tariff barriers that Mexico and a number of other Latin American countries erected in the 1950's to protect domestic enterprise from foreign competition have also helped. Foreign companies deftly leaped the barriers by setting up subsidiaries and letting licenses; once inside the barriers, companies found it relatively easy to raise consumer prices without fear of outside competition.

In searching for remedies to their technology problems, Brazil, Argentina, and, most recently, Mexico have struck on what amounts to antitrust legislation designed to regulate the free-wheeling technology trade. Particulars vary from one country to the next, but the trend is to follow the advice of U.N. groups and the OAS: Set up contract registries, screen technology agreements for especially onerous terms, and provide advice to small and medium-sized companies in bargaining with the purveyors of know-how.

Mexico's new law, for example, lists 14 conditions under which a contract can be rejected—ranging from prohibitions on research by the licensee to global prohibitions on export of his product. In enforcing the law, however, the ministry of industry and commerce will have to tread a thin line between self-defeating laxness and damaging stringency that discourages foreign investors.

The same could be said of the rest of Latin America. The rules of the technology trade are changing, but if many businessmen regard them as a demand for a free lunch, others see the new rules as an omen of stability. "At least the rules are being defined and laid on the table," a commercial counselor in one Mexico City embassy noted, "and that is an improvement." In the long run, Máximo Halty says, businessmen should recognize that what is good for the Latin American economy is good for them. "Technological independence means a higher level of development," Halty maintains, "and that means newer and larger markets."—ROBERT GILLETTE

RESEARCH NEWS

Slow Viruses (II): The Unconventional Agents

Slow viruses have been implicated in the etiologies of a number of severe neurological disorders of man and animals. These disorders—as required by the definition of "slow" infection—are characterized by a long incubation period and then a protracted course of disease that almost invariably culminates in death. Some of the slow viruses have the properties of typical viruses except for their rather unusual behavior in the living host (*Science*, 29 June 1973); however, a group of four neurological diseases are caused by transmissible agents that are not typical viruses. These agents are sometimes called the unconventional slow viruses.

The four diseases caused by the unconventional viruses are kuru and Creutzfeld-Jakob disease in the human and scrapie and transmissible mink encephalopathy (TME) in animals. The pathological changes, and even the clinical symptoms, of these conditions are quite similar. Moreover, the physical and biological properties of their causative agents appear to be very much alike. Consequently, most of what can be said about any one of these diseases also applies to the other three.

Kuru has been found only in the Fore people and their neighbors in New Guinea. At first, it was thought to be a genetic disease; however, in 1966, D. Carleton Gajdusek and Clarence J. Gibbs, Jr., of the National Institute of Neurological Diseases and Stroke, Bethesda, Maryland, demonstrated that the disease could be transmitted to chimpanzees by injecting bacteria-free extracts prepared from the brains of human kuru victims into the brains of the animals. They also demonstrated serial transmission of kuru from chimpanzee to chimpanzee, even with brain suspensions diluted as much as 1 to 10^7. Since then, they have transmitted the disease to several other species of subhuman primates.

Prevalence of Kuru

The incidence of kuru among the Fore people had been very high. According to Michael Alpers, of the University of Western Australia, Perth, 2,500 people—in a total population of only 35,000—have died from this disease since it was first studied in 1957 by Gibbs and Vincent Zigas, of the Department of Public Health, Papua, New Guinea. Kuru became so prevalent because it was transmitted during the ceremonies of ritual cannibalism by which the Fore honored their dead. With the cessation of cannibalism, the incidence of the disease has declined dramatically.

Although kuru would appear to be an exotic, isolated disease, Gajdusek and Gibbs now consider it to be one example of a type of neurological disease that may be found throughout the world. Creutzfeld-Jakob disease (C-J disease) is another; this disease is rare but its distribution is worldwide. It is one of the presenile dementias—a premature development of the mental deterioration sometimes seen in old age. Gajdusek and Gibbs found that it, too, is caused by a transmissible agent that can infect chimpanzees and other primates.

Kuru and C-J disease are clearly infectious; they can be transmitted to experimental animals by administering different kinds of preparations—including cell- and bacteria-free filtrates—made from diseased tissue. Nevertheless, neither their symptoms nor their pathology are characteristic of infectious disease. For example, the patients do not become feverish at any time.

The brain lesions of kuru and C-J disease are located mainly in the gray matter. Vacuoles form in neurons, certain glial cells proliferate, and the cerebral cortex takes on a spongy appearance. However, the investigators have observed no inflammation of the brain, even though it is found in other viral infections. Because the pathological changes of scrapie and TME closely resemble those of the human diseases, Gajdusek and Gibbs have designated the four conditions as subacute spongiform encephalopathies.

Scrapie has been recognized as a fatal disease of sheep for more than two centuries. Transmissible mink encephalopathy, a relative newcomer, apparently originated in Wisconsin a little more than 25 years ago. The physical, chemical, and biological properties of the animal unconventional viruses have been studied more thoroughly than those of the human agents because of the availability of more convenient (and

less expensive) nonprimate hosts. However, available data on the human agents indicate no significant differences between them and the animal viruses.

Robert Hanson and Richard Marsh of the University of Wisconsin, Madison, have been investigating TME. They have found that the properties of the TME agent closely resemble those reported for the scrapie agent by a number of investigators including William Hadlow, who is now at the Rocky Mountain Laboratory in Hamilton, Montana.

These agents have characteristics that are not usually associated with typical viruses consisting of a nucleic acid with a protein coat. For example, they are totally resistant to inactivation by ultraviolet radiation or are inactivated only slightly. They are also highly resistant to treatment with formalin or heat. On the other hand, treatment with phenol or ether does destroy the infectivity of these viruses.

One of the more puzzling aspects of the unconventional slow viruses is their "invisibility." Despite repeated attempts, they have not been observed with the electron microscope; estimations of the size of the agents, based on their retention by filters with pores of known dimensions, indicate that they are large enough to be detected by electron microscopy. Finally, there is their apparent lack of antigenicity. No one has ever been able to demonstrate that any of the four agents evokes the production of antibodies.

The atypical properties of the unconventional slow viruses have caused some uncertainty about their exact biochemical nature. (For this reason, some investigators prefer to call these pathogens "agents" rather than "viruses." Some investigators have proposed that the agents are replicating molecules not of nucleic acid but of protein or polysaccharide; others have suggested that they might be replicating membrane fragments.

The infectivity does appear to be associated with membranes. Inactivation by phenol or ether could be due to disruption of a necessary membrane moiety. Moreover, according to Gajdusek and Gibbs, electron micrographs of a purified preparation of scrapie agent have revealed only membrane fragments. The fact that these preparations did absorb ultraviolet light at 260 nanometers, however, indicates the presence of some nucleic acid. So far, Gajdusek and Gibbs have not been able to separate an infectious nucleic acid from the membrane fragments.

Recently, speculation in the laboratories of Gajdusek and Gibbs and of Hanson and Marsh has centered on the possibility that the unconventional slow viruses may contain a very small nucleic acid in the same size range as "viroids." Theodor O. Diener of the Plant Virology Laboratory of the U.S. Department of Agriculture's Agricultural Research Service, Beltsville, Maryland (*Science*, 17 November 1972), has suggested that the scrapie agent may actually be a viroid. Viroids are self-replicating, infectious RNA molecules that produce certain plant diseases. They are not associated with protein and they have unusually low molecular weights (50,000) in the case of one isolated by Diener). The physical and chemical properties of the viroids isolated thus far resemble those of the unconventional slow viruses. Although preliminary attempts to recover an infectious viroid from the brains of diseased animals have not been successful, the possibility that they are involved cannot be eliminated on the basis of these early experiments.

Research Handicapped

Research on the unconventional slow viruses is handicapped by the lack of a fast, reliable method of detecting their presence. Although the agents can be propagated in cell cultures derived from the brains of infected animals, they do not noticeably damage the cells. Investigators must now depend on their infectivity in susceptible hosts in which the minimum incubation period of the viruses is several months.

The absence of detectable antigenicity is especially vexing because it prevents direct comparison of the agents. Marsh and Hanson, for example, think that TME may in fact be sheep scrapie that was transmitted to mink by means of infected sheep meat in their diets. They cannot verify this hypothesis by comparing the reactivity of the two agents with antibodies. Similarly, Gajdusek and Gibbs have speculated that kuru may have originated from a rare spontaneous case of C-J disease that spread through the Fore people because of their unusual culture.

Studying the host ranges of the unconventional slow viruses is one approach to determining whether they are related. The results, however, have been somewhat inconclusive. All four diseases have now been transmitted to primates. On the other hand, the nonprimate animals tested thus far were not susceptible to kuru and C-J disease, although several did develop TME or scrapie. According to Hanson and Marsh, brain extracts from a sheep infected with scrapie produced a TME-like disease in mink, but there are differences between the host ranges of the two agents. Thus, the host ranges of the unconventional slow viruses overlap but are not identical.

In addition to their investigations of kuru and C-J disease, Gajdusek and Gibbs are trying to determine whether other, more common degenerative diseases of the central nervous system are infectious. These other diseases include amyotrophic lateral sclerosis, Parkinson's disease, Pick's disease, Alzheimer's disease, and Parkinsonism-dementia. At this time, they have found no evidence for the existence of an infectious agent in victims of these diseases. Of course, the question of what is causing these disorders is academic from the patient's point of view; as Gajdusek points out, there is no cure even for the degenerative conditions of known slow viral etiology.

Gajdusek believes that even some brain changes of normal aging may be the result of cellular injury produced by viruses. For one thing, the pathological changes of normal aged brain resemble those found in presenile dementias like C-J and Alzheimer's diseases, although the lesions of normal aging are not as severe. For another, there have been ample demonstrations of the capacity of the human to harbor viruses—both the slow viruses described in these articles and also many others—for long periods of time. As yet, however, there has been no demonstration of the involvement of any of them in normal aging.

The list of diseases caused by slow viruses—both conventional and unconventional—has been steadily growing for the last two decades. Some of the slow viruses are quite common—for example, the measles virus, which has been associated with subacute sclerosing panencephalitis. Others, such as the kuru agent, are apparently more exotic. Nevertheless, they appear to be widely distributed in both human and animal populations. Consequently, practically all degenerative diseases of unknown etiology, especially those involving the central nervous system, are candidates for the catalog of slow virus infections.

—JEAN L. MARX

Additional Reading

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