The term "slow infection" was coined originally in the veterinary literature to describe several transmissible diseases of sheep. Two of these diseases, scrapie and visna, have become the prototypes of slow infection of the central nervous system (CNS). After inoculation of sheep with tissues from an infected sheep, a latent period of one or more years ensues, during which the sheep appears well. This is followed by the insidious onset of neurological signs that progress without fever for one to six months and usually lead to death. Scrapie is characterized primarily by ataxia, and visna by progressive paralysis.

Pathologically, the diseases are quite distinct. The lesions in scrapie are confined to the CNS, where there is a proliferation of astrocytes and degeneration of neurons by cytoplasmic vacuolization. By contrast, the CNS lesions of visna are characterized by inflammation and demyelination. The agents responsible for these two slow infections also differ greatly. The scrapie agent has been transmitted to a wide variety of other animals, but the agent does not cause cytopathic changes in cell culture, and no virus particles have been definitely identified in infectious tissues by electron microscopy. Infectivity of tissue is remarkably stable upon exposure to physical and chemical treatments that inactivate classic viruses. Finally, animals naturally or experimentally infected with scrapie fail to develop any evidence of an immune response against the agent. Recently a protein has been associated with infectivity, and a fibril that could represent the infectious agent has been identified by electron microscopy. In contrast, visna virus is an enveloped RNA retrovirus. Although the agent can be transmitted only to sheep, it can be grown in cell cultures of a variety of species in which it causes acute cytopathic changes. Furthermore, in naturally and experimentally infected sheep, there are both a humoral and a cell-mediated immune response, which develop and persist throughout the evolution of pathological lesions and clinical disease (Table 1).

During the past 15 years, five chronic human neurological diseases have been demonstrated to be slow infections. Two of these, Kuru and Creutzfeldt-Jakob disease, resemble scrapie pathologically, and the agents of these diseases have properties similar to those described for the scrapie agent. The remaining three diseases, subacute sclerosing panencephalitis, progressive rubella panencephalitis and progressive multifocal leukoencephalopathy, resemble visna in being due to classic viruses capable under specific circumstances of producing a chronic inflammatory and/or demyelinating disease in the human CNS.

Kuru

Kuru is a degenerative disease of the brain limited to the remote Fore tribal people of the mountains of eastern New Guinea. Originally described only 25 years ago by Gajdusek and Zigas, this was the first human disease demonstrated to be a slow infection. The disease was most common among adult women, less common in children (but of equal frequency among boys and girls), and least common in adult males.

The disease follows a stereotyped pattern, beginning insidiously with truncal titubations and ataxia in an otherwise healthy person. The ataxia becomes progressively more severe until the slightest voluntary motion leads to violent, uncontrolled, ataxic movements. Late in the course of disease, abnormalities of extraocular movement and mentation develop. The disease invariably leads to death in three to 20 months. During its course, the patient remains afebrile. The spinal fluid shows no abnormality. Pathological changes are confined to the CNS and consist of an increase of astrocytes and degeneration...
Table 1 The Prototype Slow Infections of Sheep

<table>
<thead>
<tr>
<th></th>
<th>Scrapie</th>
<th>Visna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Worldwide</td>
<td>Classic disease limited to Iceland; other forms probably worldwide</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incubation period</td>
<td>2 to 7 years</td>
<td>2 to 7 years</td>
</tr>
<tr>
<td>Natural</td>
<td>1 to 7 years</td>
<td>2 to 5 years</td>
</tr>
<tr>
<td>Experimental Onset</td>
<td>Insidious, afebrile onset of neurologic signs</td>
<td>Insidious, afebrile onset of neurologic signs</td>
</tr>
<tr>
<td>Prominent signs</td>
<td>Ataxia</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Course</td>
<td>Relentless progression over 1 to 6 months</td>
<td>Progressive or intermittent course of many months</td>
</tr>
<tr>
<td>Cerebrospinal fluid findings</td>
<td>Normal</td>
<td>Chronic pleocytosis, elevated protein and IgG</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathology</td>
<td>Localized to gray matter, with spongiform changes and no inflammation</td>
<td>Localized to white matter, with inflammation and demyelination</td>
</tr>
<tr>
<td>Extraneural Virus</td>
<td>None</td>
<td>Often interstitial pneumonia</td>
</tr>
<tr>
<td>Host range Animal</td>
<td>Sheep, goat, mice, hamster, primates, and many others</td>
<td>Only sheep</td>
</tr>
<tr>
<td>Cell cultures</td>
<td>None</td>
<td>Sheep, goat, bovine, and other cells</td>
</tr>
<tr>
<td>Immune response</td>
<td>None</td>
<td>Humoral and cell-mediated immune responses</td>
</tr>
</tbody>
</table>

Modified from Johnson.\textsuperscript{6} p. 238.

of vacuolated neurons with a total lack of inflammation.

Because of the similarities in epidemiology, clinical course and pathology between scrapie and kuru, brain tissue from patients dying of kuru was inoculated into primates for long-term observation. After an incubation period of 18 months to four years, a similar disease developed in chimpanzees. This disease subsequently has been transmitted from chimpanzee to chimpanzee and to several other species. The agent can be transmitted with serial dilutions, proving that it replicates within the host. As with scrapie, however, the agent has not been seen by electron microscopy, does not induce cytopathic changes in cell cultures, is resistant to many physical and chemical treatments that usually inactivate viruses, and fails to evoke a demonstrable immune response in man or experimental host.\textsuperscript{8}

Although kuru was the commonest cause of death in the Fore tribe in the late 1950s and early 1960s, its incidence then declined, particularly among children, in whom it has now disappeared. This declining incidence coincided with the suppression of cannibalism in this primitive culture, and circumstantial evidence strongly indicates that kuru was transmitted in the practice of ritual cannibalism.\textsuperscript{8}

Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a presenile dementia characterized by rapid mental deterioration, myoclonic jerking and other inconstant neurological signs. The incidence of the disease is approximately one per million per year. In contrast to kuru, this is a worldwide disease of apparently uniform distribution. For approximately 10 to 15 per cent of patients, however, the disease occurs in families with pedigrees that suggest autosomal dominant inheritance.\textsuperscript{9}

Dementia develops rapidly; dissolution of intellect can be seen from week to week leading to severe dementia within six months of onset. Dementia is associated with a variety of abnormal signs. The most characteristic and constant is myoclonus, which often is stimulus-sensitive. In addition, blindness, amyotrophy, ataxia, chorea, athetosis, and pyramidal tract signs can be seen with variable frequency.\textsuperscript{10} The patient remains afebrile, and the cerebrospinal fluid shows no abnormality. The electroencephalogram becomes abnormal early in the disease and may show a characteristic pattern of diffuse slowing with superimposed bursts or sharp waves. Eighty per cent of the patients die within 12 months of onset, although some linger for up to eight years. Pathologically,
changes are limited to the nervous system and resemble those seen in scrapie and kuru but with greater involvement of the cerebral cortex and less of the cerebellum.

Despite the fact that in clinical and epidemiological features Creutzfeldt-Jakob disease differs from the other spongiform encephalopathies, the similar pathological findings stimulated experiments to transmit the disease to chimpanzees. After an incubation period of 17 to 71 months, the disease in chimpanzees simulates the disease in man. Studies of the nature of the agent again show the same unusual features found in scrapie and kuru, and the same small fibril found in scrapie has been identified by electron microscopy. 3

The mode of spread of the disease is unknown, but that it can be transmitted with tissues of familial cases suggests the importance of genetic factors or the possible vertical transmission of the agent. The failure to find increased incidence in medical personnel, laboratory investigators or spouses of patients suggests a lack of significant communicability. On the other hand, person-to-person transmission has occurred. One patient developed the disease 18 months after a corneal transplant from another patient who was proven to have it; the disease developed in two young patients less than two years after cerebral corticography using the same electrodes previously used in a patient with Creutzfeldt-Jakob disease; and the illness may be more frequent within two years after neurosurgical procedures. 12

Subacute sclerosing panencephalitis

This disease, also described in the literature as subacute inclusion encephalitis, nodular panencephalitis and subacute sclerosing leukoencephalitis, is a rare, late complication of measles virus infection. The disease has an incidence of about one per million children per year. It has been reported between the ages of 2 and 32 with an average age of onset of seven to eight years. Males are affected three times more often than females, and there is a curiously high preponderance among males of rural origins.

The temporal course of the disease is variable, but it commonly progresses through three stereotyped stages. The onset usually is insidious, with behavioral problems and decline in school performance. Over weeks to months, dementia becomes evident. The second stage of the disease is characterized by disturbed motor function, particularly the development of myoclonic jerks. Seizures occur in some patients, and retinopathy, optic atrophy, cerebellar ataxia and dystonia may develop. In the third stage, the child lapses into a stuporous, rigid state with behavioral problems and decline in school performance. In approximately 10 per cent the disease leads to death in three months; in another 10 per cent there may be protracted survival for 4 to 10 years. Particularly in this latter group, prolonged periods of stabilization and transient periods of objective improvement can be seen. Fever and headache are not present. The cerebrospinal fluid, although usually acellular, shows an elevation of IgG with oligoclonal bands demonstrating its limited heterogeneity. Serum and spinal fluid antibody titers to measles are high and with a distorted ratio that indicates local synthesis of antibody within the CNS. The electroencephalogram may show a characteristic pattern of periodic synchronous bursts of high-voltage slow and sharp waves. 6

Pathological abnormalities are seen in both gray and white matter. There is a mild leptomeningitis, and small cuffs of lymphocytes and plasma cells are found around cerebral vessels. Glialosis is present with varying degrees of demyelination, and eosinophilic intranuclear inclusion bodies are found in both glial cells and neurons. Because of these inclusions, a herpesvirus was long suspected. Electron microscopic studies of cerebral biopsies, however, showed the inclusions were composed of particles resembling the nucleocapsids of paramyxoviruses, and immunofluorescent staining revealed the presence of measles virus antigen. Nevertheless, the isolation of measles virus from the brains of patients with subacute sclerosing panencephalitis requires the establishment of cell cultures from brains of patients with the disease and subsequent co-cultivation with other cells. Both in the brains of the patients with the disease and in the cultures, there is a paucity or absence of the matrix (M) protein, a protein necessary for the enveloping and maturation of measles virus. 13 Whether this represents a defective replication of measles virus in the neural cells or a mutation of measles virus permitting persistence is unclear, but cell culture studies suggest the defect may represent defective translation. 14 Although there is no treatment for the disease, prophylactic use of measles vaccine causes a tenfold decrease in the development of subacute sclerosing panencephalitis. 15

Progressive rubella panencephalitis

Recently, a similar slow progressive panencephalitis has been associated with rubella virus. This is an extremely rare disease; only 10 cases have been described. Seven bore the stigmata of congenital rubella and three apparently followed acquired rubella. All patients have been male.

The children develop normally within limits of static congenital defects until eight to 19 years of age when deterioration of schoolwork and behavior signals an insidious onset of intellectual deterioration similar to the early stage of subacute sclerosing panencephalitis. Ataxia is the most frequent and pro-
minent neurological sign. Spasticity and dysarthria develop late. Some patients have myoclonus; optic atrophy and retinopathy also are seen. Headache and fever are absent. Cerebrospinal fluid in most cases shows some increase in mononuclear cells with protein elevation and a striking elevation of IgG that largely represents antibody against rubella virus synthesized within the CNS.16

The pathology is quite distinct from that of subacute sclerosing panencephalitis. Similar inflammation of meninges and perivascular spaces with variable degrees of demyelination occurs, but inclusion bodies are absent. In contrast, perivascular PAS positive material is prominent, indicating mineralization similar to that seen in congenital rubella encephalitis. This finding suggests the deposition of immune complexes, and immune complexes containing rubella virus have been found in high titer in serum and occasionally in spinal fluid of these patients.17 How this infection remains quiescent for many years, and then becomes active and causes lesions localized in the CNS, remains unknown. No cases have been related to the rubella virus vaccine, but data are insufficient to exonerate the vaccine virus definitely.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy is a subacute demyelinating disease that usually develops in patients with preexisting disorders of the reticuloendothelial system such as leukemia, lymphoma or sarcoidosis. It can occur in patients who have been immunosuppressed therapeutically or after organ transplantation, and has been observed in children with primary immunodeficiencies.18 Recently the disease has been seen with great frequency in patients with the acquired immunodeficiency syndrome.19 The neurological disease can occur at any time during the course of the underlying disease. Onset usually is insidious, with signs and symptoms suggesting multifocal disease. Paralysis, mental deterioration, visual loss and sensory abnormalities are common. Ataxia is less common, as are focal signs of brainstem or spinal cord involvement. Patients remain afebrile and headaches are infrequent. The disease usually follows a progressive course to death in three to six months. Cerebrospinal fluid generally is normal, with no pleocytosis and no elevation of protein content. Computerized axial tomography may show multiple radiolucent areas in the white matter. A definite diagnosis can only be made pathologically. There are obvious areas of demyelination of varying size, most prominent in the subcortical white matter. Histologically, these foci show a relative sparing of axons with loss of oligodendrocytes and myelin. Oligodendrocytes surrounding the foci are enlarged with large intranuclear inclusion bodies. Within the demyelinated foci, astrocytes are enlarged, often are bizarre and contain mitotic figures. Inflammatory cells usually are not prominent.20

The presence of inclusion bodies and their occurrence against a background of disorders associated with impaired immunologic responses led to the initial speculation that the disease might be caused by an opportunistic viral infection. Electron microscopic examination in almost all cases has shown particles in the oligodendrocyte inclusions resembling small papovaviruses.20 In the majority of cases, the virus has proved to be a human papovavirus called JC virus.18,21 This virus subsequently has been found to be a common infectious agent in man, with most people acquiring antibody in childhood. It has not been associated with any other disease, however. Whether this disease represents a primary infection of an immunologically compromised patient or reactivation of a latent or persistent papovavirus infection remains unknown.

Other chronic neurological diseases

Since viruses can cause disease after a long incubation period, can cause disease with a subacute or relapsing course, and can give rise to noninflammatory pathological changes, a possible role of slow infections has been entertained for a variety of chronic neurological diseases. Some cases of chronic focal epilepsy in the Soviet Union have been related to persistent tick-borne virus infections following acute encephalitis; but this has not been shown in chronic focal encephalitis occurring in other geographic areas.18 Because of the noninflammatory degeneration seen in spongiform encephalopathies, a possible viral etiology for amyotrophic lateral sclerosis also has been suspected, as it has been in Parkinson's disease and other forms of subacute dementia. Even greater speculation has occurred about the possibility of a viral cause of multiple sclerosis. Although there is no definitive evidence to incriminate a specific virus, the epidemiological evidence indicates that multiple sclerosis follows an early life exposure, and serological data show abnormal immune responses to viral antigens.6

REFERENCES


