CLASSIC SLOW VIRUS DISEASES

E. H. Lennette

Current knowledge of slow virus diseases provides a foundation for examining the possible viral etiology of a number of chronic degenerative diseases, including multiple sclerosis, Parkinson's disease, and diabetes mellitus.

General Comments

The designation slow virus disease refers not to the causal agent but to the fact that the diseases induced have a slow, relentlessly progressive course and a fatal termination. These diseases can be divided into two categories according to whether the causal agent is a typical, conventional virus (propagable in vitro; cytopathogenic; antigenic; associated with inflammatory lesions, for example of the central nervous system, etc.) or a transmissible agent whose properties and behavior suggest an unconventional or atypical virus.

In the latter category are four of the classic slow virus diseases, namely kuru and Creutzfeldt-Jakob disease of man (Table 1) and scrapie and mink encephalopathy of animals (Table 2). The transmissible agents involved are regarded as atypical viruses because of their nature, properties, and characteristics; and, because of the similar pathologic picture they induce, they are regarded as prototypic viruses of this group, collectively referred to as the subacute spongiform encephalopathies. The label encephalopathy rather than encephalitis is used because the widespread destructive cerebral changes present a picture of degeneration without inflammation, and the label spongiform arises from the striking cellular alteration characterized by swelling of the neurons and glia; the glia proliferation and the neuronal vacuolation and subsequent neuronal loss lead to the characteristic spongiform appearance. There is no primary demyelination, and secondary degeneration is of minor degree. In the cerebrospinal fluid there is no pleocytosis and no elevation of protein content. Patients characteristically show no fever.

Both kuru and Creutzfeldt-Jakob disease have been transmitted to nonhuman primates, so that it has become possible to study the physical, chemical and biological properties of all four viruses. They are considered here because they serve as models in studying the possible role of viruses in the causation of other encephalopathies.

The Human Diseases

Kuru

This is the first subacute progressive degenerative disease of the brain of man for which a viral etiology has been demonstrated. The virus has been transmitted from man to chimpanzees, to rhesus monkeys, and to five species of New World monkeys.

The disease, restricted to the Foré people of New Guinea, apparently was recognized...
as a new disease by these people in the early
1920's, it was first reported and described
in 1957, at which time the prevalence was
some 200 cases in a population of approxi-
mately 35,000 people distributed among
170 villages.

Some 3,500 cases of the disease in all are
known to have occurred, and transmission,
which appeared to follow a heredofamilial
pattern, is now known to be associated with
ingestion of infectious tissue attendant
upon ritual cannibalism of the dead as a
mourning ceremony. This practice has
been interdicted, and the disease as a con-
sequence has been declining in prevalence
and should soon disappear. Approximately
one-third of the cases previously were seen
in children under 15 years of age, but none
are any longer found in this age group. At
present, the current total prevalence is
about 50 cases, the decline being attributed
to disappearance of the disease in children.

In addition to the transmissible agent,
genetic factors also are believed to play a
role in the pathogenesis of kuru.

**Creutzfeldt-Jakob Disease (C-J Disease)**

Unlike kuru, which is restricted geo-
graphically, Creutzfeldt-Jakob disease, a
rare presenile dementia first described by
Creutzfeldt and Jakob in the early 1920's,
has a worldwide distribution. There is no
obvious sex difference, and onset is gener-
ally late in life—between the ages of 35 and
65. The disease generally occurs sporadical-
ly, although there are recorded instances of
familial clustering in which it has ap-
peared in close relatives over several
generations. A transmissible agent has been
demonstrated in both the sporadic and the
familial type of occurrence. Successful
transmission has been made to chimpan-
zees, to an Old World monkey, to several
species of New World monkeys, and to the
domestic cat.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Virus</th>
<th>Hosts affected</th>
<th>Incubation period</th>
<th>Clinical signs</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuru</td>
<td>Infectious agent passes</td>
<td>Man, chimpanzee, New World monkeys, Old World monkeys</td>
<td>9-240 months</td>
<td>Incoordination, progressive ataxia,</td>
<td>Progressive vacuolation in the dendritic and axonal processes of the neurons</td>
</tr>
<tr>
<td></td>
<td>through filters of 220-nm</td>
<td></td>
<td></td>
<td>tremors, loss of emotional control,</td>
<td>and to a lesser extent in astrocytes and oligodendrocytes; extensive astroglial</td>
</tr>
<tr>
<td></td>
<td>pore size</td>
<td></td>
<td></td>
<td>dementia</td>
<td>hypertrophy and proliferation; ends in status spongiosus of gray matter; no</td>
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<td>inflammatory reaction or primary demyelination; PAS-positive plaques in cerebellum</td>
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</tbody>
</table>

**Table 1. Chronic infections of the human central nervous system with unconventional agents.**

Source: Fucillo et al. (2).
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<tr>
<td>Scrapie</td>
<td>Infectious agent passes through filters of 50-nm pore size</td>
<td>Sheep, goat, mouse, rat, gerbil, mink, cynomolgus and squirrel monkey, skunk, hamster</td>
<td>30-60 months</td>
<td>Ataxia, tremors, hyperexcitability, incoordination</td>
<td>Similar to kuru, with some PAS-positive doubly refractile birefringent amyloid plaques; involvement of subcortical regions, particularly medulla; outstanding vacuolation of nerve cells</td>
</tr>
<tr>
<td>Transmissible mink encephalopathy</td>
<td>Infectious agent passes through filters of 50-nm pore size</td>
<td>Mink, skunk, raccoon, ferret (including albino ferret), hamster, goat, sheep, Old World monkeys, New World monkeys</td>
<td>4-48 months</td>
<td>Slowly progressive locomotor incoordination, excitability, convulsions</td>
<td>Similar to scrapie; involvement most prominently of cerebrum, especially its more rostral parts; marked astrogliosis and spongy degeneration of gray matter</td>
</tr>
</tbody>
</table>

Source: Fucillo et al. (2).

The Animal Diseases

Scrapie

So named because the diseased animal tends to scrape against fixed objects, scrapie was first recognized in Scotland nearly 200 years ago, and since then it has spread to other countries and continents. Certain sheep lines are highly susceptible, while others are highly resistant; it would appear that natural transmission of the disease is determined by an autosomal recessive gene. Because scrapie can be transmitted to mice, and since the disease itself closely resembles kuru and Creutzfeldt-Jakob disease, much current knowledge of this group of diseases is derived from scrapie as a model agent.

The interrelationship of these diseases and agents is suggested by the hypothesis that kuru may have arisen among the Foré people through ritual cannibalism of an individual succumbing to C-J disease. Similarly, since scrapie has been transmitted to several species of monkeys, it may also be potentially pathogenic for man. The possibility has been raised that transmissible mink encephalopathy may actually represent a fatal scrapie virus infection in this species.

Transmissible Mink Encephalopathy

TME is a relatively new disease, having first been seen on mink farms in the United States of America about 25 years ago. The natural history of the disease is still unknown, but the suggestion has been made that it may have arisen from the feeding of mink on sheep meat contaminated with scrapie virus. It is possible that a natural reservoir of the virus exists in nature—perhaps, for example, in skunks and raccoons, which are susceptible to experimental inoculation.

Nature and Properties of the Transmissible Agents

The agents of kuru, C-J disease, scrapie, and TME have much in common and, although the greater part of what is known about them has been derived from studies...
on the scrapie agent, comparisons and analogies would seem valid.

In sum, the scrapie agent is small (filterable through membranes of 45-nm but not 27-nm pore size), and it has a remarkable resistance to thermal inactivation, to formalin, to many proteolytic enzymes, to many organic reagents, and to ultraviolet irradiation. These are all properties quite different in most major respects from those of conventional viruses in general.

Ultrastructural studies of tissues infected with all four agents have failed to show the presence of any recognizable virions. Likewise, highly infective tissue suspensions do not contain identifiable viral particles. Furthermore, when examined by the electron microscope, purified material—or gradient band material containing the highly infective moiety—contains only fragmented membranes.

Indeed, some of the properties of these agents, and especially their marked resistance to inactivation by UV irradiation, have led to the suggestion that they contain little or no nucleic acid and thus represent a new category of viruses. Or they may represent pathogenic animal counterparts of several plant pathogens which are transmissible and ostensibly consist of very small (50,000 daltons) naked RNA genomes.

Future Areas of Research

What is currently known about the classic slow virus diseases and their agents,

8This applies to scrapie and TME; the agents of kuru and C-J disease fail to pass through membranes of 100-nm pore size.

together with what has been learned within the past decade or so about slow virus diseases induced by conventional agents, provides the technical and philosophical basis for considering the possible viral etiology of chronic degenerative diseases whose etiology is still unknown—e.g., multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and presenile dementias, to mention only a few affecting the central nervous system. In addition, there are such chronic disease problems as glomerulonephritis and other nephropathies; myocarditis, valvulitis, endocarditis and other cardiopathies; and diabetes mellitus and other endocrinopathies. In some of these diseases, as in kuru and Creutzfeldt-Jakob disease, genetic factors are suspected of playing some role, and in others (such as Aleutian disease of mink) genetic factors predisposing to infection are known to be important disease determinants. Besides looking for viral involvement in these various diseases, workers might well investigate the role of immunologic factors, both humoral and cell-mediated.

No recommendation is made with respect to expanding research on these particular slow virus diseases. It is suggested, however, that the methods and technics which have been applied to the study of these diseases and other slow diseases or latent infections be carried into the chronic disease field. This should yield information on the possible viral etiology of certain cardiopathies, nephropathies, and endocrinopathies, as well as of selected neoropathies such as multiple sclerosis.

SUMMARY

Two human diseases, kuru and Creutzfeldt-Jakob disease, and two animal diseases, scrapie and mink encephalopathy, comprise the group designated the subacute spongiform encephalopathies. Studies on these four classic conditions have generated a new philosophy, new concepts, and new technology that provide a basis for the study of chronic diseases and latent infections of man and animals. These aspects are discussed more broadly and in variable detail in the references listed on the following page.
REFERENCE


IMMUNOPATHOLOGIC PROCESSES IN CHRONIC VIRAL DISEASES

E.C.J. Norrby

Immune complex disease is often associated with chronic virus infections. Several human and animal diseases are known to involve deposition of immune complexes: ones affecting man include hepatitis B, subacute sclerosing panencephalitis, and Burkitt's lymphoma.

Optimum conditions for the formation of immune-pathological complications occur in infections that involve ongoing viral replication and a continuous host immune response. Two different mechanisms leading to the appearance of tissue injury can be distinguished: damage to virus-infected cells by immunologic reactions, and injury of certain tissues by deposition of antigen-antibody complexes. The possible pathogenic significance of the former type of reaction has not been clarified, but there are several human and animal diseases in which deposition of immune complexes has been shown to occur (1). The primary sites for deposition of immune complexes are the renal glomeruli, the choroid plexus of the brain, and blood vessels (mainly arteries). Injury may also occur, however, in heart, lung, joint, and skin tissue.

Deposition of circulating complexes is an active process. Initiation of a release of vasoactive agents leads to increased vascular permeability, which allows larger complexes to be deposited along filtering membranes (2). Large antigen-antibody complexes are taken up by the reticulo-endothelial system. As a consequence, a depression of this system may occur after prolonged exposure to circulating immune complexes. In most cases the viruses that cause immune complex diseases are relatively noncytopathic both in vivo and in vitro. Mainly enveloped viruses, but also naked ones, have been found capable of participating in immune complex formation.