RECENT PROGRESS

Slow Infections of the Central Nervous System

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SUMMARY. *This review describes the recent advances in slow infections of the nervous system emphasizing the pathogenetic aspects of these diseases. A theoretical model for the pathogenesis of subacute sclerosing panencephalitis (SSPE) is proposed, illustrating the factors that may affect host response to the measles virus and allow it to persist and produce the panencephalitis. The isolation of an oncogenic virus from progressive multifocal leukoencephalopathy (PML) has implications in the consideration of a viral etiology for some brain tumors. The agent responsible for the transmissibility of kuru and Creutzfeldt-Jakob disease (CJD) remains uncharacterized despite recent interest in viroids and abnormalities in replication of cell membranes. The epidemiological data on multiple sclerosis suggests an exposure to an infectious agent at an early age of life modified by the host response. No specific agent has been consistently associated with multiple sclerosis. Amyotrophic lateral sclerosis (ALS), Parkinson's disease, Mollaret's meningitis and Behcet's disease are other examples where a virus is suspect but unproven. The ability of viruses to persist in the host for months to years has linked many chronic neurologic diseases to an infectious agent, enlarging the spectrum of disease caused by viruses.*

RÉSUMÉ: *Cette revue décrit les récents développements au sujet des infections lentes du système nerveux, et insiste sur les aspects pathogénétiques de ces maladies. Un modèle théorique pour la pathogénèse de la panencéphalite sclérosante subaigue (SSPE) est proposé illustrant les facteurs pouvant influencer la réponse de l'hôte au virus de la rougeole et lui permettre de persister et de produire la panencéphalite. L'isolation d'un virus oncogène d'une leukoencéphalopathie multifocale progressive (PML) a des implications dans la considération de l'étiologie virale de certaines tumeurs du cerveau. L'agent responsable de la transmissibilité du kuru et de la maladie de Jakob-Creutzfeldt (CJD) demeure non caractérisée en dépit d'un intérêt récent pour les viroïdes et les anomalies de la "replication" des membranes cullulaires. Les données épidémiologiques sur la sclérose en plaques suggèrent une exposition à un agent infectieux dès le jeune âge modifié par la réponse de l'hôte. Pas d'agent spécifique n'a été associé de façon constante à la sclérose en plaques. La sclérose latérale amyotrophique (ALS), la maladie de Parkinson, la méningite de Mollaret et la maladie de Behcet sont d'autres exemples où la présence d'un virus est suspecte mais non prouvée. L'abilité des virus à demeurer chez l'hôte pendant des mois et des années nous permet de lier plusieurs maladies neurologiques chroniques à un agent infectieux, élargissant ainsi le spectre des maladies causées par des virus.*

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This review of slow infections is limited to diseases of the human central nervous system. The purpose is to stress the proposed mechanism of disease, knowing the pathogenesis of these diseases is poorly understood. The slow virus diseases in man are uncommon. However, the application of the principles established in understanding them provides some hope for the elucidation of etiology and pathogenesis in more common neurological diseases like multiple sclerosis and amyotrophic lateral sclerosis.

The concept of slow infections was first introduced by Sigurdsson in 1954, and later popularized by Thormar (1967), and Gibbs and Gajdusek (Gajdusek, et al., 1967; Gibbs, et al., 1968). A slow infection differs from both acute and chronic infections (Eklund and Hadlow, 1973). It is considered to be a disease in which there is a subclinical infection by an agent followed by many months or years without signs of disease, and then, after signs and symptoms have appeared, the disease has a rather regular protracted course leading to serious deterioration of health, and eventual death.

Some of the slow infections demonstrate major involvement of the nervous system of animals; for example, visna (Thormar and Palsson, 1967), scrapie (Bignami and Parry, 1972), and mink encephalopathy (Burger and Hartsough, 1965; Hartsough and Burger, 1965). (Table I). This led to speculation about the etiology of human degenerative neurologic diseases of unknown pathogenesis.

The infectious etiology of several neurological diseases was facilitated by two new methods for the dem-

onstration of a transmissible agent. The first demonstration of slow CNS infections in man was based on the inoculation of human brain material into chimpanzees and holding the animals for many years awaiting the development of neurological signs. Both kuru (Gajdusek et al., 1967), and Creutzfeldt-Jakob disease (Gibbs et al., 1968), were shown to be transmissible. The second development involved tissue culture cocultivation and cell fusion methods which resulted in the isolation of agents from subacute sclerosing panencephalitis (SSPE) (Payne et al., 1969; Horta-Barbosa et al., 1969), progressive multifocal leukoencephalopathy (PML) (Padgett et al., 1971; Weiner et al., 1972), and progressive rubella panencephalitis (PRPE) (Weil et al., 1975). Since both methods have been used for a number of years in a variety of neurological diseases, further progress will likely depend on the development of new techniques.

CLASSIFICATION OF SLOW INFECTIONS:

1. Chronic progressive panencephalitis
   a) Subacute sclerosing panencephalitis
   b) Progressive rubella panencephalitis
   c) Russian spring-summer chronic progressive panencephalitis (RSSPE)
2. Progressive multifocal leukoencephalopathy
3. Spongiform encephalopathies (agents not identified).
   a) Kuru
   b) Creutzfeldt-Jakob disease
4. Diseases of suspect viral etiology
   a) Multiple sclerosis
   b) Amyotrophic lateral sclerosis
   c) Parkinson's disease
   d) Mollaret's meningitis
   e) Behcet's disease
   f) Others

1. *Chronic Progressive Panencephalitis*

The clinical, laboratory, neuropathological and virological findings of SSPE, PRPE and RSSPE are summarized in Table II. The majority of the research in terms of disease mechanism is related to SSPE. PRPE has been reported in 3

TABLE I

	VISNA (Thormar, 1971)	SCRAPIE (Gibbs & Gajdusek, 1972)	MINK ENCEPHALOPATHY (Burger & Hartsough, 1965; March et al., 1969)
Host range	Sheep	Sheep	Mink
		(goats, mice, hamsters, rats, gerbils, mink, monkeys)	(hamsters, goats, skunks, racoons, monkeys)
Incubation period	1 to 4 yrs.	9 mos. to 4 yrs.	8 to 12 mos.
Clinical findings	stumbling, hind leg paralysis, trembling of lips, tilting of head	ataxia, tremor, excessive thirst, tendency to scratch	initially excitable, ataxia, stuporous, occasionally convulsions
Course	3 to 9 mos.	3 to 12 mos.	2 to 6 wks.
Antibody response	Yes	No	No
CSF pleocytosis	Yes	No	No
CSF protein elevation	Yes	No	No
Pathology	perivascular infiltration of mononuclear cells, patchy demyelination	neuronal vacuolation, reactive astrocytosis, PAS positive plaques	neuronal vacuolation, reactive astrocytosis
Agent			
Size	70-100 nm	35 nm	50 nm
Heat resistant	No	Yes	Yes
Formalin resistant	No	Yes	Yes
Ether resistant	No	No	No
Ultraviolet radiation resistant	No	Yes	Yes
Pathogenesis	Unclear	Gradual buildup of infectivity titre (Eklund et al., 1963)	Unclear

recent cases, resulting in exciting speculation about the persistence of rubella infection.

The pathogenesis of SSPE is incompletely understood. A variety of possibilties have been considered, but none has been proved. The viruses isolated from measles disease and SSPE share regions in their RNA genome that are at least 70% homologous (Yeh, 1973). Immunochemical (Katz et al., 1970) and morphological (Oyanagi et al., 1971) differences suggest a mutant form of measles virus in SSPE. Either the etiological agent in SSPE is a mutant measles virus to begin with or it is altered in some way by its intrinsic nature or by the host response, enabling the virus to persist (Figure I). The factors that may influence the host response are many and varied. Why it should remain latent in certain individuals and not others is unclear. Genetic factors influencing immune response to antigenic stimuli are fundamentally important. Since the majority of children who develop SSPE have had measles infections under the age of 2 years (Detels et al., 1973), immunological immaturity or persistence of maternal antibody should be considered (Payne and Baublis, 1973). The ability of measles infection to suppress cell mediated immunity may also play a role in inducing latency. Specific inhibitory factors of cellular immunity have been described but their precise nature is undetermined (Swich et al., 1976; Steele et al., 1976). The "dual virus" infection hypothesis (Koprowski et al., 1970) suggests that a second virus suppresses host response and may be responsible for the development of a persistent infection. The mechanism of persistence and the reason for expression of the disease 2 to 10 years after the initial infection is also open to speculation. Defective ribonucleoprotein particles of measles virus may interfere with the growth of virus (Rustigian, 1966). Actual expression of disease might occur when the balance between defective and complete virus particles is disturbed. With persistence of virus in culture there is a tendency toward the development of temperature sensitivity (Galasso, 1976). This sensitivity may be involved in the maintenance of the persistent infection by stabilization of the host-virus relationship. Despite the attractiveness of some of these mechanisms, they remain largely in the realm of speculation, some better supported by experimental evidence than others.

TABLE II

	SSPE (Thormar, 1971)	RPE (Townsend et al, 1975; Weil et al., 1975)	RSSE (Ogawa et al., 1973)
CLINICAL			
Age (yrs.)	4-20	8-12	50
Incubation period	Unclear	From birth	13 yrs.
Behaviour changes	+	—	+
Mental deterioration	+	+	+
Myoclonic movements	+	+	—
Ataxia	+	+	+
Chorioretinitis	+	+	?
Pyramidal signs	+	+ —	+
Generalized seizures	—	+ —	—
Antibody response (Serum & CSF)	+	+	+
CSF pleocytosis	—	+ —	+
CSF protein elevation, elevated IgG	+	+	+
PATHOLOGY			
Perivascular cuffs	+	+	+
Microglial proliferation	+	+	+
Reactive astrogliosis	+	+	?
Demyelination	+	+ —	—
Inclusions	+	—	—
AGENT			
Viral isolation	measles	rubella	—
Electron microscopy	paramyxovirus	—	—
Immunofluorescent viral antigen in brain	+	—	Not done
Serology	measles	rubella	RSSE
ANIMAL MODELS	Acute encephalitis (Katz et al., 1968); Chronic encephalitis (Byington and Johnson, 1972); Latent infection (Dubois-Dalcq et al., 1974); Distemper (Wisniewski et al., 1972)	None	None

Of related interest is the newly recognized PRPE developing in adolescence in children who have had congenital rubella. This disease is similar to SSPE. Rubella virus has been isolated from the brain of one of these patients by using tissue explants and co-cultivation of tissue with CV-1 monkey cells and human

fetal diploid lung cells (Weil et al., 1975). The pathology is also similar to SSPE except that inclusions are not demonstrable (Townsend et al., 1976).

There are several case reports of a chronic progressive encephalitis occurring 14 and 13 years after acute RSSPE. In Harada's (1970) report, information on serology and virology were lacking. In Ogawa's (1973) case report, high titres of hemagglutination inhibition antibody against RSSPE, both in serum and CSF, were present. Histological studies of the brain showed chronic inflammation of the meninges, cortex and white matter. Astrogliosis and inclusions were not described.

This group of diseases, exemplified by SSPE, has provided a means for establishing animal (Notermans et al., 1973; Thormar et al., 1973; Albrecht et al., 1977) and tissue culture (Raine et al., 1973; Castro et al., 1972) models. Both have helped clarify the phenomenon of persistence. It is suggested that mass immunization with live measles vaccine has reduced the incidence of SSPE and it may be eliminated (Johannes and Sever, 1975). On the other hand, the introduction of many live virus vaccines means that these viruses must be kept in mind in terms of potential chronic and persistent infections in humans.

2. *Progressive Multifocal Leucoencephalopathy:*

PML is a rare neurological disorder usually accompanying lymphoproliferative, malignant or immunosuppressive disorders. Mental and motor disturbances are frequent, with a 3 to 6 month duration of signs and symptoms preceding death. Multiple foci of demyelination, associated with enlarged inclusion bearing oligodendrocytes and bizarre astrocytes are characteristic. These peculiar astrocytes are of great interest. They are often binucleate, with pleomorphic giant nuclei and abundant distorted glial processes. However, only rarely do these astrocytes produce a frank glioblastoma multiforme. In the single case report of such an occurrence (Castaigne et al., 1974), multifocal glioblastoma multiforme was found in a background of characteristic PML from which papovavirus was isolated. Two types of papovaviruses related to Simian virus 40 (SV40) have become associated with PML (Padgett et al., 1971; Weiner et al., 1972). The oncogenicity of these human isolates (Walker et al., 1973), and their ability to transform astrocytes (Shein, 1967) increases their candidacy in studies of human cerebral oncogenesis (Becker et al., 1975). The pathogenesis of the demyelination is based on the destruction of the oligodendrocytes with loss of their cytoplasmic extensions which form the myelin sheaths. Serological studies indicate that antibody formation against these papovaviruses is common. The majority of adults have antibody against the JC virus (Padgett and Walker, 1973), and this virus is acquired during childhood. Therefore, PML is produced as a de novo infection or as an activation of latent infection. Although a high proportion of patients have defects in the cell mediated immune response (Narayan et al., 1973), the manner in which the virus and host interact to product PML is unclear.

3. *Spongiform Encephalopathies:*

The transmissible spongiform encephalopathies, CJD and kuru, are compared in Table III according to their respective clinical and pathological characteristics.

The transmissibility of kuru is thought to be through ritualistic cannibalism. Kuru is an exotic disease of the Fore tribal areas of New Guinea where cannibalism was practiced primarily by the women and their children who ate brain tissue from their dead relatives. Consumption was preceded by minimal cooking, therefore, it is possible that an infectious agent could be transmitted in this fashion (Glasse, 1967). A decline in cannibalism has been associated with a decline in kuru (Lampert et al., 1972).

CJD has been transmitted inadvertantly to a corneal transplant recipient (Duffy et al., 1974) and a neurosurgeon (Gajdusek et al., 1973). Therefore, precautions must be taken by neuropathologists and neurosurgeons to avoid self-inoculation with contaminated brain. It is suggested by Traub et al. (1974) that any suspect contaminated surgical or autopsy instruments be autoclaved for 30 minutes and surfaces in contact with contaminated tissues be washed with 0.4% NaOCL solution.

Although kuru, CJD and scrapie have been shown to be transmissible,

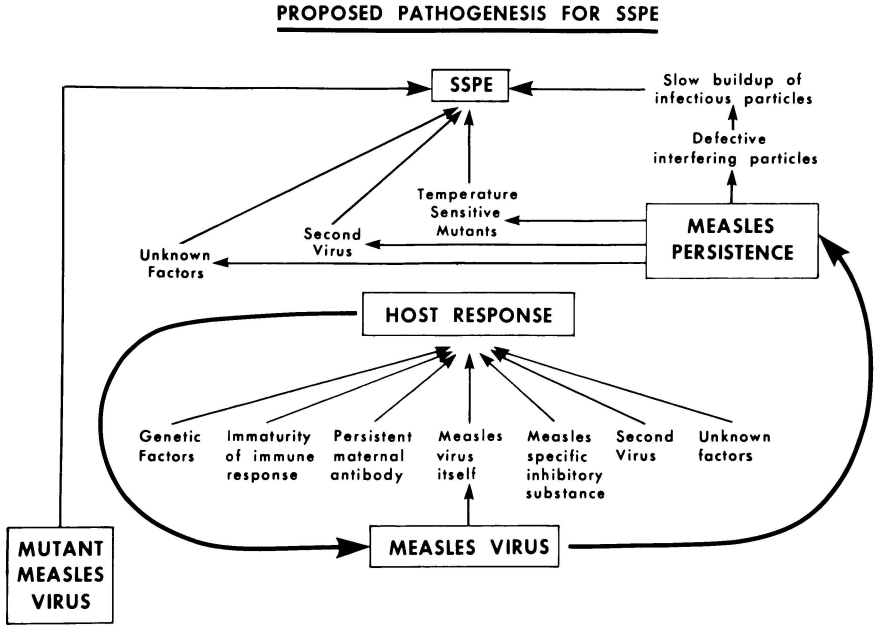

Figure 1—A theoretical model for the pathogenesis of SSPE.

the nature of the agent that is being transmitted is unclear. It has been suggested (Diener, 1972), that the scrapie agent (or kuru or CJD agent) might be a viroid. A viroid is the simplest infectious unit described; an agent composed solely of nucleic acid and insensitive to phenol extraction (Diener, 1971). If the scrapie agent is a viroid its infectivity should not be decreased by phenol extraction. In such an extraction experiment infectivity was reduced beyond the level of detection (Ward et al., 1974), suggesting the scrapie agent is not a viroid. Other hypotheses concerning a transmissible agent have been suggested; a replicating agent without nucleic acid (Alper et al., 1966), a small nucleic acid core with a large polysaccharide coat (Adams and Caspary, 1967), and a provirus (virus covalently bonded to cellular DNA) able to link to a replicating membrane (Field, 1969). It has also been proposed that an abnormality in the replication of cell membranes might be responsible for scrapie (Gibbons and Hunter, 1967), because the plasma membranes show the highest infectivity (Millson et al., 1971). However, the precise nature of the transmissible agent in the spongiform encephalopathies remains a mystery.

TABLE III

	CJD (Roos et al., 1973)	KURU (Gajdusek & Zigas, 1957) (Lampert et al., 1972)
CLINICAL		
Age (yrs.)	35-65	Adult females and children
Incubation period	Unknown	4 yrs.
Dementia	++	+
Pyramidal	+	+−
Ataxia	+	++
Extrapyramidal	+	+
Myoclonus	++	+−
Tremors	+−	+
Seizures	+−	−
COURSE	1 yr.	1 yr.
Antibody response	−	−
CSF pleocytosis	−	−
CSF protein elevation	−	−
PATHOLOGY		
Astrocytic vacuolation	+	−
Neuronal vacuolation	+	+
Reactive astrocytosis	+	+
PAS positive plaques	+−	+
AGENT		
Size	220 nm	220 nm
Heat resistant	Yes	Yes
Formalin resistant	Yes	?
Ultraviolet radiation resistant	?	?
ANIMAL MODELS	Chimpanzee, monkey, cat	Chimpanzee, monkey

4. *Diseases of Suspect Viral Etiology:*

The list of diseases in which it is thought that a virus may be implicated is long, but the supporting evidence is in many cases minimal and controversial. The emphasis here will be on virologic studies of multiple sclerosis and amyotrophic lateral sclerosis.

The epidemiological data on multiple sclerosis are suggestive of an infectious etiology. The virological, serological, and morphological studies are inconclusive. Increased incidence of multiple sclerosis in northern latitudes, a maintenance of high-risk with migration from high- to low-risk areas, a higher familial incidence, lack of greater concordance in monozygotic than in dizygotic twins, and lack of higher conjugal incidence, suggest exposure to an infectious agent at an early age of life without the influence of any major genetic factors (Brody, 1972). Claims for viral isolations from multiple sclerosis patients include rabies virus (Dick et al., 1958), herpes simplex virus (Gudnadottir et al., 1974), scrapie (Palsson et al., 1965), parainfluenza-1 (ter Meulen et al., 1972), and a recently described transferable agent referred to as the multiple sclerosis associated agent (Koldovsky et al., 1975). Increased serum or CSF antibody titres to measles, herpes simplex, mumps, varicella, influenza, and parainfluenza viruses have been reported (Brody et al., 1972). Arnason et al (1974) have shown that the increases in measles antibody levels may be related to an unusual distribution of histocompatibility antigens in patients with multiple sclerosis. Individuals with HLA-3 had increased measles antibody titres irrespective of having multiple sclerosis. Since patients with multiple sclerosis have a high prevalence of HLA-3, the elevated measles antibody may just reflect histocompatibility type. Reports on possible suppression of measles-specific cell-mediated immunity are conflicting (Utermahlen and Zabriskie, 1973; Fuccillo et al., 1975). Structures resembling myxovirus nucleocapsids have been described in the sites of active demyelination in a patient dying of multiple sclerosis (Prineas, 1972), but these are not specific for this disease and there is some suggestion that these represent altered chromatin rather than virus (Lampert and Lampert, 1975). Levy et al. (1976) have described a blood test for multiple sclerosis, based on in vitro rosette formation of lymphocytes mixed with epithelial cells persistently infected with measles virus. The positivity of the test in patients with multiple sclerosis was not affected by the severity, duration or activity of disease. Wider clinical trials are necessary before the diag-

nostic importance of the test can be established. Therefore, the research activity, related to virus or the interaction between immunocyte and virus, remains inconsistent and incomplete but, nevertheless, relevant to the understanding of the etiology and pathogenesis of multiple sclerosis.

It has been suggested that ALS may be caused by a virus, because the striking damage to anterior horn cells resembles poliomyelitis. Some neurologists (Poskanzer et al., 1969), claim that patients with sequelae of old poliomyelitis more frequently develop ALS. It has been suggested that the late progression is a recrudescence of a viral infection (Mulder et al., 1972), perhaps akin to recrudescence of rubella in the panencephalitis occurring in adolescence. Soviet scientists have reported transmission of amyotrophic lateral sclerosis to monkeys (Zil'ber et al., 1963), But Gibbs and Gajdusek (1972) have been unable to provide confirmation.

The significance of the miscellany of viral-related observations in multiple sclerosis and ALS is completely obscure. A virus remains a possibility in any etiological discussion of these entities but other non-viral factors should also be considered at this stage in our understanding (Wolfgram and Myers, 1973; Horwich et al., 1974).

Parkinson's disease, following Von Economo's encephalitis (Duvoisin and Yahr, 1965), epilepsia partialis continua, following tick-borne encephalitis (Aguilar and Rasmussen, 1960); Mollaret's meningitis, associated with a hemagglutinating agent in chick embryos (Mollaret and Castaigne, 1952); Behcet's disease associated with transmission of lesions to rabbits, guinea pigs, mice and embryonated eggs (Nakagawa and Shingu, 1958; Mortada and Imam, 1969; Sezer, 1953), and many other chronic inflammatory brain lesions, unassociated with attempts at viral isolation, have provided examples for speculation and future investigation. Some of the claims of virus isolation or disease transmission may represent contaminants or viruses indigenous to the laboratory animal under investigation. The possibility of a normal flora in the brain has been suggested by the isolation of a spectrum of viruses from the brain of chimpanzees (Rogers et al., 1967). Long-term suppression of the immune system by therapy or chronic disease may activate latent agents in the brain to produce, for example, the high incidence of lymphomas in renal transplantation patients (Schneck and Penn, 1971).

This review, then, has emphasized slow virus investigation in various neurological disorders illustrating a number of diseases possibly caused by viruses.

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