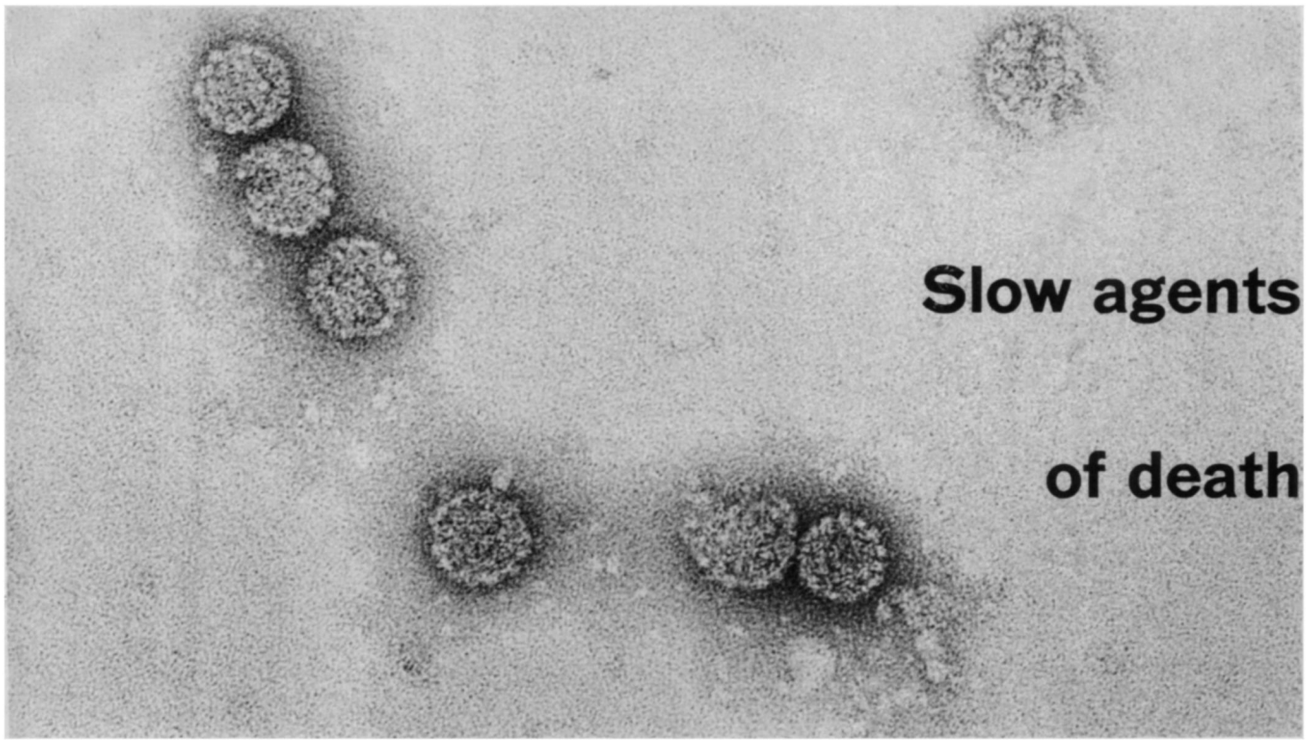


Albertina Albert, U. of Wis.

JC viruses purportedly cause progressive multifocal leukoencephalopathy (PML), a slow, fatal brain disease.

Viruses may lie in wait months, even years before triggering human diseases

by Joan Arehart-Treichel

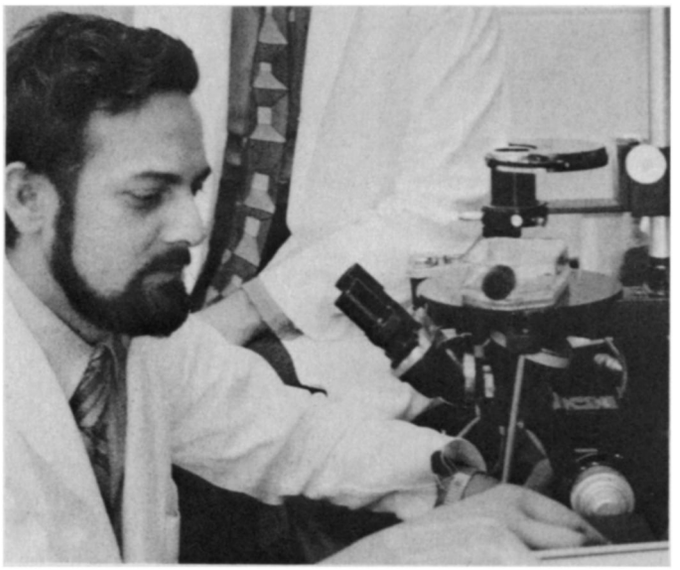
In the mid 1950's, a medical patrol officer in Australia, Victor Zigas, discovered that thousands of persons living in the highlands of New Guinea suffered from a strange brain disease. They trembled, became rigid, fell down, swayed like drunkards, experienced seizures, passed into comas and died. The highlanders called the disease "kuru," which means "fear of trembling." Zigas reported the disease to the Australian authorities. Subsequently he and D. Carlton Gajdusek of the National Institute of Neurological Diseases and Stroke published scientific papers on kuru. Gajdusek then devoted several years to studying the pathology and transmission of kuru.

In 1959 William Hadlow, an American veterinarian pathologist, was working in England and heard about kuru. He noted a striking similarity between the clinical manifestations of kuru and the brain damage it inflicts and the pathology of scrapie and the brain damage it causes. Scrapie is a fatal brain disease of sheep, which more and more investigators were beginning to believe was caused by a slow-acting infectious agent, probably a virus. Hadlow thought it quite possible that kuru might also be induced by a so-called slow virus. He sent a brief account of his observations to the British medical journal LANCET. In his letter to LANCET he also called attention to B. Sigurdsśon, director of the Institute for Experimental Pathology in Keldur, Iceland. Sigurdsśon first coined the term "slow infection" and formulated basic criteria for this type of infection.

After reading Hadlow's letter, Gajdusek visited laboratories in Iceland and Europe that were working on scrapie. Then, with the approval of the National Institutes of Health, he set up a program to look into progressive degenerative human diseases that might be caused by slow viruses. The program was based on Sigurdsśon's criteria for slow viruses. In 1967 Gajdusek and his colleague Clarence Gibbs Jr. reported that the material from kuru victims infected chimpanzees and spider monkeys with 100 percent success. Before injecting the material, they had passed it through a filter that prevented the passage of anything bigger than a virus (except for a few strains of bacteria), so they were reasonably sure that kuru was caused by a virus. And as it took over three years for the infected primates to contract kuru, just as it takes months or several years for lab animals to contract scrapie, they were also quite certain that kuru is triggered by a slow virus.

Their evidence was bolstered by the virtual disappearance of kuru among New Guinea highlanders after the early 1960's. At that time the highlanders were advised to give up their cannibalistic rite of eating brain tissue of deceased relatives, or of rubbing the tissue over their own bodies and hair. Apparently a kuru virus was transmitted by swallowing, breathing or bodily contact. Gajdusek and Gibbs have since shown that the tissue teemed with infectious agents.

The kuru drama that has unfolded during the past decade or so is remarkable for several reasons. It is the first fairly tight evidence for a slow virus disease in humans, although strong evidence for several slow virus diseases in animals has been building since the 1950's. The drama has also opened new frontiers for neurological and pathological research. In fact universities have even created new departments so that researchers can probe for other slow virus diseases in man. In spite of the relative novelty of this field of research, the need to deploy investigators from various disciplines and the stringencies and cost of waiting months or years for suspect agents to infect lab animals, researchers are coming up with answers. Some of the latest evidence is reported in medical journals and was detailed at a recent symposium on slow viruses,



Johnson views human brain infected with PML virus, which is almost same as SV 40 cancer virus. Since persons with PML often have cancer, the same virus may cause both diseases.

Sandra Peeler, Johns Hopkins

sponsored by the American Associations of Pathologists, Bacteriologists and Neurologists.

Gibbs and Gajdusek have also shown that a slow virus causes Creutzfeldt-Jakob disease, a form of senility in man that is marked by spasticity, progressive mental deterioration and death. Brain extracts from victims of the disease infected chimpanzees with it.

Last June a flu virus was taken from the brains of two persons who had died from multiple sclerosis, a disease of the myelin sheaths that surround nerve fibers and which may or may not cause mental deterioration. Gajdusek, Gibbs, and E. Norrby of the Karolinska Institute in Stockholm have found that persons with multiple sclerosis have more antibodies to measles virus in their central nervous systems than do other persons. Norrby thinks a measles virus causes multiple sclerosis. Gibbs thinks a measles virus causes the disease in some persons, whereas a flu virus or another kind of virus causes the disease in others.

Scientists have also identified a measles virus in the brains of victims of subacute sclerosing panencephalitis (SSPE), a disease that causes stiffness, jerkiness, mental deterioration and death in persons under age 20. A measles virus has also infected hamsters with SSPE. One young American who was vaccinated with the live measles virus has come down with SSPE, and 59 others who were vaccinated showed symptoms of related diseases, Philip J. Landrigan of the Center for Disease Control in Atlanta reports in the March 26 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. This incidence is far from proof that an attenuated live measles virus vaccine causes SSPE, though. Over 50 million American children vaccinated with the virus between 1963 and 1971 failed to contract SSPE or any other slow virus diseases.

Gajdusek, Gibbs and Wolfgang Zeman, a neuropathologist at Indiana University School of Medicine, think a slow virus may cause Altsheimer's disease, a kind of senility. Leslie Weiner and R. T. Johnson of Johns Hopkins Hospital have identified a SV 40 virus and a related virus known as the JC virus in brain tissue from victims of progressive multifocal leukoencephalopathy (PML). Like multiple sclerosis, PML destroys the myelin sheaths that surround nerve fibers. PML is inevitably fatal. There is also the possibility that in some instances diabetes, a widespread disease of the pancreas, is caused by a mump virus.

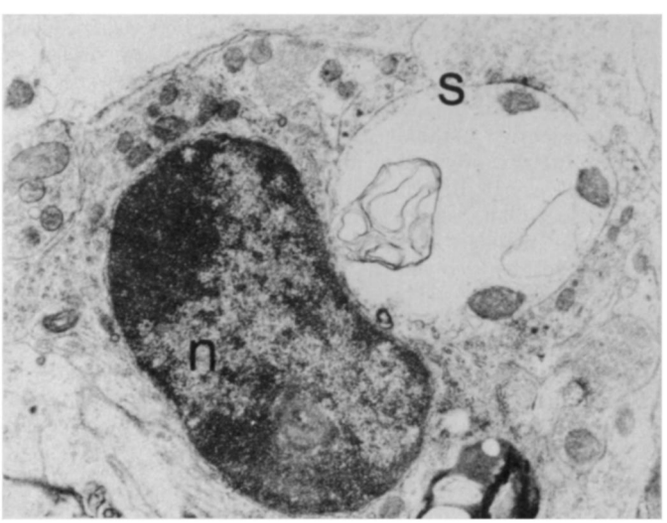
All this evidence linking slow viruses with human diseases is tenuous. Still, some striking patterns are emerging. For one, nearly all diseases thus far attributed to slow viruses are diseases of the central nervous system. Slow virus diseases in animals are also confined to this system. The progression of slow virus diseases in human and animals is also similar. When either human tissues or animal tissues containing slow viruses are injected into laboratory animals, it takes months or several years for disease to manifest itself. And when disease finally appears, its destruction is swift, dramatic and nearly always fatal.

Slow viruses may prefer white matter, gray matter, myelin sheaths or other areas of the central nervous system. Gabriele ZuRhein of the University of Wisconsin has found that transmissible mink encephalopathy (TME), a fatal slow virus disease of mink, destroys the cerebellum and hypothalamus, which control limb function, posture, appetite and personality.

The nature of viruses causing kuru, Creutzfeldt-Jakob disease, scrapie and other slow virus diseases has not been determined. Might environmental influences transform conventional viruses, such as the flu, measles and mumps viruses, into killers? Might the virus that causes kuru be a once-benign virus that became defective as it was transferred from brain to brain in a cannibalistic society? Or might slow viruses not be complete viruses at all, but molecules of RNA or DNA without protein coats? Last year Theodor O. Diener of the U.S. Department of Agriculture reported the first evidence for a partial virus. It was a naked RNA molecule that causes a disease in potato plants. Diener dubbed it a "viroid" (SN: 2/12/72, p. 102). Diener speculates that the agent that causes scrapie might be a cousin of his potato viroid.

What is the relationship, if any, between slow viruses and cancer viruses? The SV 40 virus taken from the brains of PML victims is virtually identical to the SV 40 virus that causes cancer in monkeys. Robert Gallo of the National Institutes of Health reports in the March 30 SCIENCE that the virus that causes visna, a slow neurological sheep disease, contains genes identical to those in RNA tumor viruses.

Scientists are mystified by how slow viruses attack their hosts. But from what they have gathered so far, the



Slow-acting TME virus alters neuron membrane and synapse (S), forms vacuoles (large white circle) and indents neighboring nerve cell (N).

ZuRhein

membrane is a favorite target. ZuRhein reports that TME disrupts the membranes of nerve cells. Gibbs and Gajdusek have shown that in humans and animals infected with scrapie, kuru or other slow virus diseases, the main damage is the formation of vacuoles in nerve cells. The vacuoles are filled with fragments of cell membrane. The researchers propose that the viruses that cause these diseases are small strands of nucleic acid, probably DNA, that bind to the membrane.

Investigators are also perplexed by the immunological responses of humans and animals to slow viruses. Johnson notes that kuru victims fail to defend themselves against infection. Zeman suggests that slow virus diseases consist of a host's slow immunological response to a conventionaal virus.

Researchers are perhaps more disturbed than mystified by the possible transmission of slow viruses from one species to another. Creutzfeldt-Jakob disease and kuru have been transmitted to monkeys and cats. Since monkeys recently got scrapie, scrapie "may not be innocuous to man," Gibbs warns. Even more perturbing is the possible transmission of slow viruses from person to person. It may be more than an accident that most of the diseases now suspected of being caused by slow viruses used to be thought to be inherited. In other words, the prevalence of a disease in one family might be the result of family members infecting each other. A French patient with Creutzfeldt-Jakob disease had a mother with it and possibly some aunts with it. An American with the disease had parents with it, possibly a brother and sister with it, and two of his brothers may have died with it.

Most nettling, many investigators agree, is the remarkable resistance of slow virus agents to ultraviolet light and chemicals that usually inactivate more conventional viruses.

So given the newness of slow virus research, the many unanswered questions, and the apparent resilience of slow viral agents, it may be some years before the role of slow viruses in human diseases is understood and treatment or prevention provided. "It is clear," says Richard Kimberlin of the Institute for Research on Animal Diseases, Berkshire, England, "that future success of human medicine in coping with slow virus disease depends on understanding not only the enigmatic nature of agents such as scrapie, but also the way in which these agents interact with their host cells." Declares Hadlow, who is now with the Rocky Mountain Laboratory in Hamilton, Mont., "Slow viruses may represent an intellectual challenge for the remaining decades of this century." □