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# EDITORIAL

## Subacute Sclerosing Panencephalitis

As the endemic of encephalitis lethargica (von Economo's disease) abated in this country in the 1930's, James Dawson delineated a clinical and pathological form of subacute encephalitis described as an atypical form of encephalitis lethargica with intranuclear inclusion bodies [1]. Later, the disease came to be called subacute inclusion encephalitis [2]. In subsequent years, nosologic confusion arose with the description of similar diseases under the appellations of nodular panencephalitis of Pette and Döring [3] and subacute sclerosing leucoencephalitis of van Bogaert [4]. It is now widely agreed, however, that all three represent the same clinical and pathological entity. In a spirit of international compromise, epithets from each of the 3 classical descriptions have been united, and Dawson's encephalitis has been given the name subacute sclerosing panencephalitis or SSPE.

SSPE is an uncommon disease affecting children and adolescents between the ages of 4 and 20 years. The clinical course is usually quite stereotyped, beginning insidiously with behavioral disorders and deterioration of school work. After several weeks or months, obvious neurologic signs develop, the most characteristic of which are myoclonic jerks. The disease usually terminates after a third stage of stupor, blindness, dementia, and decorticate rigidity. In most cases the disease follows a relentlessly progressive course, but in some children, prolonged periods without obvious deterioration are seen and rarely there are transient periods of apparent clinical improvement [5]. Fever and headache are not characteristic of this disease. The cerebrospinal fluid usually shows no increase in cells or pressure, but a marked elevation of gamma-globulin content gives rise to a first-zone colloidal gold curve. Particularly during the period of active myoclonus, the electroencephalogram shows a pattern of general suppression with sudden synchronous bursts of activity, a pattern regarded by some as pathognomonic of the disease. Pathologically, the brain is usually grossly normal but may show mild atrophy. Microscopically, there are characteristic findings of perivascular infiltrations of mononuclear cells and the presence of eosinophilic intranuclear inclusions in both neurons and glial cells.

Although SSPE is a slowly progressive disease with an afebrile course, a viral etiology was suspected from the outset because of these pathological findings. Dawson was impressed by the similarity of the inclusions to those produced by herpes simplex virus and attempted, unsuccessfully, to isolate virus in a variety of animals [1]. In subsequent years, other infectious agents were postulated and, in several instances, there were unconfirmed reports of isolations of unidentified agents. Many investigators, however, continued to regard the disease as an atypical or chronic form of herpes simplex virus encephalitis, and considerable impetus was given to this idea in 1961 when Sherman et al. [6] reported the presence of specific fluorescent antibody staining for herpes simplex antigen in the brain of one patient.

In the past 4 years, there has been a burgeoning of interest in this disease with the implication of measles or a measles-like virus in its pathogenesis. Interestingly, this new direction of investigation was not stimulated by virological, but by electron-microscopic, studies. Bouteille et al. [7], in 1965, described in the brain of a patient with SSPE viruslike particles that resembled the helical nucleocapsids of the measles-distemper group of paramyxoviruses. This finding was rapidly confirmed by a number of other electron-microscopists. In 1967, Connolly et al. [8] reported the finding of astonishingly high levels of measles virus antibody in the sera of patients with SSPE, as well as the presence of a specific immunofluorescent staining for measles virus antigen in brain. These serological and immunofluorescence studies were also confirmed by other laboratories.

Sufficient excitement had been generated that a special conference on "Measles Virus and Subacute Sclerosing Panencephalitis" was held in Bethesda in September, 1967 [9]. Although no one, at that time, had been successful in isolating

measles virus from the brain of a patient with SSPE, many considered the experimental work to have firmly established the etiology of SSPE. The suggestion was even made that the disease be renamed "slow measles encephalitis." Some remained skeptical, including Dr. Katz and his colleagues from the Wistar Institute who, at that time, were studying a possible transmissible agent in ferrets that did not appear to be measles virus. Their preliminary report of these studies, which appeared the following year, suggested that the last gun had not been sounded on the etiology of SSPE [10].

The really incontrovertible evidence for a role of a measles virus was short in coming with the report of Baublis and Payne [11], who maintained trypsinized brain cells from a patient with SSPE in culture. They demonstrated the development of syncytia and inclusion bodies, and the presence of measles antigen in these cultures. Furthermore, similar changes and fluorescence could be demonstrated in human and monkey cell cultures inoculated with trypsinized cells from the original cultures (but not from uncultured brain cells), and these effects could be neutralized with measles antibodies. Chen et al. [12] soon reported similar results from an independent study. In both, however, the antigen and cytopathological changes could be passed only with intact cells, and extracellular measles virus could not be recovered. This was first achieved with the studies of Horta-Barbosa et al. [13], but the isolation of extracellular measles virus necessitated multiple passages of the cells derived from the patient's brain followed by the coculture of these cells with HeLa cells. Usual laboratory strains of measles virus were found to grow readily in the cultures derived from the SSPE brains and to produce extracellular measles virus without necessitating multiple passages and coculture with other cells.

Thus, measles virus or a measleslike virus is present in the brains of children suffering from SSPE. The apparent profusion of virus in the brain as judged by electron-microscopic and immunofluorescence studies makes it hard to deny that the agent is related to the disease. Yet the most intriguing question remains unanswered—how is this common agent related to a rare disease occurring in children who otherwise appear to be in good health? Almost all of these patients have a history of uncomplicated measles years in the past. Furthermore, there is little similarity clinically or pathologically between SSPE and the acute parainfectious encephalomyelitis, which more frequently complicates measles. The latter is an acute disease and is characterized pathologically by perivenular demyelination. Also, why can measles virus be isolated from SSPE only following the prolonged culture of brain cells followed by coculturing with other cell lines? Initially, the failure to isolate measles virus from patients with SSPE was ascribed to their high levels of antibody, but these results of Horta-Barbosa and his co-workers indicate that some other explanation is needed.

Several mechanisms might be postulated for the pathogenesis of SSPE. These could include (*1*) an abnormal host immune response to infection with measles virus, (*2*) an unusual measles virus causing slow infection in an otherwise normal host, or (*3*) disease resulting from measles virus in concert with a second agent.

The first alternative has been given wide consideration. The finding of high levels of antibody to measles in sera and spinal fluids of patients has naturally led to speculation that SSPE is an immunopathologic process [14]. However, if the disease simply represents an excessive immune response to measles virus in the brain, the unlikely assumption must be made that the measles virus is normally present in the brain in large amounts for prolonged periods following measles. Conversely, Burnet [15] has postulated an immunological deficiency in which the thymus-differentiated cells have a specific tolerance to measles antigen, while the antibody system remains active. A subsequent report of very active transformation of lymphocytes from a patient with SSPE when the cells were exposed to measles virus antigen would tend to oppose this theory [16], but further studies are needed. Furthermore, these immunologic theories fail to explain why the measles virus continues to remain cell-associated after serial cultures in vitro.

Some mechanism dependent on a strain variant of virus appears more attractive. If the initial infection were due to some unusual strain of measles or a measleslike virus, then outbreaks of SSPE should occur, rather than random rare cases in children contracting measles during the usual periodic epidemics. Although some geographic and temporal clustering of cases has been sug-

gested,[1] this is not established. Alternatively, initial infection might be due to the classical measles virus which, in the course of replication in the host, could give rise to a mutant. Such a mutant might be cell-associated, persist in brain cells, and have the potential, after a latent period of years, to cause subacute disease. This hypothesis, that SSPE is a slow infection due to the occasional aberrant adaptation of measles virus to neural cells [17], would be consistent with the rare random occurrence of SSPE, the difficulty in isolation of the measles from brains, and the unusual disease induced in ferrets. Furthermore, Rustigian's adaptation of measles to HeLa cells, where a persistent, cell-associated, noncytolytic infection occurs, demonstrates the potential of measles virus to achieve such a virus-host relationship [18, 19].

The possibility of a dual infection must be considered, and certainly the results of Katz et al., reported previously [10, 20] and in this issue [21], are rather suggestive of that hypothesis. Although immunofluorescence with measles antiserum and measleslike particles have been found in their explant cultures of brain biopsies from patients, similar findings have not been made in brains of their "ferrets with SSPE."

The ferret studies pursued by the group at the Wistar Institute have met with a certain disdain from other laboratories. Their methods have been controversial, for certainly the use of electroencephalograms of ferrets as a viral indicator system could hardly be more unorthodox. Yet, the correlation of their electroencephalographic findings with pathological changes gives them credence. Indeed, the ferret model may prove to be the system in which the many unanswered questions about the pathogenesis of this curious disease can be explored further.

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[1] J. T. Jabbour, D. Duenas, J. L. Sever, and L. Horta-Barbosa. "Epidemiologic study in measles-induced subacute sclerosing panencephalitis (Dawson's encephalitis and van Bogaert's leucoencephalitis)," presented to the American Public Health Association, Philadelphia, November 13, 1969.

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