (Gordon, Sherman et al.) find no intellectual impairment in spite of severe emotional disorder.

There may or may not be progressive mental deterioration among encephalitis patients in the higher age groups. Sherman found no evidence of such deterioration in patients examined eleven months after the acute attack, while Dawson et al. (31) report a definite intellectual deterioration observable within a few days to five years after the onset of the illness. Molitch (119) found that the presence or absence of such a sequel varied with the individual.

In summarizing then the mental sequelae, we may say that the manifestations vary from mild changes in character and emotional instability to severe syndromes closely resembling the true psychoses. Children are most liable to severe mental sequelae, especially since in these patients there is often arrest or impairment of the intellect. The mental sequelae tend to be tran-
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sient, and in not a few instances, especially in the behavior disorders, may be considerably ameliorated by psychotherapy.

Physical Sequelae

(1) Cranial Nerve Palsies:

These are among the most common sequelae of epidemic encephalitis. Duncan (34) found them in 76% of his patients Grossman in 64% of his. Nearly every defect seems to grow out of a similar one in the acute stage. More often than not (Duncan) the cranial nerve palsies are accompanied by other neurological findings; often several cranial nerves are involved in the same patient.

As in the acute stage of the disease, ophthalmoplegia is the most frequent of the cranial nerve palsies. Duncan finds that pupillary changes, such as irregularity, inequality, eccentricity, defective light or accommodation reflexes, more frequent than the ocular alterations, including ptosis, strabismus, nystagmus, etc. Pupillary changes are commonly multiple; that is, in nearly all cases, any inequality is associated with some other defect, such as irregularity or impaired reflexes. Bilateral involvement is usual in these cases. Of the ocular defects, weak convergence or otherwise impaired motion of the eyes is complained of most often. Stabismus may be either internal or external. Diplopia associated with it is rarely constant; the usual complaint is that of double vision when tired or after prolonged use of the eyes. It tends to gradually disappear in most cases (Duncan). Ptosis, usually incomplete, is often associated with
the other indications of third nerve lesions, stabismus, weakness of convergence, etc.

Impairment of vision, apart from diplopia, appears to depend upon defective power of convergence and accommodation. Optic atrophy is a rare sequel to epidemic encephalitis (Grossman, Price, Duncan).

Nystagmoid movements, usually coarse, irregular, and in an horizontal plane, are occasionally observed (Duncan, Zentay). Spasm of the ocular muscles is sometimes a distressing sequel. These so-called oculogyrlic crises will be discussed later on under the somatic motor disturbances.

Impaired movement of one or both sides of the face is found almost as frequently as ocular palsies. Duncan reports 36 out 125 chronic encephalitics studied had varying degrees of seventh nerve involvement, most often in association with parkinsonism. Grossman (68) found 66% of his patients with cranial nerve palsies, had some facial inequality. Facial nerve impairment is more often of the lower motor neurone type. In most cases of facial paresis, there are other evidences of cranial nerve involvement, particularly paresis of the tongue or soft palate and tremors of the lips or eyelids.

The tongue is often affected. It may show atrophy of one or both sides with marked limitation of movement, or there may be complete paralysis without wasting. Coarse tremors are manifest in some cases, usually unaccompanied by wasting.

Difficulty in swallowing or in mastication and dibb-
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Excessive salivation may be present in patients with advanced Parkinsonian rigidity. Articulation is not uncommonly defective depending on paresis of the tongue and lips. Deafness may rarely follow epidemic encephalitis (Price).

(2) **Somatic Motor Disorders:**

These may be outlined according to the most generally accepted location of the lesion (Riley).

A. Cortical and Subcortical:

1. Irritative—general or local convulsive seizures.

2. Paralytic—monoplegias, hemiplegia, or tetraplegia.

B. Basal Nuclear:

1. Choreiform, choreo-athetotic, and athetotic movements.

2. Parkinsonism (with or without tremor).

3. Myospiasms, tics, progressive lenticular degeneration.

C. Brain Stem:

1. Oculogyric and oculocephalogyric crises.

2. Masticatory and deglutitional disorders.

3. Facial tics.

D. Cerebellar: Ataxia or asynergia.

E. Spinal:

1. Involvement of the anterior horn cells—local atrophies.

2. Involvement of the posterior horn cells—segmental irritative manifestations and sensory loses.

3. Involvement of the long tracts—mixed syndromes.
A. Cortical and Subcortical:

1. Irritative: Local or general convulsions, which may be epileptiform, have occasionally been reported. A few cases of grand mal and petit mal epilepsy following epidemic encephalitis are on record (Grossman, Abrahamson, Price, Marshall). Marshall (105) suggests that the basis for these manifestations is a lesion interrupting the cortical projections to the midbrain, producing temporary decerebration with loss of cortical inhibition over the lower motor mechanisms.

2. Paralytic: Hemiplegias and diplegias, which are commonly observed during the acute and subacute stages of the disease, practically always disappear within a short time (Courtney). However, Tilden (179) and Price (138) find muscle weakness a common complaint among chronic encephalitis. The patient tires quickly, and his legs do not feel strong enough to hold him; his grip is also weak. Abrahamson (1) found an occasional case with hemiplegic, spastic attitude of the upper extremity, dragging of the leg, increased resistance to passive movements, and exaggerated deep reflexes. Similar cases presenting signs of pyramidal tract involvement—just where in its course being undetermined—including progressive spasticity, pathologic reflexes, etc., have been observed (Grinker, Marshall).

The exact localization of the lesions causing these irritative and paralytic manifestations is still far from clear. However, Grinker (67) suggests that definite lesions of the cerebral cortex may be responsible. He has examined brains which
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showed profound fatty degeneration of the cortical cells and quoted von Economo's observation of examples of severe cortical damage in the chronic phase of encephalitis.

B. Basal Nuclear:

1. Involuntary movements: A large group of post-encephalitic patients may be considered together under this heading since they all present various types of involuntary, purposeless movements. These commonly appear within a relatively short time after the acute attack (within eight weeks, according to Duncan).

In the mildest degree, these movements are slight, abrupt twichings of a purposeless and non-repetitive nature. Occurring frequently in the limbs, face, and tongue, but rarely in the trunk (Archambault), they make the patient appear restless and fidgety. In the most severe form, the affected limb or even the whole body may be violently jerked by abrupt contractions of one muscle or groups of muscles, or there may be increasing irregular movements of varying rapidity. If generalized, these movements may be more marked on one side, but rarely are they unilateral (Duncan); they may be limited to one or more regions. In patients showing slight twitchings, the muscles are usually hypotonic, while more continuous movements are usually associated with some degree of rigidity of the muscles (Duncan). Co-ordination is usually good. The movements can be inhibited or arrested by voluntary effort at fixation in mild cases, and even in the most violent forms may be completely inhibited during associated involuntary movements; during sleep they usually cease.

A striking feature of the choreiform movements is their
tendency to diminish; Duncan finds that they disappear within a few weeks in many cases, although in some they persist two to four years. Other neurological findings do not often accompany these choreiform movements. Neither are there any associated mental sequelae which are characteristic, although Archambault (4) describes a series of cases which he titles "choreopsychotic", in whom variable degrees of psychic disturbance, including confusion, disorientation, hallucinatory delerium, and delusional states, accompany the choreiform jerkings.

The majority of the theories relating to the cause of these choreo-athetotic movements place the lesion within the striopallidal region, although Archambault's choreopsychotic cases suggest that the lesions are not confined to the mesencephalon and the adjoining areas of the brain, but may involve the cortex also. Archambault, however, states that "there can be no doubt that choreiform and athetoid disturbances are intimately related to minute lesions either within or bordering on the caudate and lenticular nuclei." He cites the observations of Marie and Lhermitte in Huntington's chorea of chronic leptomeningitis, cortical atrophy, and massive atrophy of the corpora striata; they attributed the mental disorder to the meningo-cortical lesions, and the choreiform manifestations to the changes in the corpora striata. Reasoning by analogy, Archambault states that there is no reason why the meningeal inflammation, adventitial lymphocytic infiltration, multiple, minute hemorrhagic areas and cellular disorganizations in epidemic encephalitis cannot give rise, according to the focal prominence, either: (1) to combined psychotic
and choreiform manifestations, resembling chronic degenerative chorea, but differing in its rapid onset and early favorable or fatal outcome; or (2) to well-characterized athetosis or hemi-athetosis, closely resembling classic athetosis.

The absence of objective sensory loses and hemianopsia speaks against serious thalamic involvement (Archambault), while the lack of spinal irritative phenomena, such as fibrillations, myoclonus of part of a muscle or a single muscle eliminates the spinal cord as a site of the lesion. Thus an intralenticular or paralenticular localization asserts itself as the probable underlying cause of the spasmodic choreiform movements, (Morat). Frequent lesions of the corpora striata favor such an hypothesis.

Morat (137) states that the corpus striatum contains sensory and motor elements which transmit impulses from the higher centers, in order to produce automatic, involuntary movements of locomotion in the limbs. These movements "cease when another impulse arrests the preceding one (initiating the movements) and brings the automatic system back to a state of repose; they continue during the interval between these two impulses. The initiation and its cessation is alone voluntary, and, therefore, the impulse which produces it comes from the cortex, or must have passed through it." When the corpus is damaged, the mechanism whereby a cessation of automatic movements can be brought about is impaired, whereas the mechanism concerned in the initiation of the automatic movements (cortex) is intact. Hence the patient is
capable of voluntary execution of a motion but is not able to inhibit it.

Wilson (109) believes that injury to the corpus striatum cuts out the mechanism for inhibition of the tonus-maintaining centers in the brain and of an inherent neuro-muscular, rhythmical tremor low down in the physiological hierarchy.

It may be said, therefore, that while the general consensus of opinion is that the origin of these hyperkinetic phenomena lies in disease of the extra-pyramidal system, the exact mechanism concerned is still unsettled.

2. Parkinsonism: Forty to fifty percent of chronic encephalitics present the features characteristically seen in Parkinson's disease, viz., tremor, rigidity, and the peculiar posture, gait, and expression (Price, Marshall and Chambers, Pankboner). These cases may be grouped together as parkinsonism; most of them fall in the 30-40 age period (Duncan). Steady progression is observed in most (Price). In them all degrees of severity are seen, from merely mask-like expression plus slight rigidity with slight disability to excessive rigidity with or without involuntary, rhythmical movements. This state may arise in the acute phase and persist, or may develop weeks or months after the acute symptoms have subsided.

Certain features of parkinsonism require more detailed consideration:

(a) Tremor: This is produced by alternate contractions of opposing muscle groups and may be unilateral or bilateral with
one side more affected than the other. It is usually most marked in the upper limb, being maximal at the elbow; in the lower extremity, movement is maximal at the ankle (Duncan). It may be fine or coarse, and except during sleep, is constantly present. Emotional disturbances increase it, but it can be temporarily arrested by voluntary fixation of the limb, although Tildon (179) finds that voluntary movement often increases both its rate and extent. In more than half of these patients, tremor of the limbs is accompanied by tremors of the lips and tongue.

(b) Rigidity: Rigidity is a constant feature of parkinsonism but varies from slight rigidity on passive movement to marked general rigidity with typical stooping posture and festinant gait. Even catalepsy may be present (Grossman, Duncan) As a rule, the flexors are more affected than the extensors. Voluntary power, however, even in advanced cases may be surprisingly good, although all movements are slowly performed; new attitudes tend to be maintained for abnormally long periods.

(c) Reflexes: The tendon reflexes are nearly always, except in mild cases, exaggerated (Price), and some degree of ankle or patellar clonus may be present (Duncan). The latter finds that the abdominal reflexes are commonly altered, being exaggerated, absent, or rapidly fatiguable. The plantar reflex is equally variable. In cases with marked rigidity and hyperactive reflexes, an extensor response (Babinski) may be present; it may be extensor on the more rigid side, and flexor on the less affected side.

(d) Cranial nerve palsies: These are found in a large
percentage of cases (in nine-tenths of Duncan's series). Oculo-motor defects are the most common, although weakness of the face and tongue are not infrequent.

(e) Mental State: It is not easy to estimate the amount of mental defect in these cases on account of the coexisting motor disability. However, it may be said that the degree of mental impairment in these cases seems to vary directly with the severity of the physical condition. In moderately severe cases, little mental change or variable syndromes differing in no way from those in patients without parkinsonism (Duncan), may be present. Emotional instability and depression are found quite commonly in advanced cases by Duncan, while Smith (165) states that in these patients mental activity may seem to be almost absent, the patient lying motionless, apparently hearing and seeing nothing; yet he may have perfect perception. Mental deterioration proportional to the physical defect is not necessarily present (Duncan).

It is evident that in their main clinical features, there is a close resemblance between parkinsonism and paralysis agitans. In each there is general rigidity, giving rise to the mask-like face, typical posture, and gait; tremor is usually present, and in both there is steady progression to a fatal ending. Indeed, some consider them clinical and pathological entities (Netter and Souques). However, most authorities agree that slight but constant differences exist between the two conditions.

The mask-like face is an early manifestation in the encephalitic type, often rapid or abrupt in appearance; in paralysis
agitans, this symptom is usual gradual in development. The tremor in Parkinson's disease is slower and is most marked in the thumb and finger, giving the pill-rolling appearance, in contrast with the postencephalitic alternating flexion and extension of the elbow. Alterations in reflexes suggestive of pyramidal tract involvement, cranial nerve palsies, and mental impairment are features very rarely seen in Parkinson's disease. Other marked differences are those of age, sex, and clinical course. Paralysis agitans rarely occurs before the age of 45, is more common in men, and progresses very slowly, often for years, before reaching its fully developed form. Parkinsonism is much more common before the age of 36, is seen in women at least as frequently as in men, and often runs a very rapidly progressive course, sometimes ending in death within twelve to fifteen months. The course of the latter is more irregular with relapses and remissions which are not seen in Parkinson's disease; furthermore, there is usually the history of an acute attack of encephalitis preceding the onset of parkinsonism.

There is still, however, considerable dispute as to the difference in the localization of lesions in the two Parkinsonian conditions. Most investigators are agreed that in both conditions the lesions are located somewhere within the extrapyramidal system, but the exact site is the subject of much speculation. Some investigators (C. and O. Vogt) state that the striatal system, the corpus striatum and to a lesser degree the globus pallidus are in a state of degeneration. Ramsay Hunt (81) also points to lesions in the large multipolar cells of the cor-
pus striatum and pallidum, the lesions in paralysis agitans being vascular, and in parkinsonism, progressive atrophy of the motor neurones. Bremer, Goldstein, and Foix (73) and McKinley (118), on the other hand, believe that in both Parkinsonian states, the substantia nigra is mainly thought not exclusively involved. Globus and Strauss (73), Jacob (73), and several others find in addition changes in the basal ganglia, less marked, however, than those in the substantia nigra. Wimmer (73) reports shrinkage, and sclerosis of the ganglion cells, hyaline degeneration of the blood vessels, and glial proliferation in the substantia nigra and also in the globus pallidus, in both parkinsonism and Parkinson's disease. McAlpine (110) found in the substantia nigra marked reduction in the number of cells and degenerative changes in the remaining cells, but only slight changes in the other masses of gray matter (including the globus pallidus) of the extrapyramidal system in parkinsonism; in paralysis agitans, on the other hand, he found the pathological changes chiefly in the corpus striatum.

The mechanism concerned in the production of the characteristic muscular hypertonus of this condition has not been definitely determined. Tilney and Howe (180) would base it on an essentially extrapyramidal involvement, while Walshe (109) considers it of reflex (over the proprioceptive pathways) origin. Hassin and Bassoe (73) conclude that at present they can only claim that in paralysis agitans and allied conditions, the so-called extrapyramidal system, including the corpus striatum, globus pallidus, and subthalamicum, is involved. They suggest
that in paralysis agitans, degenerative lesions alone are present, while in postencephalitic states, degenerative changes are combined with inflammatory changes.

Because of the inconclusive state of our knowledge regarding the mechanism concerned in the production of the Parkinsonian states, their treatment is purely empirical. Each symptom is treated separately. The most widely used drugs in these conditions are atropine and hyoscine, which in the hands of some (Harris, McCowan, and Mann) have proven very helpful in reducing the hypertonus and the tremors.

In addition to the more commonly observed choreo-athetoid and parkinsonian syndromes, certain isolated myospasms and tics, which do not fall into either of these groups, have been reported from time to time. Courtney (23) reports several cases presenting persistent clonic myospasms of more or less generalized distribution; he attributes both clonic and tonic myospasms to partial degeneration of the cortical motor cells. Price (138) records a few cases with spasm of the abdominal muscles and an occasional case of spasmodic torticollis.

Then there are some patients who show tremors but no other signs of parkinsonism. Grossman (68) reports intention tremors, characterized by large, coarse, irregular oscillations, like those seen in multiple sclerosis and cerebellar disease, in five patients, present in both arms, or head and arms, or in all extremities. He also makes note of several patients with rapid, clonic twitchings of the muscles supplied by one or more
branches of the facial nerve, or with fine tremors, like those seen in hyperthyroidism, of the lips and tongue; coarse tremors, like those seen in toxic states, affecting the head or upper and lower extremities, were also found.

C. Brain Stem:

Of the various manifestations considered to be the result of lesions in the brain stem, by far the most frequently observed and the most distressing are the so-called oculogyric or oculocephalogyric crises. Most of these states are found in association with parkinsonism, appearing late in the development of this syndrome. Wimmer (86) reports a case which developed seven years after the initial encephalitis.

According to Jelliffe (86), the clinical symptomatology may be divided into four components, namely, the eye movements, the thought disturbance, the emotional state, and the nature of the consciousness.

A typical crisis presents in varying degree these four main components. The onset is most frequently correlated with some affective disturbance, or with fatigue, general or of the eyes, or with sudden stimulation by lights, sounds, commands, etc. The main outstanding feature is a paroxysmal, spasmodic conjugate deviation of the eyeballs, most frequently upward and to the right, but also directly vertical, to the left, or rarely downward to the left or right. In the majority of cases, there is a period, usually in the beginning of the attack, when direct forward staring is observed. During the ocular movements, pain in the eyes themselves or displaced to other regions of the head.
and violent vascular pulsation are often present.

Cephalogyric accompaniments, believed to be connected with the associated postural reflex activities of the eyes and head and manifested by retraction or turning down to one side of the head, are not infrequent (Holmes, Jelliffe, Grinker). There may be also general restlessness and mental distress or dizziness, with flushing of the face and diplopia. Existing tremor may be increased, and there may be associated opening of the mouth. A great variety of facial, masticatory, swallowing, speech, respiratory, arm, leg, or bodily torsion, etc., have been reported in the literature as occasional accompaniments. "Thought-blocking" or a "trance state" (Jelliffe) is often found, as well as all degrees of affective reaction from mild anxieties to grave psychotic behavior, differing with the individual and even varying in different attacks in the same patient.

These crises may appear frequently, several times a day, or rarely once a month, or at longer intervals, which may be regular or irregular. There tends to be a piling up of attacks late in the day, probably because of fatigue. The attacks may last a few minutes or may persist two or three days, during which time the patient is helpless. In most cases the attacks end in sleep, and the patient awakes quite free from the seizure; at other times the attacks cease spontaneously. During the interval between attacks, the eyes do not show any evidence of paralysis, and even during the attack itself, the eyes readily follow the examining finger.

The pathogenesis of these attacks is indefinite.
Jelliffe (96), who has extensively studied the condition, seeks to prove that they represent various forms of compulsive-impulsive behavior reaction, having strong affective components, which he explains as arising from subconscious conflicts. No conclusive evidence of an organic basis for these attacks has been presented.

Various other brain stem syndromes have occasionally been reported in the literature. Zentay (135) reports a case of irresistible mastication. Von Economo recorded a case with many symptoms suggestive of brain stem involvement, such as dysphagia, dysarthria, dysphonia. Facial tics, such as grimacing, facial spasm, blepharospasm, have been mentioned under the cranial nerve syndromes.

E. Cerebellar:

Occasionally ataxias and asynergias persist over into the chronic stage. Price (138) has reported several such cases. However, these sequelae are rare, and the literature contains but scant reference to them.

F. Spinal:

1. Involvement of the anterior horn cells: Local atrophies have been observed in a few cases (Grinker, Price).

2. Involvement of the posterior horn cells: Symptoms due to posterior horn involvement are more common. In the acute stage, irritative manifestations, such as radicular pains, hypesthesias, hyperesthesias, etc., signalize this type of involvement. These sensory signs persist over into the chronic stage.
in variable degree. Duncan (34) observed two cases of anesthesias, one with paraplegia, one in an hysterical state. Abnormal subjective sensations are more common; these include formication and tingling sensations in the extremities, and shooting pains in the lower limbs. Pains in the body and extremities are reported by Grossman (68) to be common in those who had suffered from the radicular type of encephalitis.

3. Involvement of the long tracts: Peculiar mixed syndromes due presumably to lesions of the long spinal tracts, such as amyotrophic lateral sclerosis (Riley) or multiple neuritis (Grossman), have been reported.

(3) Trophic Changes:

Duncan (34) states that most cases of advanced parkinsonism show more or less wasting and that in cases of hemiplegia, the affected muscles may show some atrophy, probably due to disuse. Price (138), however finds such changes rare. Obesity is seen in some postencephalitics. This will be discussed later on under endocrine disorders.

(4) Vegetative Disorders:

Under this heading we shall include bulbar syndromes, autonomic disturbances, and endocrine syndromes, since may investigators (Naccarati, in particular) believe that the vegeto-sympathetic centers in the diencephalon and mesencephalon are closely linked up with the endocrine system.

Under the bulbar, or parasympathetic disorders, according to Riley (140), may be noted, (1) salivary, (2) pneic, and (3)
cardiac disturbances. Excess salivation, with secretion of large amounts of thick, ropy saliva, is a common sequel (Price, Gilma). It is usually most marked in parkinsonism, in which the difficulty in swallowing due to muscular rigidity makes drooling common.

Pneic, or respiratory, disorders play a large and important part in the general postencephalitic picture (Jelliffe, Turner and Critchley). They may be classified as follows (Turner and Critchley):

(1) Disorders of the respiratory rate: Tachypnea, bradypnea.

(2) Dysrhythmias, or disorders of respiratory rhythm: Cheyne-Stokes breathing, breath-holding spells, sighs, forced or noisy expiration, inversion of the inspiration-expiration ratio, etc.

(3) Respiratory tics: Yawning, hiccough, spasmodic sniffling, etc.

Turner and Critchley (131) found any combination of the above types coexisting, with or without other sequelae of epidemic encephalitis, but Jelliffe (85) states that he has yet to observe a case of respiratory disorder without some accompaniments.

(1) Disorders of Respiratory Rate:

Tachypnea: This is one of the commonest respiratory manifestations, especially among children. It may be either continuous or paroxysmal, although Jelliffe maintains that even in the apparently continuous cases, there is a rise and fall in the intensity of the attack. Turner and Critchley report neither cyanosis nor much inconvenience to the individual in their cases,
while Jelliffe states that both cyanosis and inconvenience are common accompaniments of these attacks. Attacks may come on during both waking and sleeping hours, or during sleep only. The respiration are usually not only rapid but also shallow, which may be due to thoracic or diaphragmatic rigidity (Beriel). The lungs in these cases are normal, and tachycardia is not an accompanying feature (Turner and Critchley). Attacks may come three or four times daily, or even several times within one hour in the paroxysmal type. Usually the patient can voluntarily control them for a short time. Their intensity and frequency are increased by emotional stimuli, and conversely decreased when attention is distracted, as during the act of swallowing. Tetany, due to hyperventilation, may occur if the respirations are of full amplitude instead of shallow.

**Bradypnea:** This is a much rarer phenomenon, and may also be paroxysmal or apparently continuous. The respiratory rate may fall as low as six per minute, each inspiration being of increased amplitude and each expiration prolonged and noisy.

(2) Dysrhythmias:

**Sighs:** These are common, and consist of a deep sigh occurring in the course of a normal breath and followed by a short period of compensatory apnea. Exertion sometimes brings them on, but they occur just as often during sleep (Turner). At times these sighs appear with a regular periodicity, each one occurring after a definite number of respirations.
Apneic pauses: Intervals in which breathing ceases may take place as a result of sighing inspiration, during a spell of breath-holding, or during the course of normal respiration, especially during sleep.

Inversion of the inspiration ratio: Normally, inspiration is shorter than expiration in the ratio of five to eight in the waking state; during sleep, the reverse is true. In certain postencephalitic patients, the normal ratio is reversed.

Cheyne-Stokes respiration: Graphic records of respiration (Marie, quoted by Turner and Critchley) in some cases reveal a regular arrhythmia in the amplitude of respiration. Breathing may be alternately deep and shallow (bigeminal or alternating respiration), or a deep breath may be succeeded by two of smaller amplitude (trigeminal respiration). These anomalies are often associated with sighs or apneic pauses.

Breath-holding spells: These differ from the simple apneic pauses in that the breath is held in almost full inspiration. Paroxysms occur at irregular intervals and may or may not be interposed with periods of normal breathing. Following a series of deep, forced respirations, a deep inspiration is taken and held for ten to thirty second; the attack is terminated by a forced expiration followed by a short period of compensatory apnea. Accompanying choreo-athetoid movements, bizarre attitudes, or peculiar grimaces are common, but cyanosis is rare (Turner and Critchley). In severe cases, consciousness may be lost momentarily.
(3) Respiratory tics:

These include: hiccough, which is perhaps the commonest; involuntary, and sometimes paroxysmal, yawning, usually in parkinsonism; "soufflement" of the French writers, a tic-like blowing of the nose (Babinski, Carpentier); spasmodic, short, dry, hacking cough, for which no pulmonary, laryngeal, or pharyngeal cause can be found. These tics are especially common in children, and show an increased frequency toward nightfall.

Respiratory phenomena may arise at any stage of epidemic encephalitis. Although respiratory tics may follow diaphragmatic myoclonia in the acute stage (Zingerle—quoted by Jelliffe), usually there is no relation between the symptomatology of the acute stage and the subsequent respiratory disorders (Turner and Critchley). Usually these disorders are accompanied by other physical after-effects of encephalitis, especially with inverted sleep rhythm.

The pathogenesis of these respiratory disorders remains obscure. Some investigators have been content to dismiss them as hysterical manifestations. They point to the diversity and inconsistency of the clinical manifestations, the bizarre accompanying gestures, the marked affective reaction, and the fact that strong suggestion may terminate an attack. However, many definitely organic postencephalitic manifestations, such as tremors in parkinsonism, are similarly influenced by the emotional state of the patient and may in some cases be controlled for a
short time by a strong effort of will. Furthermore, other features of hysteria are lacking, and the condition, instead of yielding to treatment as do hysterical respiratory manifestations, tends to become progressively worse.

Changes in the acid-base balance and CO₂ tension of the blood have not been constantly demonstrated in these cases, and furthermore, such changes could hardly account for the variety of the respiratory disorders. Accordingly, we must look for some change in the nervous control of respiration as the basis for these disturbances. There are three possible sites of damage, in the: (1) peripheral (muscular) organs of respiration; (2) thalamus; (3) medullary centers.

(1) Theory of Peripheral (Muscular) Origin:

Several investigators have suggested that the tachypnea may be compensatory for the shallowness of respiration, due to intercostal muscular rigidity (Beriel) or to diaphragmatic immobility (Vincent and Bernard). However, muscular rigidity is usually seen only in parkinsonism, and Turner and Critchley find by fluoroscopic examination normal diaphragmatic excursion in almost all cases. While, therefore, it is improbable that peripheral disorders play any part in the pathogenesis of respiratory disorders, they may modify the respiratory movements.

(2) Theory of Thalamic (Basal) Origin:

Pardee (181) states that the association of emotional instability, sleep disturbances, and mask-like features
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with respiratory disorders is in favor of basal ganglion lesion. Lhermitte (181) found affection of the respiratory musculature in some cases of pallidal lesions. However, this theory of the site of the lesion is not accepted by many investigators.

(3) Theory of Medullary (Bulbar) Origin:

The majority of writers are inclined to regard the various post-encephalitic respiratory disorders as resulting from lesions of the respiratory center. This center is believed by many investigators (Legallois and Flourens, Turner and Critchley) to, at least in part, lie in the medulla in close association with the nucleus of the vagus. Medullary changes, especially in the dorsal nucleus of the vagus, found in postencephalitic cases by Archard, Levy, Foix (181), give support to such a theory. While the automaticity of this center depends upon the CO₂ tension of the blood, its rate and rhythm is regulated by impulses coming in from visceral and cutaneous areas as well as down from the cortex along the psychomotor pathways (Spencer). Since no alterations in the afferent impulses to the center (proprioceptive from the alveoli and thoracic musculature) have been demonstrated, and the efferent neuro-muscular mechanisms have not been shown to be concerned in the pathogenesis of respiratory disorders, Turner and Critchley postulate that either the so-called "pneumotaxic" center, which inhibits the inspiratory center, or one of the psychomotor supranuclear mechanisms is the site of the disease. The lack of resemblance between the encephalitic respiratory disturbances and
the dyspnea of bulbar origin, and the absence of clinical manifesta-
tions indicative of involvement of the other important medul-
lar nuclei make it doubtful that the respiratory center itself
is involved. The frequent psychical and sleep disturbances and
the emotional instability in these cases suggest lesions of the
psychomotor pathways and their transcortical projections. Turner
and Critchley (181) point out that interruption of these latter
fibers would abolish the unconscious control normally exercised by
the pyramidal tracts over the emotional factors of respiration,
leaving the long cortico-bulbar fibers of the pyramids, which
carry voluntary respiratory impulses, intact. This would result
in an unstable type of respiration, influenced by every variety
of emotional play.

These respiratory syndromes are usually of no serious
prognostic import. No treatment which will definitely improve
them is known. Oxygen may be necessary in severe apneic attacks,
and in the interval, sedatives may be tried. Jelliffe (85) re­
ports a large series of cases, in whom he found a psychogenic
factor, which have been benefited by psychotherapy.

Cardiac manifestations are rare, usually transient,
and cause the patient little inconvenience. Cases of tachycardia
(Duncan) and of bradycardia (Riley) have been reported. No ana-
tomic background for these changes has been established.

Among other symptoms referable to derangement of the
autonomic system (sympathetic division-Riley) may be mentioned:
hyperhidrosis, altered smooth muscle tonus, seborrhea, herpes,
digestive disorders, lacrimation, exophthalmos, and loss of hair.

**Endocrine Disorders**

Typical endocrine syndromes are rarely found in epidemic encephalitis (Naccarati, Abrahamson). General nutritional disturbances, such as is shown in cases of obesity (Abrahamson, Archard), of dystrophica adiposis genitalis (Barkman, Rivet, Westphal), of lipodystrophy, glycosuria, and diabetes insipidus (Naccarati), have led some clinicians to suspect pituitary involvement. However, von Economo (121), Marinesco (121), and several others have found the hypophysis histologically intact following the acute stage, in which a few acute histological changes have been reported to be present in the gland (Tucker, Lhermitte quoted by Naccarati). A center for urinary regulation has been found (Naccarati) in the region of the tuber cinereum and the floor of the third ventricle, whose damage in encephalitis could explain cases of diabetes insipidus without recurring to the hypothesis of an hypophyseal lesion.

Cases of precociously puberty (macrogenitosomia praecox) following epidemic encephalitis (Stern and Wimmer) suggest the involvement of the pineal gland or of the adjacent brain structures. No autopsy material has been reported, however, and it is impossible to determine whether the gland itself or nearby nerve tissue is damaged. Naccarati (121) inclines toward the latter belief.

Cases with symptoms suggestive of thyroid involvement,
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such as slight enlargement of the gland (Wimmer), exophthalmos (Grossman), and eye changes (Abrahamson), in each case with no accompanying toxic manifestations, or even typical thyroideal syndromes (Naccarati), have been reported. However, finding no thyroid pathology, Naccarati (121) relates all these symptoms to alterations in the sympathetic system.

Other endocrine syndromes which have been occasionally encountered include: those of the sexual sphere, such as frigidity, feminism, amenorrhea, and abortion (Abrahamson); and rapid and pronounced emaciation (Wimmer). No conclusions regarding the site of the responsible lesions have been made.

In general no constant or marked pathological changes have been found in any of the endocrine glands in the chronic phase of epidemic encephalitis, (Naccarati). In view of this failure to find lesions which might be considered responsible for the endocrine-like syndromes, this investigator suggests that all sympathetic-endocrine symptoms are referable to lesions in the central sympathetic centers, for pathological changes are often found in the diencephalic and mesencephalic areas known to have vegetative functions. He further suggests that different vegetative functions possess independent but closely related centers in this region, several centers being called into play for the completion of any one important vegetative function. This latter hypothesis would explain the polymorphism of the vegetative disorders, as well the rarity of permanent and complete abolition of any of the important vegetative functions, for such a result would require loss of more nervous
substance than is compatible with life.

Naccarati and Stevenin and Ferraro (121) likewise connect alterations in basal metabolic rate which they have found in certain postencephalitic patients with changes in the vegetosympathetic centers lying in the gray matter about the third ventricle and the aqueduct of Sylvius. However, no constant alterations in basal metabolic rate have been reported even by these investigators. Naccarati found in 53% of his patients, an increase in the metabolic rate, Stevenin and Ferraro, a lowering in 55% of their cases.

Several unusual post-encephalitic syndromes deserve brief consideration. Cadwalder (19) reports a few cases with bilateral impairment of deep sensation (recognition of position, passive movement, and vibration sense), which he attributed to a medullary lesion, implicating the lemniscus. Haxthausen (quoted by Rattner) described certain changes in the skin in chronic encephalitics, including pigmentary anomalies, especially a ring of hyperpigmentation on the forehead, unusual eczemas, hypertrichosis, prurigo, and excessively greasy face. Rattner (139) himself, however, found only seborrhea in a few cases.

Factors Influencing Physical Sequelae.

Severe physical sequelae are most common in patients between the ages of twenty and forty (Duncan). With few exceptions, according to this investigator, severe and progressive cases of parkinsonism occur in patients thirteen to thirty-five.
Duncan finds that sex bears no relation to physical sequelae.

The type and severity of these sequelae are in only a few cases apparently related to the manifestations and course of the acute stage. Hemiplegias when present usually follow similar conditions in the acute stage (Duncan), but the nature of the acute phase has no influence on the parkinsonism which may follow. According to this same authority, a relatively long period of recovery before the appearance of sequelae is usually associated with severe and progressive sequelae, while physical conditions developing shortly after the acute phase are comparatively mild and only slowly progressive, if at all.

**Prognosis**

Grossman (68) reports a 20% mortality in 145 cases, Duncan, a 26% mortality in 136 cases. The latter also noted a further mortality of 6% among chronic encephalitics as a direct result of the disease. Other reports indicate that the direct mortality is around 20% (Neal).

A large number of survivors, however, are left with more or less damage to mind and body, or both. Duncan (34) finds 50% of patients up to fourteen years of age are unfitted for further instruction, two-fifths over fourteen are incapacitated for work, one-fourth partially incapacitated; only one-twentieth in his series remained normal after an attack of the disease. Grossman, on the other hand, found that 90% of patients make a good functional recovery in six to twenty-four months after the
acute attack. Smith (165) on re-examining 128 cases one year after the acute attack found: 62% with some disablement, and 36% incapacitated for work or school.

Sudden death not infrequently occurs in chronic encephalitis patients (Grinker). Coma appears suddenly, and the patient dies within a few hours of respiratory failure. Small hemorrhages are found in the midbrain, pons, and medulla, but their significance is unknown.
CONCLUSIONS

In conclusion, it may be said that the disease syndrome called epidemic encephalitis has evidently appeared sporadically from time to time for several centuries, but only within the last thirty years has shown true epidemic tendencies. With the exception of certain definitely localized epidemics of acute encephalitis, which apparently are closely allied to but have been proved not to be identical with the original epidemic encephalitis as it appeared in 1917, this disease tends to show recurring waves which spread widely but not densely within any one area.

The causative agent is as yet undetermined, although it seem likely that in the von Economo type, some type of filtrable virus, closely related in immune reactions and in effects upon experimental animals to the herpes virus, is responsible, while in the other types of acute encephalitis (Japanese, Australian X-disease, and St. Louis type), independent viruses, apparently unrelated immunologically or otherwise either to the herpes virus and its encephalitic strains or to each other, are considered the probable etiologic factors.

A wide variety of both mental and physical sequelae may appear in direct sequence to an acute attack of epidemic encephalitis, either within varying intervals after the acute attack or without any preceding acute manifestations. The question of the pathogenesis of these sequelae is still unanswered. The variety of the manifestations in chronic encephalitis makes impossible their explanation simply on the basis of the lesions
found in the midbrain and diencephalon. The combination of mental, emotional, and physical symptoms is not constant; they vary in individual cases and in the same individual tend to shift from time to time. This inconstancy suggests a gradual progression of morphological changes, but this has not been shown. Jelliffe (86) has given a new angle to this problem by considering not exactly placed lesions as the basis for the individual manifestations, but rather the behavior as a whole, in the light of the specific reactions of the individual to the presence of a process of organic dissolution. The patient tends to regress psychologically to lower levels, for example, to the respiratory level, effecting the exteriorization of his emotional life through respiratory movements.

The treatment of these chronic manifestations is characterized by its inefficiency, probably because the chronic stage presents so many syndromes, each with a varying therapeutic problem. The treatment is, therefore, entirely symptomatic. The results vary so widely in different hands that no conclusions as to the relative merits of any type of treatment may be made.
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