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Postencephalitic parkinsonism – a review

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Summary. The pandemic of von Economo's disease which began in January 1917 preceded that of influenza of 1918–1919 by more than a year. Though it has been customary to link the two it seems unlikely that the latter was responsible for the former as has been proposed. It has been assumed that von Economo's disease (ED) was caused by a virus; but in fact the etiology is in question as no virus has yet been transmitted to experimental animals or cells in culture. However, the presence of oligoclonal IgG bands in the CSF of suspected cases and the finding of chronic active lesions in the brain tissue at autopsy suggests a viral etiology. Occasional, sporadic presumed cases of the disease have been reported within the last 25 years. Encephalitides due to established neurotropic viruses or to other viruses that may on occasion invade the CNS only rarely produce parkinsonism, and when they do it differs from that seen in ED. The present report reviews the overall concept of a viral etiology of Parkinson's disease with particular reference to von Economo's disease.

Keywords: Postencephalitic parkinsonism, etiology, von Economo's disease, encephalitis lethargica, primary viral encephalitides.

Introduction

It has been generally accepted that von Economo's disease (ED) including its sequela, post-ED parkinsonism (PEDP), has become an extinct disease; and that primary encephalitides as well as encephalopathies caused by established viruses seldom lead to postencephalitic parkinsonism (PEP). Consequently, cases of Parkinson's disease seen at the present time are of the idiopathic type or related to other non-encephalitic disorders (Duvoisin and Yahr, 1965; Yahr, 1978).

Reports of recent cases of illness similar to ED have occasionally appared since 1979, the most recent by Howard and Lees (1987). The possibility of a causal relationship between influenza and ED has been newly raised (Ravenholt and Foege, 1982); and agreement has been expressed by Hudson

and Rice (1990) with the hypothesis that influenza virus was the cause of ED. In view of this it seems opportune to reexamine the connection between influenza and ED, the relationship between primary viral encephalitides and PEP, as well as to evaluate the evidence concerning the existence of contemporary cases of ED, with or without PEDP. Possible etiological agents other than viruses are not addressed in this review.

Relationship between the pandemics of ED, 1917–1927, and influenza, 1918–1919

A review of the records show that numerous cases of ED had been reported prior to the outbreak of the influenza pandemic. The first recorded credible cases of ED, with onsets in April and May, 1915, occurred in Bucarest, Rumania and were later described by Urechia (1921). Somewhat later, in 1915 and 1916, 40 cases were seen in French Military Hospitals (Cruchet et al., 1917); additional cases in the French army in August 1915 and May 1916 were reported by Etienne (1917). von Economo's 13 initial cases (von Economo, 1917) had onsets between February and April, 1917, in Vienna. While it is possible that the disease had been seen at the same time or earlier than by von Economo, there is not doubt that the credit belongs to him for realizing that he was dealing with a new nosological entity and for providing the medical community a description that has become classical (Yahr, 1978).

The influenza pandemic consisted of 3 waves: the first from May to August, 1918, was relatively mild but very widespread; the second in October and November of the same year, was extremely severe with excessive mortality; and the third, from January to April, 1919, was of intermediate severity. The incidence of cases of ED reported in the literature in the few years prior to the time of onset of the 1918–1919 influenza pandemic were: 10 in 1915, 28 in 1916, 99 in 1917 and 110 from January 1st, 1918 to the end of March, 1918 (The Matheson Commission, 1929).

Since reported cases of ED antedate the beginning of the influenza by at least 1 year, and even more likely 3, it is illogical to use the temporal association of the 2 pandemics as an argument in support of the view that the influenza pandemic agent of 1918–1919 was the cause of the ED pandemic that began in 1917 or perhaps sooner.

Etiology of ED: early studies

Toxins, chemical agents, bacteria, viruses and protozoa were at various times implicated as responsible for ED. Only 3 aspects of early etiological studies are reviewed here, mainly because they involved outstanding investigators of the day.

Studies by von Economo and von Wiesner

Von Economo in 1931 stated "Up till now the virus of encephalitis lethargica has not been discovered" (von Economo, 1931). The assumption that ED was viral in origin was prevalent in 1931 and has continued to the present (Yahr,

1978; Ravenholt and Foege, 1982). Clinical, pathological and epidemiological features contributed to the perception of ED as a viral disease although it lacked contagion. In attempts to transmit the disease to an experimental animal, von Wiesner (1917) inoculated subdurally an unfiltered suspension of brain tissue from one of von Economo's patients into a Macacus Rhesus monkey. It developed somnolence, stupor and coma and died in 46 hours. The same material was inoculated intraperitoneally into a rabbit causing its death in 20 hours. However, inoculation of the filtered suspension into a second monkey failed to cause disease or death. In addition from the brain tissue of the patient and, subsequently, from a dozen more patients, as well as from the brain tissue of the monkey inoculated the unfiltered material, von Wiesner isolated in broth cultures a diplostreptococcus which he considered to be the etiological agent of ED. While at first von Economo may have accepted von Wiesner's conclusion, soon after (von Economo, 1923) he changed his opinion and wrote: "The statement that the virus (sic) is cultivable and visible has not subsequently been confirmed." However, von Economo still maintained in 1931 (von Economo, 1931) that he and von Wiesner had proved the transmissibility of the disease and therefore its infectious nature.

Studies on herpes virus

Levaditi and Harvier (1920) isolated a virus from a fatal case of ED using intracerebral inoculation of a brain tissue suspension to a rabbit, which died 8 days later with signs and lesions of encephalitis. Subsequently, these investigators isolated a second viral strain from the nasal secretions of another patient using corneal scarification in a rabbit which developed keratoconjunctivitis. A subpassage of the corneal exudate in a rabbit caused encephalitis. Subsequent virus isolations by Levaditi were rare, with a total of 3 successes in more than 30 attempts (Levaditi, 1921, 1922); occasionally a similar virus was isolated from the saliva of healthy individuals (Levaditi et al., 1921). Extensive studies demonstrated that the strains isolated by Levaditi were closely related to herpes virus, particularly by cross-immunity tests.

Flexner and associates (Flexner, 1923) made a long term effort to transmit ED to experimental animals. The first inoculations in 1919 were done with suspensions of human brain tissue into monkeys. These studies of material from "several" cases were negative. Other materials were subsequently added, including nasopharyngeal washings, extracts of nasopharyngeal mucosae and CSF, using the rabbit as experimental animal. Between 1920 and 1922 they tested, by intracerebral inoculation, materials from 40 or more cases of ED; the number of samples exceeded 100. The results were negative, with the exception of a sample from an individual that had no ED, but yielded herpes virus.

Between 1920 and 1925 only 9 strains of herpes virus were isolated worldwide from ED patients: 5 from brain tissue, 3 from CSF and 1 from nasopharyngeal secretions (The Matheson Commission, 1929). Four or 5 additional strains poorly characterized may have been isolated up to 1932 (Neal, 1934). After nearly 10 years of efforts to establish the etiology of ED,

Flexner (1927) concluded "up to the present the etiology of epidemic encephalitis has not been determined". Attempts to link herpes virus with ED failed to be persuasive for various reasons, particularly the paucity of isolations from patients in the many attempts which were made by Flexner and the fact that the virus was not infrequently isolated from CSF and oral secretions from normal individuals.

Studies on influenza

According to von Economo (1931) the reason for an etiological association between influenza and encephalitis lethargica was due to the fact that the latter became known not when he described it in 1917, but one and one-half years later. At that time the influenza pandemic of 1918–1919 broke out and in its wake there was a renewed outbreak of pandemic proportions of ED. The medical profession looked at ED as a form of influenza, indeed "cerebral influenza". von Economo rejected the assimilation of ED with influenza on several grounds: 1) time, as ED appearing at an earlier date; 2) contagiousness, ED was not contagious, whereas influenza was highly so; 3) clinical picture; and 4) pathology, with typical midbrain lesions in ED and later in PEDP contrasting with the pulmonary ones in influenza and, in the rare cases of postinfluenzal encephalopathy, with diffuse brain congestion and edema.

Similar conclusions were reached at about the same time by Jordan (1927): it was not possible to identify the ED of 1917–1927 with the neurological disorders accompanying or following historical pandemics of influenza. A detailed comparison of the two diseases in New York and Chicago as well as in several European countries failed to support the hypothesis of a genuine time relationship. Finally " a coincidence in prevalence does not prove a common cause."

In their monumental survey of the literature on influenza Thomson and Thomson (1934) state their conclusions on the relationship between ED and influenza as follows: "One view suggests the possible existence of a neurotropic form of the influenza virus and that epidemic encephalitis may be a manifestation of this virus. We have shown, however, that the evidence on this is purely hypothetical and unproven." The second view to which these authors subscribe is that ED is an entity in and of itself and entirely separate from influenza.

The concept that ED and influenza were etiologically related, in fact that they were a single disease has lately been revived. Ravenholt and Foege (1982) state: "The evidence that the pandemic of influenza beginning in 1918 and the pandemic of ED generally beginning the following year, had a common etiology seems compelling." Their evidence, in part, is that both pandemics "were closely related in time, and only one etiological agent (swine influenza virus) has been reliably identified" and "a large proportion of individual encephalitis lethargica cases had had clinical influenza." As we have documented above, the time sequence given by Ravenholt and Foege is not only incorrect, but it is hard to follow the logic that because only the cause

of one of two diseases that occurred simultaneously has been identified – swine influenza virus – the second disease is necessarily due to the same agent. And finally, since the pandemic of influenza affected at least 500 million persons (Laidlaw, 1935) or over one-fourth of the world's population at the time, it is no wonder that many individuals who had ED or, for that matter, any disease might have had influenza. Hudson and Rice (1990) maintain that influenza virus is the cause of ED and possibly other neurological diseases adducing in support of their supposition a tendency of influenza A virus to cause latent infections and to develop neurotropic variants. In fact (Kilbourne, 1975) "there is little to suggest that influenza viruses have the potential for persistency and latency", except the largely unconfirmed studies of Shope (1941, 1943) on swine influenza. As for a tendency to develop neurotropic variants, only one, possibly two strains of influenza A have been adapted to propagate in the brain tissue of a laboratory animal, the mouse, and this only after a laborious process of adaptation (Stuart-Harris, 1939; Francis and Moore, 1940). With respect to influenza encephalitis in man "very few virologically documented instances of influenza encephalopathy have been published." (Kilbourne, 1987).

The etiology of human influenza was established in 1933, by which time cases of ED had practically ceased. Therefore no human acute specimens were available to continue attempts to isolate an agent and compare it with influenza virus. If indeed ED is an extinct disease the only remaining possible sources of antigen for further identification studies are: brain tissue from PEDP survivors who voluntarily donate their bodies for autopsy; properly preserved pathological specimens; and, very unlikely, victims of the disease who died during the pandemic and who due to extraordinary circumstances were buried in permafrost areas. Current methods, perhaps also others yet to be developed, consisting in extraction of genomic nucleic acids, amplification by polymerase chain reaction (PCR) and sequencing may be the last resort to solve the etiology of the ED pandemic (Elizan and Casals, 1991).

Etiology of ED: recent studies

Renewed efforts to find an etiological agent for ED and/or PEDP have been ongoing since about 1970 using techniques not available or fully developed previously. These consist of immunocytochemistry and immunofluorescence for detection of in situ antigens, specific antibodies in serum or CSF and autoantibodies; examination of possible correlations between PEDP and HLA antigents; and search of immunoglobulin bands in CSF. Thus far attempts to detect specific genomic sequences from contemporary suspected cases or from old stored specimens of ED or PEDP have not been reported.

Search for antigenic material in acute phase ED

All reported current studies with specimens from the 1917–1927 period have been performed with stored paraffin-embedded brain tissue sections from one

patient, a 17-year-old male who died of ED on the 7th day from onset in The London Hospital in 1920. Cerebrum and brain stem sections were tested by the peroxidase-antiperoxidase (PAP) test against a herpes virus rabbit antiserum (Esiri and Swash, 1984); the result was negative. Similar sections from the same patient were tested also by the PAP test with antisera for the following viruses: influenza A (strains A-2-Japan 305/57, WS 33, A/swine/1976/31, A/New Jersey and NWS neurotropic), influenza B/Hong Kong, herpes virus 1, rubella, cytomegalovirus, measles and mumps, with negative result (Elizan et al., 1989).

Search for antigenic material in chronic phase ED, PEDP

Gamboa et al. (1974) tested hypothalamus and midbrain tissue sections from 6 PEDP patients who had died between 1 and 30 years after the acute encephalitic phase, using the direct immunofluorescence test; antibodies for 6 strains of influenza A, including 2 neuroadapted to mice, NWS and WSN, were employed. Only the sera against the neuroadapted strains were positive against the sections from each patient. These are tantalizing results that require confirmation. A recent finding (Taubenberger et al., 1997) is highly pertinent to this subject. These investigators identified a strain of influenza A virus that caused the death of a US soldier in November, 1918. From lung tissue samples in paraffin blocks they isolated fragments of RNA which after amplification and sequencing were compared with sequences of many influenza strains. The 1918 strain sequences were very close to those of the early subtypes N1H1 and, particularly close in the phylogenetic trees, to those of the neuroadapted strains WSN and NWS as well as to WS strain from which the 2 neuroadapted derived. As described above, antibodies against strains NWS and WSN were the only ones that reacted against an antigen present in all 6 cases investigated by Gamboa et al. (1974).

Using the PAP test Elizan et al. (1989) failed to detect antigens in autopsied brain tissue from a PEDP patient which nearly total destruction of the substantia nigra neurons. The antisera were against 5 different strains of influenza A and one each against influenza B, herpes virus 1, rubella, measles, cytomegalovirus and mumps.

Search for antibodies

Contemporary attempts to determine the etiology of ED have, in part, relied on uncovering indirect evidence, mainly detection of antibodies against particular viruses. Elizan and associates (Elizan et al., 1978, 1979a,b) tested sera from 168 persons of which 29 were PEDP patients, 65 Parkinson's disease (PD) patients and 74 had non-neurological diseases or were healthy controls, as well as CSF from 75 PD and 125 controls. The sera and CSF were tested against the following viruses: 7 alphaviridae, 7 flaviviridae, 4 bunyaviridae, 12 subtypes or strains of influenza A and 2 of type B; and other assorted viruses including parainfluenza type 1, mumps, measles, coxsackie B3 and B4, varicella-zoster, cytomegalovirus, herpes virus types 1 and 2, rubella and lymphocytic choriomeningitis. The tests used were complement fixation (CF),

indirect immunofluorescence (IIF) and, when antigens were available, hemagglutination inhibition (HI) and indirect hemagglutination (IHA). Not all the sera and CSF were tested against all the viruses. A substantial number of sera reacted positively with one or more viruses, as anticipated. However, there were no significant differences in the distribution of positive sera and their titers among the three groups of donors, PEDP, PD and controls; additionally, there were hardly any positives in the CSF and their distribution was random and at low titers. These results indicate that none of the viruses used as probes were associated with either type of parkinsonism.

In a series of reports published between 1977 and 1982, Marttila and associates described their efforts to determine whether specific antibodies in serum or CSF are associated with PEDP or PD. In the first paper (Marttila et al., 1977a) the results are given with sera from 23 PEDP and 421 PD patients and their controls who were variously tested by CF, HI and IIF against 15 viruses and mycoplasma pneumoniae. The viruses were: adenovirus, coxsackie A9, coxsackie B5, cytomegalovirus, echovirus 6, Epstein-Barr, herpes, 2 subtypes of influenza A, influenza B, measles, mumps, poliovirus type 3, respiratory syncytial virus, rubella and varicella-zoster. The only significant result was that by CF test the mean titer of the sera from the patients was higher than that of the controls uniquely against herpes virus, the titers being 1:30 and 1:24, respectively; the authors stress that there was no difference between the sera from PEDP and PD patients. Additionally (Marttila et al., 1977b) sera from 20 PEDP and 55 PD patients tested by HI against 4 strains of influenza A, showed no difference between patients and their controls or between the two groups of patients. In their subsequent work (Marttila et al., 1978a,b, 1981, 1982) these investigators concentrated on the reactivity of sera and CSF only against herpes virus antigens and the use of more sensitive tests; they used only specimens from PD patients, but since they had found no difference between them and those from PEDP patients, their results are pertinent to this review. The tests used were radioimmunoassay (RIA), indirect hemagglutination (IHA) in addition to HI; as antigens were used subunits of the herpes virion, capsid and envelope, as well as whole virions; and in many instances IgG was used instead of whole serum. Furthermore in a number of cases serum IgG and CSF from the same individual were tested simultaneously in order to find out whether there had been intrathecal production of antibody. Again they observed that generally serum antibodies against herpes virus antigens in parkinsonians had slightly higher titers than against control antigen and that antibodies in CSF against herpes virus were very low and randomly distributed in patients and matched controls. The final comments from Marttila and associates was that after testing 530 sera and CSF from parkinsonians, including 43 PEDP as well as PD patients, and a similar number of matched controls, the parkinsonians showed barely a two fold increased mean antibody titer against herpes virus as compared with the controls. But the ratio of antibody titers in serum and CSF in each individual tested was such that there was no suggestion of continuous antibody production in the CNS and therefore a causal role of herpes virus in PEDP and PD is unlikely.

Search for autoantibodies

Autoimmune antibodies that react with neurofilament antigens present in rat spinal cord have been reported in sera from individuals with certain neurological diseases, kuru and Creutzfeldt-Jakob disease (CJD), as well as in healthy individuals (Sotelo et al., 1980; Bahmanyar et al., 1982, 1983). Similar antibodies against filaments in human sympathetic ganglia neurons were reported in PD patients and to a lower rate in normal persons (Pouplard and Emile, 1984). Elizan et al. (1983) using IIF and longitudinal rat cord sections tested sera from 298 persons, including 27 with PEDP, 75 with PD, 54 with other neurological diseases and 142 with non-neurological illnesses or normal controls; the ages were from 1 year or less to 70 or over. The presence of antifilament antibodies was unrelated to disease or health, the only statistically significant difference between groups of sera being related to the age of the donors: in the group 70 years old or older 18 of 76 were positive and in the group 69 years old or younger 29 of 222 were positive with a barely significant chi-square of 4.04 or a probability of $0.05 > p > 0.01$. The evidence does not support an autoimmune mechanism in PEDP or PD.

Role of HLA antigens

Davidovitz et al. (1977) reported in a group of 50 PD patients a frequency of 46 percent positive for HLA-A2 and 20 percent positives for HLA-A28 compared with 30 percent and 10 percent, respectively, in controls. Emile et al. (1977) indicate a "higher prevalence of HLA-B17 and HLA-B18" in PD patients than in controls. Marttila et al. (1982) examined the distribution of HLA antigents in 48 PD patients. All the patients were tested with probes for 8 HLA-A, 17 HLA-B and 6 HLA-C; in addition, 26 of these patients for 4 HLA-Dw antigens. The investigators concluded that "no significant deviation in the HLA types of patients with PD were found in comparison with a sample of the Finnish general population". Elizan et al. (1980) investigated the distribution of these antigens in 18 PEDP patients, 17 PD patients and 147 normal individuals. The typing sera were for 15 HLA-A, 18 HLA-B and 4 HLA-C antigens. No differences were found between the controls and the PD patients; on the other hand, compared with these two groups the PEDP patients showed a highly significant increase in the frequency of HLA-B14 antigen, 44 percent in patients compared with 8 percent in the controls, $p = 0.001$. Lees et al. (1982) typed 21 PEDP patients and 153 controls for HLA-A, -B, -C and -Dr antigens and could not confirm the positive results reported by others; their results failed to support the hypothesis of a genetic susceptibility to ED. As for PD, the preponderance of the evidence is that no link between the disease and particular HLA antigens has been incontrovertibly established.

Histological evidence

A marked astrocytosis was described (Elizan and Casals, 1991) in the frontal and temporal white matter in a case of ED and another of PEDP in the absence of other demonstrable lesions in these areas or nearby cortex.

This intense astrocytic reaction in ED and PEDP in areas distant from the detectable primary lesion seem to indicate a generalized brain tissue response as might be caused by a toxic or viral pathogen. In the PEDP patient the astrocytic reaction was present 15 years after onset, indicating a chronic process. Evidence of an active neuropathological process in PD has been reported by McGeer et al. (1988) who found a significant number of reactive microglia phagocytizing dopaminergic neurons; they interpreted this lesion as a manifestation of an active chronic infection or an autoimmuno-process following an earlier insult. These two observations give positive facts that could support a viral etiology for ED and PD.

Suspected recent cases of ED and PEDP

Sporadic cases of ED, considered to be associated with the 1917–1927 pandemic, occurred until the early 30s after which time the disease disappeared; PEDP associated with such late cases of the acute disease could hardly be expected to appear after the middle 50s. Between 1979 and 1993, 15 patients with presumed ED/PEDP have been reported with onsets after 1959, which cases are considered to be unrelated to the pandemic.

Williams et al. (1979) described 2 cases. The first was a woman born in 1940 who in 1959 had an acute encephalitis with daytime lethargy and noctural insomnia, from which she recovered in 6 weeks. Ten years later, at age 29, she developed weakness of left side with bradykinesia and cogwheel rigidity. When seen again 2 years later, she had bilateral resting tremor, generalized bradykinesia, rigidity, festinating gait and micrography. In later years she slowly deteriorated; even small doses of levodopa induced violent diskinesias. No oculogyric crises or ocular paralyses were noted. No mention is made of the outcome.

The second patient, also a woman, was born in 1927, was well until age 49 when, in a day, she developed malaise and coma of 6 days duration and an EEG indicating acute encephalitis. The acute phase was immediately followed by difficulty in walking and breathing, slurred speech and resting tremor of legs. She was stable for 2 years but in the following 6 months she gradually deteriorated; increased walking difficulty, more prominent tremor of legs, general bradykinesia, incoordination and parkinsonian gait, but no disturbance of eye movements. Laboratory studies in both patients consisting in antibody determination in serum and CSF against more than 12 viruses were negative or within normal limits. In the CSF, cell counts, IgG and total protein were normal, but both patients had 2 oligoclonal protein bands. Considering the clinical evidence, progress of the disease and laboratory results the authors concluded that a diagnosis of ED/PEDP was plausible.

Rail et al. (1981) described 8 cases of ED/PEDP of which only 6, with onset after 1960, are considered here. The patients, 3 males and 3 females, were between 20 and 50 years old at onset, with an average age of 37 years. Four of the patients had an acute phase with encephalitis, or, in one instance, an influenza-like disease; in all these patients a chronic phase developped acutely or after a delay of months or years, with parkinsonian features,

rigidity, bradykinesia, tremor, expressionless face, dystonia and occasional ptosis, impaired convergence and accommodation. Slow progressive deterioration was observed which in some cases led to the patient being wheelchair bound. In 2 patients, no acute phase was noticed; one of these patients developed a chronic illness over a period of 4 years with drowsiness, mutism, depression, convulsions and finally akinesia, tremors and rigidity. The second patient with no acute phase developped tremors, bradykinesia, rigidity and recurrent occulogyric crises; her condition at first improved with levodopa but later she became severely disabled and died of bronchopneumonia at age 56, 16 years after onset. Examination of the CNS after necropsy showed nearly total loss of neurons in the substantia nigra and locus ceruleus; no Lewy bodies were seen in the few remaining neurons of the substantia nigra, but neurofibrillary tangles were present. No Alzheimer plaques or neurofibrillary tangles were seen in the cerebral cortex. Small glial scars in the substantia nigra were considered to be confirmatory evidence of a previous encephalitic illness.

The patients were observed for short periods of time in 3 instances; the other 3, during 7, 9 and 16 years, respectively. The observations by Rail and associates are in many respects similar to the descriptions recorded during the 1917–1927 pandemic. Notable are the relatively young age of the patients at onset, an encephalitic illness with parkinsonian features developing acutely or after long delays, reversed sleeping cycle, oculogyric crisis, cortico-spinal tract signs and long duration of the parkinsonian phase and, in the single case in which an autopsy was performed, the pathological findings were typical of parkinsonism following von Economo's disease.

Clough et al. (1982) reported the case of a male born in 1945. He was well until 1972 when, in January, he became acutely ill with high fever followed by difficulty of ambulation, involuntary movements and oculogyric crises. In March he was hospitalized with fever, dysphagia, abnormal eye movements, tremor of arms, rigidity and slow walk. An EEG supported the diagnosis of encephalitis; with medication and rest he improved and was discharged. A month later he was readmitted and diagnosed as having "pseudo parkinsonism", with tremors, rigidity, bradykinesia, difficulty of speech and shuffling gait. Levodopa brought about a dramatic improvement, but 3 years later an "on-off" response developed with severe dyskinesias. In 1977 he was admitted to a neurological service severely disabled. He manifested signs and symptoms of parkinsonism, had recurrent oculogyric crises and was particularly reactive to levodopa. Extensive tests for antibodies against viruses and other pathogens were undiagnostic. The patient died 19 years from onset after a gradual, slow worsening of his condition.

Johnson and Lacey (1987) described 2 cases. The first, a 23-year-old male, was well adjusted until age 20 when he developed a depressive illness with sleep inversion. He was hospitalized 3 or 4 times, each time lapsing into a catatonic stupor which improved with electroshock. At the time of his last hospitalization he presented mute, akinetic, incontient of urine, severe blepharospasms, maintained imposed postures, would stand for hours in a bowed position with flexed arms and compulsive motor rituals. CAT scan, CSF and EEG were normal. The possibility that his catatonic stupor was due

to ED was considered and was treated with levodopa with clear improvement; began to speak after 3 months of mutism, could dress, walk, eventually converse freely and his motor rituals subsided completely. Seen 6 months after his last discharge his progress continued and lived a reasonable normal life at home.

The second patient was a 17-year-old male who was admitted to hospital after a drug overdose during a depressive illness. He was mute, akinetic, negative, had hypertonia of limbs and catalepsy, would freeze on an induced posture, had low grade fever and an EEG compatible with encephalopathy; he improved with electroshock treatment. Two years later, seen in prison, he had poverty of expression but no other neurological or psychiatric signs.

These 2 cases fit the description of von Economo's amyostatic-akinetic type; such cases were observed in London in 1918 and named "epidemic or catatonic stupor" (von Economo, 1931).

Howard and Lees (1987) described the early phase of a disease which they considered to be ED in 4 patients, with onset between 1980 and 1985. These patients ages were 17, 23, 21 and 63 years and they were followed 6 months, 5 years, 3 months and 7 months, respectively. The signs and symptoms in 2 of the patients were predominantly those in von Economo's hyperkinetic type (von Economo, 1931), presenting or developing agitation, uncooperative attitude, bizarre and disinhibited manner and dystonic posturing; the other 2, with lethargy, sleep inversion, rigidity, ocular paralysis were typical of von Economo's somnolent-ophthalmologic type. In addition the patients showed at various times fever, akinesia, signs of basal ganglia involvement, obsessive-compulsive behaviour and psychiatric disturbances of various degrees; 3 of the 4 patients had recurring oculgyric crises. It is of considerable interest that 3 of the patients had oligoclonal IgG banding in the CSF during the acute illness, which as Howard and Lees state "would be in keeping with a viral etiology'. One of the patients died as result of a chest infection 7 months from onset; a post-mortem examination showed inflammatory changes throughout the cerebral hemispheres, subcortical regions and brain stem. There was extensive perivascular lymphocytic infiltration in several areas of the brain, pons and medulla. In the substantia nigra there was a mild neuronal loss and extraneuronal pigment; no neurofibriallry tangles were seen. The excellent description of these patients by Howard and Lees highly favors their conclusion that they were dealing with cases of ED.

Postencephalitic parkinsonism (PEP) associated with established viruses

When considering the possibility that PEDP may be caused by a virus it seems logical to inquire whether parkinsonism can be induced by currently defined neurotropic viruses or other viruses that occasionally develop neurotropic tendencies.

California encephalitis

Reported only in US, the disease was first described in 1964, has an incidence between 30 and 100 cases, occasionally higher. It occurs mainly in males

between 1 and 14 years of age. Most cases are caused by LaCrosse virus (Bunyavirus) and the total number of cases reported until 1993 is about 2,000 with a mortality of 0.3 percent (Anonymous, 1986, 1991). The disease lasts from 7 to 10 days, is usually mild ending in complete recovery. Efforts to uncover neurological, psychiatric and psychological sequelae for periods from 1 to 8 years have been reported (Chun, 1983). Focal neurological signs when present are of short duration, seizures seen during the acute phase may recur. Cognitive and intellectual functions are not impaired and parkinsonism has not been reported.

Coxackie virus diseases

Coxsackie viruses are a group of picornaviruses that cause several diseases among which are encephalitis, myelitis, meningitis, myocarditis and general systemic disorders. Infection with these viruses is highly prevalent in early life; a causal relationship between it and a subsequent parkinsonism after a long symptomless period is difficult to establish. Parkinsonism as an immediate sequela to an encephalitis caused by a specific coxsackie virus has been reported.

Walters (1960) described a disease in an adult female who was hospitalized with high fever and severe headache. On admission she was severely ill, drowsy and had nuchal rigidity; she remained in hospital for 4 weeks with restlessness, anxiety, insomnia, aches and pains. She was discharged slightly improved but was readmitted at 4 months from onset with parkinsonian signs: mincing gait, small steps, propulsion, no associated movements, masked facies with loss of eye blinking, greasy skin, resting tremor of 4 limbs and cogwheel rigidity; no ophthalmoplegia or oculogyric crises. She improved with treatment and was discharged, but some abnormalities remained when last seen 1 month later. The diagnosis was "progressively severe and unremitting parkinsonian syndrome". The specific diagnosis was based on an early isolation of coxackie virus type B-2 from a stool specimen and a rise on serum neutralizing antibody titer between days 1 and 28.

A second case (Posner et al., 1969) was a 16-year-old male who was hospitalized with fever, headache, backache, nuchal rigidity, dysconjugate gaze and unsteadiness on standing. Laboratory tests were nondiagnostic except for an EEG on the 4th day which showed generalized disorganization. On the 7th day he had parkinsonian features: shuffling gait, cogwheel rigidity, absence of associated movements, lay rigid and immobile in bed and was mute. On day 20 he began to improve and was discharged after 5 weeks. He was seen 18 months after onset for the last time and had an entirely normal examination; he never had ophthalmoplegia or oculogyric crises. The specific diagnosis was based on a 32-fold increase of neutralizing antibody titer between days 1 and 8 from onset against coxsackie virus type B-2.

Cytomegalovirus (CMV) infection

Invasion of the CNS by CMV was extremely uncommon in the past, being seen mainly in fetal infections that resulted in the CMV inclusion

disease. With the advent of AIDS, infection of the brain by CMV has become frequent, this virus acting as an opportunistic pathogen. CMV has been associated with several clinico-pathological manifestations in AIDS patients: mononucleosis, pneumonia, hepatitis, gastrointestinal illness, chorioretinitis and encephalitis. No PEP has been reported in these patients.

Eastern equine encephalitis (EEE)

This illness in man has been reported only in the Western hemisphere, almost exclusively in the eastern and southern part of US, and rarely in other countries, Dominican Republic and Jamaica. The disease is very rare; since 1938 when it was first described until 1995 the total number of cases reported to CDC and additional ones in the literature is about 280 (Feemster, 1938; Hammon, 1943; Howitt et al., 1948; Eklund et al., 1951; Anonymous, 1986, 1991). The disease has appeared in small outbreaks from 10 to 38 cases on 5 or 6 occasions, but usually occurs, in from 1 to 4 or 5 sporadic cases annually. The disease is extremely severe particularly in infants and children with mortality rates from 30 to 70 percent. Survivors are generally left with crippling sequelae such as mental deficits, seizures, severe paralyses and other neurological disorders. No parkinsonian syndrome associated with the disease has been reported in an 8-year follow-up of clinical and subclinical cases (Goldfield et al., 1968). Subclinical infections are rare (Przelomski et al., 1988). In view of the rarity of the disease, its high mortality rate in the acute phase and its low rate of subclinical infections it is unlikely that EEE virus infection may lead to PEP.

Herpes virus infection

Infection of man with herpes virus is one of the most prevalent human infections caused by a virus; it occurs worldwide and with advancing age it affects nearly everyone. The virus can cause a most severe encephalitis but, considering its high prevalence, such is a rare event. Nahmias et al. (1989) state that the number of fatal cases of herpes encephalitis reported to CDC is about 20 each year; however, this must be gross underreporting since these authors estimate the incidence of the disease to be 1 or 2 cases per million. Olson et al. (1967) consider herpes encephalitis to be the commonest lethal sporadic viral encephalitis in US. These investigators reported 25 deaths in 36 of their cases; of 8 survivors followed up from 1 to 8 years, 3 showed no residua but 5 had severe sequelae: personality changes, motor deficits, incoordination, seizures and aphasia. There is no mention of PEP.

Whitley et al. (1981) reported their observations on survivors from herpes encephalitis following chemotherapy; 49 were followed up for 1 year at which time 9 were severely impaired, 15 moderately impaired and 25 were normal. The sequelae in the 24 impaired patients were: speech difficulty, aphasia, ataxia, dysphagia, cognitive and motor deficits requiring institutionalization, seizures and hemipareses; Parkinsonism is not mentioned.

Human immunodeficiency virus (HIV)

Neurological manifestations in the course of AIDS have been increasingly reported since the disease was first recognized (Anonymous, 1981). Through 1995 the cumulative number of AIDS cases in US was over 590,000 (Anonymous, 1991a, 1996). Worldwide it was estimated by WHO that 19.5 million individuals had been infected by the HIV; given such large number of patients a large proportion of whom develop neurological complications, it seems reasonable to inquire whether any of the complications resemble PEP.

Snider et al. (1983) were among the first to report neurological complications of AIDS. In their study, 160 patients were evaluated over a 3-year period; half developed CNS involvement of whom 18 patients had a slowly progressive subacute encephalitis. The increasing awareness of the frequency with which AIDS is complicated by CNS dysfunction was well documented by Navia and Price (1987); they described a common disorder unique to AIDS characterized by progressive dementia accompanied by motor and behavioral problems which they designated AIDS dementia complex. Jansen et al. (1992) conducted a survey of the prevalence of HIV encephalopathy in US; over a 4-year period (1987 to 1991) of 144, 184 reported cases of AIDS, 10,553 or 7.3 percent presented with HIV encephalopathy. Subsequently additional patients up to a total of 20 to 30 percent developed neurological complications.

There is no mention of parkinsonism as a manifestation of AIDS encephalopathy or dementia complex in the 3 papers quoted. Furthermore, no mention is made of parkinsonism in the CDC case definition for AIDS (Anonymous, 1987) or in the report by the American Academy of Neurology (Anonymous, 1991b). It appears that in spite of the very high prevalence of AIDS, parkinsonism has not been a feature of the disease.

Infectious mononucleosis

Infectious mononucleosis is an acute disease caused by primary infection with the Epstein-Barr (EB) virus, a member of the herpesviridae family. The classical disease with fever, pharyngitis and cervical lymphadenopathy occurs primarily during adolescence. Infectious mononucleosis has a worldwide distribution but its incidence is low in developing countries because infection occurs during childhood when the infection is inapparent. Following recovery, which is the norm, the virus can be recovered from larynx and lymphocytes for months and years (Evans, 1974). Neurological complications appear during the early phase in 1 percent of the cases, mainly encephalitis and meningitis with complete recovery as a rule. A chronic infectious mononucleosis syndrome occurs sporadically due to reactivation of the virus, shortly after the acute illness or years later, with fatigue, weakness, fever, adenopathy, neuralgias, headache, paresthesias and depression; this illness has no resemblance to PEP.

Influenza viruses

Earlier accounts of influenza epidemics stress the presence of neurological complications. Harris (quoted by Jordan, 1927) stated that "there is no

malady after which disturbances of the nervous systems are so frequent as after influenza and none that has such varied nervous sequelae". Later accounts in general express a different opinion. During the 1957–1958 influenza pandemic in Dundee (Dunbar et al., 1958) over a 2-month period 468 patients required hospitalization; 4 were diagnosed as encephalitis of whom 1 died and 3 completely recovered. The total number of influenza cases in Dundee during the same period was estimated a 3,600, therefore the rate of encephalitis to influenza was about 100 per 100,000.

In a survey of 20 years of influenza epidemics, Stuart-Harris (1961) stated that neurological syndromes are "unusual complications of Asian influenza", such complications being either true encephalitis or toxic encephalopathy. As to their frequency, Stuart-Harris points out that in the period between 1955 and 1959 there were in England and Wales 19,622 deaths due to influenza of which only 52 were attributed to encephalitis or, approximately, 1 per 400; no mention if made of PEP as a sequela of influenza virus infection.

Kilbourne (1987) points out that influenza is an unvarying disease caused by a varying virus and that unusual clinical manifestations of infection by influenza virus are rare; encephalopathy may occur but rarely, encephalitis is even rarer and PEP associated with influenza virus is not even mentioned. Influenza virus is antigenically highly mutable; on the other hand, mutants with tissue affinities other than respiratory track are exceptional and thus far only laboratory generated, NWS (Stuart-Harris, 1939) and WSN (Francis and Moore, 1940). The existence of neurotropic strains of influenza virus in nature although conceivable (Yahr, 1978) has not been demonstrated.

Following the influenza pandemic of 1957–1958 (so-called Asian influenza, caused by a type A, subtype H2N2 strain) there was a moderate revival of interest as to whether influenza virus can cause encephalitis.

Dubovitz (1958) reported specifically diagnosed influenza A in 2 children who within a few days from onset became very ill, drowsy, unconscious and comatose in a period of 12 hours, with Babinski signs; one of them in addition had focal sign of CNS involvement. After 2 or 3 days both patients made spontaneous complete recoveries. Flewett and Hoult (1958) saw a number of patients with neurological disturbances during the pandemic; 12 of them had also been diagnosed as having influenza type A by virus isolation and/or antibody development. At the height of the influenza attack 6 of them developed convulsions or clinical "encephalitis' and died. Autopsy showed heavily congested brains. Four other patients had "encephalitis" with onset 2 to 14 days after influenza with confusion proceeding to coma, and flaccid paralysis of the limbs; they survived with complete recovery except for 1 who after a slow recovery had residual spasticity. The last 2 patients had a Guillain-Barre syndrome but no encephalitis. The investigators pointed out the difficulty of establishing an etiological relationship between influenza and encephalitis when 50 or 60 percent of the community had the former. Further they state that as for their patients "we think that encephalopathy is a better designation than encephalitis". They concluded that an etiological relationship between influenza virus and encephalitis was not proven. McConkey and Daws (1958) describe 4 patients with a short febrile illness with malaise and coryza which

was specifically diagnosed influenza A, Asian subtype. Four or 5 days from onset the patients exhibited headache, confusion, drowsiness and coma, and Babinski, were severely ill but totally recovered: EEGs were compatible with encephalitis. Horner (1958) mentions 3 cases of encephalopathy that developed within a few days after recovery of specifically diagnosed influenza; 1 patient died and 1 of the survivors remained with marked mental and motor damage. Anderson and Jaros (1958) saw 3 young adults in 1957 in whom Asian influenza was followed by severe encephalitis; all survived, 2 with no sequelae but the third seen 4 months later had residual tremor of upper extremities and generalized muscular weakness. A report by Oseasohn et al. (1959) is particularly interesting; they investigated 33 fatal cases of specifically diagnosed Asian influenza in 1957. Signs of CNS involvement were noted in 4 of the patients, aged from 10 to 27 years: convulsive seizures, extensor spasms and coma but no focal signs. No microscopical changes indicating encephalitis were seen nor was influenza virus isolated from brain tissue; the brain alterations were congestion, edema and swelling. The conclusion of the investigators was that "they were cases of encephalopathy".

In more recent years there has been a marked decrease of reports on the association between encephalitis and influenza. Murphy and Hawkes (1970) had a brief report claiming isolation of influenza virus from the brain tissue of each of 3 patients who died of encephalitis following typical influenza; no follow-up could be located. Isgreen et al. (1976) described an illness in a 14-year-old male who developed a mild fever, lethargy, dysphagia, drooling and sluggish walk; he was hospitalized with masked facies, sialorrhea, monotonous whispered speech, stooped posture, lack of associated movements, tremor of hands and cogwheel rigidity. All signs subsided and he went home after 2 weeks, but 2 days later he developed choreic movements which disappeared in a few days and he remained well during a 2-month follow-up. He had a high but unchanging antibody titer against influenza A virus, leaving the etiological relationship unresolved. In another attempt to connect specifically diagnosed influenza with CNS disease, Delorme and Middleton (1979) report 6 children seen between 1972 and 1976 who developed acute encephalopathy, some becoming comatose within 24 hours; none died, mostly they recovered completely in a few days but 1 had trouble with fine motor coordination after 2 years. Sulkava et al. (1981) reported 4 cases of "severe encephalitis" in Finnish adults specifically diagnosed as having influenza A; one week after this illness the patients had a rapid rise in temperature, decrease in consciousness with stupor in 2 and coma in the other 2; all had EEGs compatible with encephalitis. All recovered completely in from 2 to 25 days, with no sequelae when seen 2 and one half months later.

In summary, there are no specifically documented cases of severe encephalitis caused by influenza virus. All the well studied cases appear to be instances of encephalopathy with brain congestion, edema and swelling, which may be a reactive process to a systematic infection and/or its treatment. The frequency of these cases is in the range between 10 and 100 per 100,000 cases of influenza and, with some exceptions, the patients generally recover. PEP is not associated with influenza virus; if at all seen, it is transitory.

Japanese encephalitis (JE, JBE)

JBE was first reported in Japan in 1924 in epidemic form, overlapping in part with the then prevalent epidemic of ED. Kaneka and Aoki (The Matheson Commission, 1929) who recorded 6,949 cases of JBE with 4,159 deaths stated: "The parkinsonian syndrome is exceptional in encephalitis type B, whereas headache, irritability and sleeplessness frequently followed it."

One year after an outbreak of JBE in Okinawa in 1945 in which 127 persons were affected, 38 survivors could be located (Simpson and Miklejohn, 1947); 3 had incapacitating sequelae, quadriplegia, hemiplegia, aphasia, advanced mental deficit; 2 had minor problems and 6 recalled mild symptoms with total recovery within the 12-month period. No mention is made of parkinsonism in this outbreak; in fact very few neuropsychiatric abnormalities among hundreds of Okinawan patients were seen that could be attributed to any familiar neurotropic virus. A similar view is expressed by Lewis et al. (1947) who state that among thousands of civilian patients treated in military hospitals very few shoed symptoms of possible PEP.

Dickerson et al. (1952) followed up 65 survivors of JE for a period of 3 months, at which time all but 8 had completely recovered: of these, 5 were totally incapacitated with mental deficits and 3 showed significant motor impairment, hemiplegia, localized flaccid paralysis and muscular atrophy. None developed parkinsonism.

In the course of overlapping outbreaks of JBE and mumps in Guam in 1947–1948, there were 54 cases of encephalitis, 16 associated with JBE virus alone and 15 with JBE and mumps viruses. Ten years later (Pieper and Kurland, 1958), 23 survivors, 11 with JEB alone and 12 with JEB and mumps were examined; 13 had no sequelae at any time, 10 had sequelae of various degrees of severity, from cortico-spinal deficits only to severe retardation, ocular movement problems, ataxia, brain stem and cerebellar dysfunction, convulsive seizures and cortical sensory impairment. No parkinsonism was reported.

During an epidemic of JBE in Japan in 1946 involving over 6,000 patients, 628 were admitted to 2 special hospitals of whom 163 died during the acute phase (Richter and Shimojyo, 1961; Shiraki et al., 1963). Of the survivors, 117 manifested neuropsychiatric troubles one month after onset and they plus an unspecified number of additional patients were followed up by Shiraki and associates for 3 to 10 years. The majority of the patients with sequelae were children at the time of onset, the sequelae were psychiatric and mental deficiencies and focal neurological deficits that generally followed the acute phase with no interval. Parkinsonism was found in 8 patients, but according to Shiraki et al. (1963) "it was different from parkinsonsim of von Economo's disease; it was benign, the ocular and autonomic problems and tremors were mild and present only at the early stage of the disease".

Richter and Shimojyo (1961) underline the severity of the neurological sequelae in 8 cases of JE. Four recovered in one month; 1 died 11 days after onset; 3 developed incapacitation sequelae following the acute phase, psychoses, mental deficiencies, cerebral atrophy and hemipareses. In addition,

one of the patients 3 months after onset developed transitory "parkinsonian symptoms" which cleared in 10 weeks. The patients deteriorated progressively over a period of 17 to 21 months, 2 becoming home-bound and the last one incarcerated.

Ishii et al. (1977) report the clinical and pathological features in 4 institutionalized patients who survived from 12 to 67 years after JE. The acute phase with high fever, convulsions and coma was followed at various intervals by a chronic phase with mental retardation, seizures, dysarthria, ataxic gait, tremors, rigidity and antisocial behavior. The clinical diagnosis was confirmed by serology in 2 cases attempted. The lesions were similar in distribution, substantia nigra, thalamus and Ammon's Horn, and nature, "light circumscribed foci" of small necrotic areas with few neurons surrounded by glial-mesenchymal scars. The authors conclusion is: "with regards to the slow ongoing process we are reminded of postencephalitic parkinsonism of the von Economo type."

Shoji et al. (1993) describe an illness in a 61-year-old man presenting with 4-limb rigidity, high fever, conciousness impairment and meningeal signs. Admitted to hospital he was unresponsive and developed amnesia and rigidity; a serological diagnosis of JE was made. Three months after onset he had conspicuous tremor, akinesia and rigidity and the diagnosis was made of JE followed by parkinsonism. After 3 years the parkinsonian signs continued with little change although they improved with levodopa treatment.

JE is the world's most prevalent primary encephalitis, though it concentrates in eastern and southeastern Asia. In Japan alone 21,355 cases were reported from 1924 to 1937 (The Matheson Commission, 1929, 1932, 1939) and 36,871 from 1948 to 1954 (Richter and Shimojyo, 1961). An update on the worldwide status of the disease (Umenai et al., 1985) shows that the disease has nearly disappeared in Japan, probably due to effective vaccination, but that it is present in substantial numbers in China, India, Korea, Thailand and other countries with an estimated over 15,000 cases annually of which 10,000 in China. Given the large number of past and current patients, it is reasonable to assume that, if postencephalitic parkinsonism occurred frequently following JE it would have been noticed and reported; with rare exceptions, this has not been the case.

Lymphocytic choriomeningitis (LCM)

LCM virus discovered in 1933 was shortly after associated with acute aseptic meningitis of man. The clinical course of LCM is usually benign but with a long convalescence; fatal cases are rare. Sequelae such as mental retardation, aphasia and paralyses have been reported but are infrequent. Scheid et al. (1968) described a patient with LCM who developed a disorder of the CNS that "in all respects resembled classical encephalitis lethargica (von Economo)" but recovered completely. Adair et al. (1953) conducted a survey of US military personnel suffering from aseptic meningitis or encephalitis between 1941 and 1952; of 845 cases 79 were specifically, or likely to be, caused by LCM virus. Two of these patients died in the acute phase from

bulbar paralysis and another 2 were found 6 and 24 months later to have "typical parkinsonism". Meyer et al. (1960) continued the survey between 1953 and 1958 and collected 713 cases of CNS syndromes of "viral etiology"; 58 were due to LCM, 38 with meningitis and 20 with encephalitis; all these patients recovered totally with the exception of one with encephalitis who developed an undescribed sequela, probably not parkinsonism. The collected evidence is hardly persuasive that LCM virus causes PEP.

Mumps

Mumps virus can induce encephalitis, meningitis and meningoencephalitis. Prior to the development of a vaccine, this virus was considered the most common cause of viral cases of these diseases in US (Adair et al., 1953) but with vaccination its importance diminished (Anonymous, 1991). The rate of encephalitis is about 3 per 1,000 cases of mumps and it is usually mild although deaths occur, 2 per 10,000 cases of mumps. Pieper and Kurland (1958) located 11 survivors of an outbreak of mumps encephalitis in Guam 10 years after onset; 3 had minor neurological residua but lived normal lives. Levitt et al. (1970) followed up 19 patients who had developed encephalitis after mumps and survived; they were seen from 6 to 51 months. All were well except one who 3 years after onset had a minimal neurological deficit; no mention is made of PEP.

Murray valley encephalitis (MVE)

The disease first reported in 1952 occurs in Australia and less so in New Guinea. It has been infrequent with sporadic annual cases and 2 outbreaks. The total number of reported cases is about 200; there are subclinical infections. It is a severe disease with mortality rates up to 15 percent. In 1950–1951 there were 40 cases (Anderson, 1952) and in 1974 (Bennett et al., 1976) 58 of whom 22 were thoroughly followed up. Eleven had a relatively mild disease with 7 patients recovering completely and 4 with residual but mild disabilities. The remaining 11 patients had a severe illness; 4 died and 7 were left with severe mental deficits or physical handicaps including quadriplegia. One patient showed "features of Parkinson's disease" but no details are given.

Eadie et al. (1965) tested 43 parkinsonian patients for antibodies against MVE virus and found no evidence of a relationship between the virus and PEP; a similar conclusion was reached by Marshall (1988).

Papovaviruses

Progressive multifocal leukoencephalopathy (PML) was a rare chronic neurological disease caused by JC virus, a human papilloma virus. As of 1980 no more than 250 instances of the disease had been reported worldwide. Since the advent of AIDS this has changed radically. Gillespie et al. (1991) concluded that 2 percent of AIDS patients will develop PML; Simpson and Berger (1996) consider HIV infection the most common immunodeficient state predisposing to PML, with 4 percent of patients with AIDS developing

PML. Clinically, the signs and symptoms of PML point to multifocal lesions; with few exceptions, the disease is fatal in 3 to 6 months. No complication resembling PEP has been associated with JC virus infection.

Polioviruses

Cases of poliomyelitis with unusual features reminiscent of the acute and early chronic phases of ED have been described. Bickerstaffer and Clarke (1951) reported 3 young adult patients who developed drowsiness, oculomotor disturbances and lower brain stem involvement; the duration of the illness was 2, 6 and 18 months, respectively. The patient with the longest illness had a period of "typical parkinsonism" and at some point 2 of the patients seemed moribund, but in time all completely recovered. Thieffrey (1963) reported that in his personal experience 17 out of about 1,500 cases of poliomyelitis had definite encephalitic features. These patients presented with or developed combinations of, fever, tremor, ataxia, violent abnormal movements of body and extremities, hypotonus with akinesia and a parkinsonian syndrome with plastic rigidity, exageration of postural reflexes, cogwheel rigidity, perseverance of attitude, monotonous speech, hypersialorrhea and slow movements; along with these there were signs of poliomyelitis such as pareses and paralyses. In all instances when parkinsonism appeared and the patient survived the parkinsonism was transitory.

It has been estimated that in 1986 there were in US 300,000 survivors of poliomyelitis (Dalakas et al., 1986); the continuing observation of these aging survivors led to the discovery of a new clinical entity designated progressive postpoliomyeltic muscular atrophy (PPMA). If for no other reason, due to the interest on PPMA (Dalakas et al., 1986) survivors of poliomyelitis have been under surveillance for long periods of time; if a postpoliomyelitic type of parkinsonsim had developed in these patients it would have been reported, but this has not been the case.

Rubella

Rubella or German measles is a mild disease with low mortality and no sequelae. However, complications may occur, some involving the CNS, congenital rubella syndrome, progressive rubella panencephalitis and encephalitis. Following vaccination, the incidence of the disease and its complications decreased dramatically; in the period between 1985 and 1990 the annual number of cases of rubella was between 225 and 1,125 with from 0 to 11 cases of congenital syndrome in US (Anonymous, 1991). PEP is not mentioned among the sequelae of rubella (Waxham and Wolinski, 1984).

Rubeola, measles

In general this is not a severe disease and the great majority of patients survive with no sequelae. However, an acute postinfectious encephalitis, immunologically mediated does occur in 1 or 2 per 2,000 cases of the disease; patients with such encephalitis show mortality between 10 and 20 percent, with

some survivors developing neurological deficits, but the majority recover completely. Subacute sclerosing panencephalitis (SSPE) is a late, very rare sequela affecting children and adolescents, invariable fatal, but occurs only in 1 per 100,000 cases of measles. PEP has not been associated with measles.

Russian spring-summer encephalitis (RSSE), European tick-borne encephalitis (ETBE)

These diseases are caused by 2 distinct subtypes of a flavivirus, RSSE and ETBE viruses. RSSE is present mainly in the Russian Far East and eastern Siberia, perhaps also in Korea; the disease was established as a nosological entity in 1937. Sporadic cases or small outbreaks have occurred in the endemic areas, but the incidence is poorly documented, probably not high. RSSE is usually tick-transmitted, is a severe febrile illness with mortality up to 30 to 40 percent and prominent sequelae among which a crippling flaccid paralysis of the shoulder girdle muscles is distinctive; another is Kozhevnikov's epilepsy. In one occasion was reported (Ogawa et al., 1973) a chronic progressive from of encephalitis lasting 13 years with mental, visual and auditory impairment, oculomotor involvement, dysphasia and pyramidal and cerebellar signs.

ETBE is localized in central and eastern Europe; substantial outbreaks have been reported in Slovakia and pre-Ural Russia, but generally the incidence is moderate. The disease is transmitted by tick bite or by the digestive route through milk contaminated with virus; it is a mild disease with low mortality, 1 or 2 percent, a biphasic course and there are no lasting or severe sequelae. The largest recorded epidemic occurred in 1951 in Roznava, Slovakia (Henner and Hantal, 1957, 1963); the first phase involved 660 persons, was thought to be influenza, no one was hospitalized. The second phase affected only 271 persons, all were hospitalized; no deaths were reported and most patients recovered fully. The second phase was a meningoencephalitis with marked somnolence; the possibility of encephalitis lethargica was entertained but was soon dismissed and most patients healed completely in 1 or 2 weeks. Ten to 20 months later 99 of the patients were seen again, half of them had no problem whatever; the rest had an assortment of minor complaints and although at some time 81 of these patients had shown extrapyramidal signs they disappeared completely; no PEP was observed during the follow-up.

A survey of the disease in Slovenia (Radsel-Medvescek et al., 1980) included 79 hospitalized patients in 1974 and 1975, all specifically diagnosed. Three and 4 years later 49 were located, of whom 21 had completely recovered, 5 had residual minor complaints and 23 had major complaints mostly subjective which did not require a change of life style: headache, memory disturbances, irritability, sleeping disorders and tremors but parkinsonism is not mentioned. From the available evidence it appears that PEP has not been observed to follow RSSE or ETBE.

St. Louis encephalitis

With few exceptions the disease has been reported only in US where it first appeared in 1933; cases have since been observed almost yearly including

2 epidemics involving 300 and 1,800 cases, respectively. The total number of cases has been estimated at 10,000 with about 1,000 deaths (Chamberlain, 1980; Anonymous, 1986, 1991). The disease is caused by a flavivirus, is mosquito transmitted, occurs in late summer and fall and is widely prevalent but mainly in the central States, eastern Texas and California. Overall, 845 survivors have been under surveillance for periods from 2 months to 18 years after convalescence. Bredeck et al. (1938) reported on 331 survivors of the 1933 epidemic followed up from 18 to 24 months; a large proportion had mild nervous complaints like headache, irritability and drowsiness and 32, in addition, complained of muscular tremors, but none had evidence of parkinsonism. A follow-up in California begun in 1945 and continued for 18 years involved 204 confirmed cases (Finley, 1958; Finley and Rigs, 1980). The most frequent sequelae were: emotional disturbances, headache, dizziness, nervousness, irritability and sleeplessness, the "convalescent fatigue syndrome"; a persisting sequela was a dystonia with tremor. A typical parkinsonian syndrome has not been reported after SLE.

Varicella-zoster virus (VZV) infection

Initial exposure to VZV in infancy results in varicella; on recovery the virus remains latent in tissues and its reactivation may later on result in herpes zoster. Varicella is highly contagious being estimated that between 2.8 and 3.5 million cases occur in US each year (Spring et al., 1994; Elliot, 1994) yet only 150,000 to 200,000 are reported (Anonymous, 1991). Although varicella is a mild disease usually with complete recovery, neurological complications develop in 1 to 4 instances for each 1,000 patients, the most frequent of which is encephalitis with a mortality rate of 5 percent. No mention is made in available recent surveys (Preblund, 1981; Guess et al., 1986) of PEP as a sequela to this infection.

Venezuelan equine encephalitis (VEE)

The human disease in nature, first reportd in 1954, presents 2 forms, a systemic influenza-like illness of 3–5 days duration or an encephalitis lasting 8 to 10 days; 4 percent of patients develop encephalitis of whom 15 percent die. Complete recovery is the rule in survivors. An outbreak in 1952 in Colombia involved 70 or more persons (Sanmartin-Barberi et al., 1954); none died nor short term sequelae were seen. A large epidemic in Venezuela from 1962 to 1964 affected 32,000 individuals, with 190 deaths (Sellers et al., 1965; Briceno-Rossi, 1967). In the course of an epizootic that began in 1967 in Ecuador and progressed to Texas in 1971, the disease spilled over to man; morbidity estimates are available for 1971 in Mexico with 16,992 cases and 45 deaths (Vilchis-Villasenor, 1972) and in Texas, 110 cases and no deaths (Bowen et al., 1976). Sporadic cases or small episodes are frequently reported in Central America. Attempts to uncover long delayed sequelae have been very few; Bowen et al. (1976) followed up 100 patients of whom 88 recovered completely after 1 week and 12 had some persisting symptoms at 30 days,

but recovery was complete at 9–12 months. Leon et al. (1975) followed 7 survivors from severe encephalitis for up to 4 years and observed motor disturbances an convulsions. No cases of PEP associated with VEE have been reported.

Western equine encephalitis (WEE)

The disease in man was observed for the first time in 1938 in California and, subsequently, in other parts of US and in Canada. The incidence in US has been between a few cases and 40 to 50, with the exceptions of 1975 when 175 were recorded and 1941 when a large epidemic broke out in areas of US and Canada – Minnesota, North Dakota, Saskatchewan and Manitoba – involving about 3,500 persons (Leake, 1941; Donovan and Bowman, 1942; Davison, 1942; Jackson, 1943).

A second instance in which WEE in man became a serious problem was by its long endemicity in a highly developed agricultural area in the San Joaquin valley in California (Finley, 1958; Finley et al., 1967). The typical disease is an acute encephalitis with sudden onset, fever, headache, drowsiness, stupor, and convulsions in infants. There is a long convalescence, mortality is between 2 and 4 percent and recovery in survivors is usually complete, except in infants aged under 3 or 4 months.

After the 1941 epidemic there was an interest to determine the frequency of long term sequelae. Jackson (1943) surveyed 256 survivors in Manitoba 10 months after onset; 139 had completely recovered, 117 had disabilities such as fatigue, weakness, headaches and diplopia but parkinsonism is not mentioned. Eklund (1946) reported his findings in 857 survivors mostly from Minnesota, of whom 360 had antibodies for WEE virus. Sequelae consisted of marked personality change in 1 person; mental retardation, convulsions and spastic paralyses in 4 infants; quadriplegia and sensory loss in a 5-year-old child; no mention of parkinsonism. Fulton and Burton (1953) investigated survivors of WEE in Saskatchewan with onset between 1940 and 1952; of 101 persons 15 showed sequelae. Two adults "had developed parkinsonism" but no details are given; the remaining, mostly children, had a variety of syndromes, cerebral palsies, retardation, neuroses and epileptic seizures. In the California episode, Finley (1958) and Finley et al. (1967) maintained a 15-year surveillance over about 600 cases of specifically diagnosed WEE between 1946 and 1958; parkinsonism was seen in only 2 patients, but according to Finley it probably was not related to WEE. In a study in Texas (Earnest et al., 1971) 35 cases of WEE with onset between 1963 and 1966 were followed from 2 to 7 years; no PEP was detected.

In sharp contrast with the above (Mulder et al., 1951) described on outbreak of WEE in Colorado in 1949 involving 25 patients of whom 15, 3 infants and 12 adults, were followed during 7 months. The infants and 6 adults developed serious sequelae; cogwheel rigidity, resting tremor, masked facies, bradykinesia and, in 1 patient, 2 oculogyric crises. This observation is unique; the preponderance of reported evidence with more survivors and longer periods of observation is that PEP is not a sequela of WEE.

Postencephalitic parkinsonism (PEP) suspected to be associated with as yet unidentified viruses

Parkinsonism associated with ED belongs in this group. In this section are described cases of parkinsonism following an encephalitis suspected of being of viral etiology other than ED.

Bojinov (1971) described 11 sporadic cases in Bulgaria with onsets between 1952 and 1969; 7 occurred in summer, none in winter. All presented with fever, headache and lethargy. Parkinsonism developed shortly after onset and reached its peak between 1 to 3 weeks: amimia, cogwheel rigidity, atonal speech, resting tremor, bradykinesia and parkinsonian gait; ophthalmoplegias were noted but no oculogyric crises. Seven patients survived of whom 6 recovered completely between 6 and 12 weeks from onset and 1 in 2 years; of the 4 fatal cases 3 died between 9 and 22 days from onset and the fourth died of unrelated causes 4 months from onset after complete recovery from parkinsonism. Postmortem showed severe cell loss in substantia nigra which Bojinov did not consider typical of ED; for this reason as well as owing to the summer seasonal occurrence, the complete disappearance of parkinsonism in the survivors and also to the fact that ED had not been seen for decades he rejected the diagnosis of PEDP. For various reasons were also rejected the diagnoses of JE, RSSE, poliomyelitis and coxsackie virus infection. Bojinov concluded that his cases were "specific, primary acute viral parkinsonian encephalitis of unsolved etiology."

Misra and Hay (1971) report 3 patients that were hospitalized as cases of acute schizophrenia with no neurological signs. From 2 to 4 days after admission they developed an encephalitic syndrome with fever, somnolescence or restlessness, Babinski sign and abnormal EEG. Two months after onset one of the patients developed PEP which persisted for at least 3 years; the second patient made a gradual and complete recovery. The third patient developed dilated pupils, lack of reaction to convergence or light and ankle tonus; he improve gradually and recovered in 1 month, except for his mental status which 3 years later was diagnosed as chronic schizophrenia.

Herishanu and Noah (1973) described an acute illness in a 2-year-old boy who developed fever, generalized convulsions and coma; an EEG was abnormal. After 10 days he had recovered complete consciousness but then gradually developed indifference to surroundings, listlessness, lack of expression, slurred speech, fine tremor at rest, marked akinesia, cogwheel rigidity, hyperreflexia and hesitating broadbased gait. This phase lasted 3 weeks after which he gradually improved and was discharged 5 weeks from onset; when last seen 2 months later he was well. The investigators concluded that this was a possible case of ED with the acute phase followed immediately by parkinsonism.

Miyasaki and Fujita (1977) described a mild encephalitis and subsequent parkinsonism in an adult. In April 1969, the patient had a 2-day fever with no other signs or symptoms; 3 months later his motions became slow and he developed fingers' tremors. One and one-half years after the febrile episode he progressively developed rigidity, tremors, bradykinesia, propulsion,

salivation, dilated pupils, absence of light and convergence reflexes and micrography. He was hospitalized and later developed altered behavior becoming obnoxious; he required help to eat and walk. Five years after the febrile episode he had a fall and died 2 months later. Autopsy revealed a subdural hematoma and, microscopically, extensive degeneration and loss of substantia nigra neurons, neurofibrillary tangles and a single Lewy body. The authors state that while clinically and pathologically the case was similar to PEDP, they had to rule out ED because the patient was born in 1942, years after any physician had seen a case of the disease. The authors also ruled out JE because the encephalitic episode occurred in April, months before the JE season begins, and the lesions were unlike those seen in JE; the diagnosis given was "encephalitis of unknown cause immediately followed by parkinsonism."

Conclusions

The etiology of von Economo's disease, including the post-von Economo's disease parkinsonism, is unknown. Much effort has gone into attempts to isolate an agent from patients' tissues and secretions and to detect circulating antibodies specifically reactive with established viruses or their antigens used as probes to indicate previous infection but the results have been negative. From the time of the initial description by von Economo the disease has been considered to be caused by a virus, but this is only an assumption. Recent findings, however, support this assumption: 1) Oligoclonal IgG bands have been observed in the CSF during the acute phase of suspected cases of the disease (Williams et al., 1979; Howard and Lees, 1987); 2) A marked, diffuse astrocytic reaction has been observed during the acute and the late phase of the disease in archival cases (Elizan and Casals, 1991) which could be the result of a persistent chronic infection as may be caused, among other things, by a virus. Determination of the special agent will, however, require the application of more efficient methods than heretofore used, such as in-situ hybridization with specific antibodies; or extraction of genetic material from archival specimens followed by polymerase chain reaction (CRP), cloning, sequencing and comparison with similar sequences derived from existing viruses, as has been recently done with influenza virus (Taubenberger et al., 1997).

Presumed cases of von Economo's disease parkinsonism have been reported in small numbers since 1970; the clinical and, when available, the pathological data are fairly convincing. However, lacking a specific confirmation the doubt will remain concerning the authenticity of the diagnosis.

The question of postencephalitic parkinsonism following encephalitides caused by established viruses has been investigated. Some of the neurotropic viruses have such low incidence, such as EEE and Murray Valley encephalitis with no more than a few hundreds of cases on record since the diseases were first reported many decades ago, that PEP would hardly be a public health problem.

Other encephalitides, such as Japanese encephalitis, occur in thousands of new cases annually, so that the possibility of PEP is a real problem. A survey of the literature indicates that PEP is a rare event with any of the neurotropic

viruses. If it occurs at all it is very different from the classical PEDP; as it is evident immediately following the acute disease, is mild, transitory with most cases recovering in a few weeks. It lacks oculogyric crises, a hallmark of PEDP.

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