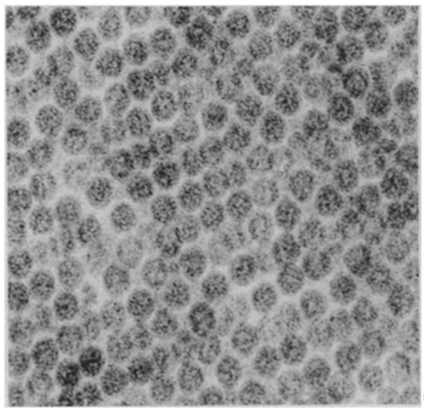
By JULIE ANN MILLER

Slow Viruses: The Body's Secret Agents

Slow viruses, infectious agents that may exist without effect in the body for decades, are becoming the focus of new research techniques



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The contest between a disease-carrying virus and a susceptible victim generally follows a standard pattern of play. A person is exposed to the virus, then after a short incubation period, the illness appears and the virus-host match is on. The host's immune system may triumph early and completely, eliminating the virus and terminating the illness. Or the virus may overwhelm its host to produce severe illness and possibly the host's death.

While this sequence is the common game plan, some viruses play by quite different rules. These infectious agents lurk within a person's body for years, or even decades, and then suddenly produce a devastating disease. How these agents hide and why they become unmasked are problems still unanswered. These agents, sometimes called slow viruses, have become the focus of new research techniques. Scientists met at a recent seminar presented by the National Institute of Neurological and Communicative Disorders and Stroke to discuss slow viruses.

Two distinct groups of infectious agents trigger, after a delay of years, serious degenerative diseases of the brain and spinal cord. The first to be identified were those caused by "unconventional agents." The first human disease to be put in this category was kuru. Observed in the highlands of New Guinea, kuru is a brain disease in which victims tremble, experience seizures, pass into comas and die. D. Carleton Gajdusek and colleagues determined the disease was transmitted when highlanders ritually handled and ate the brains of deceased relatives. The illness appeared years after the contact, but then progressed rapidly toward death. The incidence of the disease has fallen consistently since the brain-handling ritual was stopped, and the victims are now invariably older people who participated in the ritual years ago.

The infectious agents responsible for kuru and for another degenerative nervous system disorder called Creutzfeldt-Jakob disease (and also an animal disease, scrapie) remain not only unknown but almost unimaginable. They do not seem to trigger any antibody response in their victims and scientists have not been able to see the tiny agents or even demonstrate that the agents contain nucleic acids, the standard genetic material (SN: 2/27/82, p. 135). Clarence J. Gibbs Jr. of NINCDS says, "There is no evidence of nucleic acids present, but no one is willing to stick his neck out and say they are absent." There have been many proposals as to the nature of the agent, including that it is a self-replicating membrane. Gibbs and Gajdusek say evidence is compelling that the agents are a separate class of microorganism.

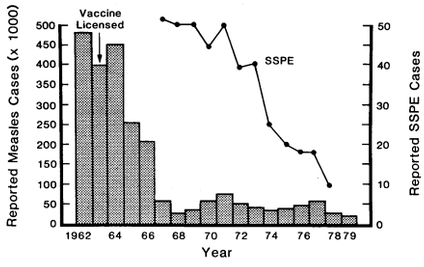
Unconventional, persistent agents may be responsible for other diseases, such as dementias. Gibbs has found two cases of familiar Alzheimer's disease in which brain tissue transferred to monkeys induced brain damage characteristic of kuru or scrapie, but not of Alzheimer's disease. He cannot yet tell whether the diseases are related or whether the patients simply harbored two different infectious agents. For viruses with such a long persistence, the incubation period can be greater than a given person's lifespan. Gibbs suggests that far more people may carry an unconventional infectious agent than ever show clinical signs.

The other category of "slow infection" causing degenerative nervous system disease involves much more mundane infectious agents, but just as devastating consequences. Years after an unexceptional case of measles, for example, a child may succumb to a progressive and usually fatal neurological disease due to the same virus.

Persistent infection of the central nervous system with measles virus is the cause of the rare disease called subacute sclerosing panencephalitis (SSPE). "We've now seen hundreds of cases," John L. Sever of NINCDS told the recent International Symposium on Measles Vaccination in Washington, D.C. The incidence is six to 22 cases of SSPE per million measles infections. SSPE generally occurs seven to twelve years after a child has had measles and its symptoms are first deterioration of school work and subtle personality changes, then muscle jerks and seizures, finally coma and loss of higher brain function. Patients live an average of only 1.5 years after SSPE is diagnosed. In one study of 94 patients, only four recovered enough to get out of bed and perform simple tasks.

What is different about children who develop SSPE? The answer is not clear. Epidemiological studies have pointed out a few possibilities. The incidence of SSPE is highest in the southeastern part of the United States and higher in rural than in urban areas. There are more male patients than females, more whites than blacks, and the majority of patients had measles while quite young, 55 percent before 2 years of age. Other factors that may be important include infection with other viruses, exposure to wild and domestic animals and head injuries.

Reported Measles and SSPE Cases, United States

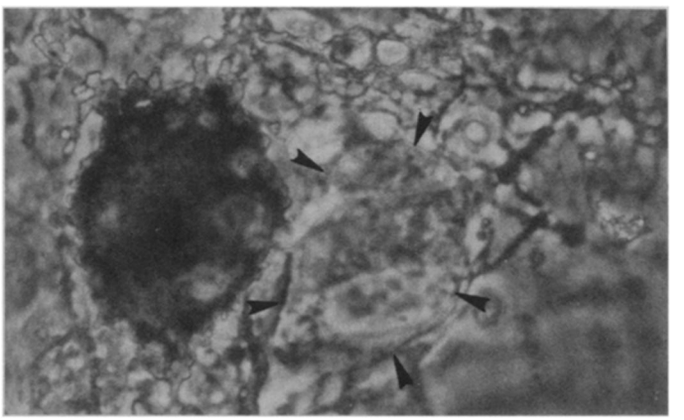


The mechanism by which the virus lurks in cells is still a puzzle. The virus may become defective and never makes complete new viruses for release during that period. The host nerve cells themselves may play a crucial role in harboring the virus. In the March Proceedings of the National Academy of Sciences (Vol. 79, No. 5, p. 1629), Carol A. Miller of the University of Southern California and Donald R. Carrigan of the University of Maryland report results that suggest one aspect of cellular metabolism, the level of cyclic nucleotides, may determine the shift between acute and persistent measles infection.

No therapy against SSPE has proved successful. The only current hope is prevention, and there is good news on that front, at least in the United States. "SSPE has been disappearing since the early 1970s," Sever reports. Ten years ago about 50 new cases were reported in the United States each year; last year there were only six cases. The decrease parallels the drop, due to measles immunizations, in the number of measles cases (SN: 3/27/82, p. 215). Sever says there has been no fall in SSPE incidence in other countries with

Detail of a crystalloid aggregate of JC virus particles from a glial nucleus of a brain with progressive multifocal leukoencephalopathy (left). The particles are about 35 to 40 nanometers in width. (Total magnification is x 91,980.)

Light micrograph of a cultured mouse neuron chronically infected with measles virus for 18 days. The dark area shows where measles virus proteins are made in neuron cell body and in its neurite network. A non-infected neuron is surrounded by arrows. (Magnification x 430.)



Rentier, Dubois-Dalcq, Int'l. Rev. Exp. Path. © Academic Pr., 1979

good medical care, but which do not have successful vaccination programs. For example, in France, where only 25 percent of the children are vaccinated against measles, 32 cases of SSPE were reported in 1980.

"It is now hard to find new SSPE patients in this country," Sever says. "We frequently need to bring cases to the NIH [National Institutes of Health] from other countries to continue our studies."

Measles is not the only conventional virus that causes a progressive neurological disease. Although it happens rarely, rubella (German measles) virus also can linger in the nervous system for years after a standard bout of childhood illness, then cause a disease similar to SSPE. Only about 15 cases of this Progressive Rubella Panencephalitis have been identified, says Sydney A. Houff of NINCDS. In some cases the affected child was born with rubella contracted from the mother. In other cases the child acquired rubella at an early age. In both groups, PRP appears about 12 years after the initial rubella infection.

A third rare disease is attributed to persistent infection with a virus that causes no immediate illness. The virus is called JC, the initials of the patient from whom it was first isolated. By the time they are adults, most people carry antibodies to the JC virus, indicating a previous exposure, with no observed ill effects.

The disease caused by persistent infection with JC virus, progressive multifocal leukoencephalopathy (PML), is quite rare. Only 130 cases have been reported in the world's medical literature, Houff says. It usually occurs in patients whose immune systems are suppressed or who have such diseases as leukemia and lymphoma. At first PML may appear to be a stroke, with weakness on one side of the body. Over a period of a year or two, there is progressive mental deterioration or abnormalities of sensation and movement. "It is invariably progressive and fatal," Houff says. Brain biopsies show loss of myelin, the insulating material covering nerve cells, and loss or abnormalities of the glial cells that produce these insulating sheaths.

Scientists are examining the JC virus to determine how it resides in brain cells. The problem is especially challenging because the virus is difficult to grow in cells in laboratory culture. Eugene Major of Loyola University, who is spending a year working at NINCDS, finds that JC virus expresses all 5 of its genes — and thus can multiply and kill its host cell — only in one of the many cell types he has tested. That cell type is glial cells of a human fetal brain. Unfortunately these cells are very difficult to maintain in the laboratory. In contrast, a closely related human virus, called BK, can multiply in a variety of human and monkey cells.

The very narrow host range for JC is paradoxical. Major explains, "Individuals who develop PML probably have virus multiplying in tissues other than brain as the primary site of infection. PML is more likely to start in cells of the respiratory tract or lungs." Major is now trying to produce special cells that can host JC virus and be easily manipulated in the laboratory. One approach is to add specific genes to cells, another is to fuse human and animal cells, maintaining some chromosomes of each. He hopes to be able to determine the function of each JC gene. "We believe that the way in which viral genes are expressed or regulated in the cell is related to the ability of the virus to remain within the host cells for long periods as a persistent infection," Major says.

Work on the JC virus unexpectedly has provided researchers with a model system to study human brain tumors. William T. London of NIH and colleagues injected owl monkeys and squirrel monkeys with JC virus in an attempt to produce PML. No animals developed the progressive neurological disease, but about half developed tumors 14 to 34 months after being inoculated with the virus. Death occurred a few days after symptoms developed.

"This primate model of viral-induced brain tumors can be utilized in the development and evaluation of diagnostic tests for human use," London says. With special CAT scan techniques, tumors 1 to 2 centimeters in diameter can be detected, even before the monkey's symptoms appear, and can be observed developing rapidly over a period of days. Human brain glial cell tumors develop similarly rapid changes, London says. They are a prominent form of cancer in children, "fast and fatal," according to William C. Wallen, also of NINCDS.

Wallen suggests the monkey-JC virus model will be useful in working out better methods to diagnose and treat human brain tumors. For example, with positron emission tomography (SN: 1/31/81, p. 76), radioactively labeled chemicals might be used to point out the malignant cells earlier than is now possible. Antibodies might also be useful eventually to identify and monitor tumors. Finally, the monkey tumors may help scientists evaluate doses and schedules of drugs, drug combinations and treatments that stimulate the immune system.

With the new tools of molecular biology, scientists also are examining how the JC virus produces a brain tumor. Nancy Miller and colleagues at NINCDS are currently investigating whether the virus's DNA or a portion of it inserts into a brain cell's genetic material and whether the viral genes are active in tumor cells. She says they hope to learn how the host animal manages to regulate the virus for up to three years before losing control, allowing the cells to become malignant.

So far Miller has used recombinant DNA techniques to produce pure viral DNA. She plans to compare this DNA to that of owl monkey tumor cells. She and colleagues are also in the midst of determining the nucleotide sequence of the JC virus DNA, which includes approximately 5,100 base pairs. They plan to compare this sequence with that of the related virus BK, which does not cause tumors or degenerative disease.

Overall progress has been slow in learning the gameplans of infectious agents, conventional or non-conventional, that linger in the nervous system to cause progressive degenerative disease. However, the work may lead to better understanding of how acute infections are controlled in normal individuals, as well as why they flare up years later in others. And once the characteristics of these infectious agents are better understood, it may be possible to identify similar agents in a variety of other, now-mysterious degenerative diseases, such as multiple sclerosis and dementias. □