Slow Viruses: Role in Persistent Disease

The slow virus infections are a group of persistent, degenerative, usually fatal diseases that afflict both man and animals. Many of these diseases specifically affect the central nervous system (CNS). The ones that occur in man and have a known viral etiology are relatively rare. Nevertheless, some investigators have begun to speculate—and it is only speculation at this time—that slow viruses may be involved in the still uncertain etiologies of a wide spectrum of degenerative diseases that includes multiple sclerosis (MS) and rheumatoid arthritis.

The slow virus infections are characterized by a long incubation period between infection by the virus and the onset of clinical symptoms. The disease then follows a protracted course that usually ends in death. Several investigators pointed out that the term "slow" virus is actually a misnomer, because most of the known viruses can replicate rapidly under the appropriate conditions. Thus, the prolonged development and progression of these diseases cannot be attributed to the properties of the virus alone. The response of the host, especially the interaction between the virus and the host's immune system, must also contribute in some way to the slow expression of the infection.

Some of the slow viruses may not even be viruses; they certainly are not conventional viruses. The causative agents of four diseases classified as slow infections (kuru and Creutzfeldt-Jakob disease in humans and scapie and transmissible mink encephalopathy in animals) do not behave like typical viruses. For example, they do not evoke a demonstrable immune reaction. Moreover, they have never been isolated. Thus, according to Robert Hanson of the University of Wisconsin, Madison, slow infections may be divided into two groups: those caused by unconventional viruses—the four diseases mentioned above—and those caused by conventional viruses. The unconventional viruses will be discussed in a second article.

Progressive multifocal leukoencephalopathy (PML) and subacute sclerosing panencephalitis (SSPE) are two slow infections of the human CNS thought to be associated with conventional viruses. Both diseases are rare; fewer than 200 cases of PML and approximately 350 cases of SSPE have been reported.

Progressive multifocal leukoencephalopathy usually occurs in individuals whose immune response has been impaired by disease (such as Hodgkin's disease or leukemia) or by immunosuppression. It does not cause inflammation in the brain but it does produce demyelination; the myelin sheaths (the layers of membranes) surrounding nerve axons are destroyed. Using electron microscopy, Gabriele ZuRhein and her colleagues at the University of Wisconsin Medical School, Madison, found virus particles in the nuclei of certain cells located in the brain lesions. They concluded that the virus was a papovavirus. The papovaviruses are a group of small DNA-containing viruses that includes human wart virus, simian virus 40 (SV40), and the polyoma virus of mice. ZuRhein thinks that the demyelination that occurs in PML may result from the destruction, by the virus, of cells required for the formation and maintenance of the myelin sheath.

Duard L. Walker and Billie Padgett, other members of the large group of investigators collaborating on slow virus research at the University of Wisconsin, were able to grow the virus in cultured human fetal glial cells. These cultivated viral particles closely resembled those found in diseased brain tissue itself.

Walker and Padgett think that this virus, which they called the JC virus, is a new human papovavirus. It resembles SV40 and polyoma virus more closely than it does human wart virus. The JC virus is not antigenically related to wart virus or polyoma virus and is related only slightly to SV40.

Papovavirus-like viruses have since been recovered from the brains of practically all of the PML patients tested, both at Wisconsin and in other laboratories. Leslie Weiner and Richard Johnson at Johns Hopkins University Medical School, Baltimore, Maryland, have isolated two such viruses. One of them is very similar, but not identical, to SV40; the other is like the JC virus. Sylvia Gardner and her colleagues at the Central Public Health Laboratory in London, England, isolated a third papovavirus from the urine of a patient who was receiving immunosuppressive therapy after a kidney transplant; however, this virus has not yet been associated with brain disease. Johnson and Weiner believe that at least two of these viruses—the JC virus and the SV40-like virus—are involved in the etiology of PML.

Although PML is a rare disease, infection with JC virus is apparently a common occurrence. Walker and Padgett found that almost 70 percent of the adults tested had antibodies to JC virus. They do not know whether the primary viral infection produces disease symptoms—for example, one of the frequent gastrointestinal or respiratory infections of childhood—or whether it causes no noticeable effect.

The disease PML appears to develop when the immunological defense mechanisms of an individual are impaired. Walker hypothesizes that the JC virus, present from childhood in a suppressed state, becomes active under these conditions. Alternatively, PML could result from the first infection of a vulnerable person who had not previously encountered the virus. If the first possibility is correct, another question—one which applies to most, if not all, slow viruses—must be answered: How does the virus persist for so long in the presence of a functioning immune system?

Because the JC virus is classified as a papovavirus in the same subgroup as polyoma and SV40, two viruses of known oncogenic potential in animals, Walker, Padgett, and ZuRhein investigated the possibility that it, too, may cause tumors. They found that when the brains of newborn hamsters were inoculated with JC virus, 83 percent of the animals developed malignant tumors within 6 months.

The observation that a virus can induce tumors in hamsters in no way proves that the same virus can cause tumors in humans. The role of viruses in human cancer is still a controversial subject. Nevertheless, Richard Johnson pointed out that the original definition of slow infection, proposed in 1954 by the late Björn Sigurdsson, included animal tumors caused by such viruses as avian leukosis virus or mouse mammary tumor virus. Moreover, some in-

vestigators consider herpes simplex to be a slow virus because people can harbor it for years in a dormant condition. Occasionally herpes simplex will flare up and produce the familiar cold sores. Recently, Albert Sabin, currently a Fogarty Fellow at the National Institutes of Health, Bethesda, Maryland, and Giulio Tarro of the University of Naples, Italy, proposed that herpes viruses are implicated in the etiology of several human cancers (*Science*, 11 May 1973, p. 572).

A conventional virus has also been isolated from the brains of patients suffering from SSPE. The virus isolated by John Sever and his colleagues at the National Institute of Neurological Diseases and Stroke, Bethesda, Maryland, was measles virus. Special culture conditions were required for the isolation of the SSPE virus, which appeared to exist in a suppressed state in the brain cells. Not until the cells were cultivated together with another type of human cells was the infectious virus released.

The suppression of the measles virus, rather than its total elimination from the host, probably requires a deficiency in the immune system of the SSPE victim. Sever, with J. T. Jabbour, of the University of Tennessee Medical units, Memphis, has studied the epidemiology of SSPE. They found that more than 50 percent of SSPE patients had had measles before the age of 2 years and that the average time from the measles infection to the development of SSPE symptoms was 6 years. (SSPE should not be confused with postinfectious encephalomyelitis, another neurological complication of measles that begins within a few days of the primary infection.) The high incidence of early measles infection in

Speaking of Science

Artificial Intelligence: A Fascination with Robots

In early 1972 Sir James Lighthill of Cambridge University undertook to survey the field of artificial intelligence (AI) for the Science Research Council of Britain. His report was sufficiently controversial that the Council held up its release for over a year until last month, when a somewhat sanitized version was published (along with comments from several other scientists) in an AI newsletter edited at the University of Edinburgh. Ironically enough, funding for AI research at Edinburgh, heretofore the largest center in Britain, was also cut back last month—in part due to the criticisms leveled by the Lighthill report against AI research in general and against the Edinburgh project in particular.

The report questions whether artificial intelligence is a coherent field of research or whether it is really two diverging kinds of investigations linked in a makeshift way by a fascination with robots. The report is cautiously optimistic about the future of research on particular aspects of AI (automation and computer studies of neurobiological functions), but downgrades work on robots as having, at best, discouraging prospects.

Researchers in artificial intelligence, for their part, have been quick to criticize the report as betraying a lack of understanding as to what the field is all about. They dispute not only the report's assessment of prospects in AI but also the division of what they see as a coherent field into artificial and misleading categories.

The ABC's of artificial intelligence, as Lighthill styled them, amount to

► Advanced automation, including pattern recognition, speech recognition, and automation of industrial processes; the emphasis, according to Lighthill, is on practical problems and on efforts oriented toward new hardware.

► Building robots, including coordination of eye and hand functions, use of natural languages for communicating with computers, automated analysis of visual scenes or environments, and problem solving techniques; Lighthill describes this category of research as forming an imperfect bridge between the practical area of advanced automation and the more basic research of category C.

► Computer-based research on the central nervous system, including associative recall, functioning of the cerebellum, psycholinguistic studies, and other theoretical (modeling) investigations related to neurobiology and psychology.

It is particularly the work on robots that Lighthill sees as having little future in itself and as being of marginal value to other areas of AI. He goes even further, suggesting that those who work on robots may be fulfilling "pseudomaternal" urges or catering to popular interest. Researchers on AI are understandably irked at these slurs on their motivations and, more substantively, do not see the rationale for Lighthill's ABC's. They believe that his description is limited and arbitrary, that it includes some subjects such as neurobiology which have little to do with AI, and that it excludes others central to the field. As one U.S. scientist put it, neither artificial intelligence nor neurophysiology is advanced enough to have anything to contribute to the other discipline.

Lighthill is a well-known scientist respected for his work in applied mathematics and hydrodynamics, and his criticisms, as one observer described them, "do not have the religious character" of earlier attacks on AI. But he is admittedly an outsider to AI research, and he qualifies his report as a "highly personal view." It is thus not impossible that his report, based on a 2-month survey, does misconstrue the field and that his view of its prospects is, as AI researchers claim, seriously misguided.

Lighthill's main criticism boils down to the claim that work on robots is not an intellectually important endeavor. Those working on artificial intelligence reply that robots are not their primary goal, but merely research tools. Marvin Minsky, of the Massachusetts Institute of Technology, believes that research on AI is important because it is really research on theories of intelligence, and that work with robots, with computer vision machines, and with other similar devices—whatever their practical applications—aids the unraveling of

SSPE patients implies that either immunological immaturity or a defective immune system permits the virus to remain in the patient. The defect in the immune system probably involves an absence of specific cellular immunity for measles virus, because SSPE patients have higher concentrations of antibodies against measles in both blood serum and spinal fluid than do other individuals.

Luiz Horta-Barbosa, in Sever's laboratory, has recovered measles virus from the lymph nodes of SSPE patients. Sever hypothesizes that the virus is carried in white blood cells during the incubation period. Eventually, some cells would invade the CNS and initiate the neurological phase of SSPE. The presence of measles antibody can slow the progress of the disease by inactivating virus particles that are released from brain cells but cannot prevent it entirely, because the virus can spread from cell to cell.

The availability of an animal species susceptible to SSPE would be advantageous for studying the disease and the role of the immune system. Donald Byington and his colleagues at Purdue University School of Veterinary Medicine, Lafayette, Indiana, were able to produce neurological disease in hamsters with measles virus isolated from the brain of a patient with documented SSPE. Byington, now with Kenneth Johnson at Case Western Reserve University School of Medicine, Cleveland, Ohio, has found that the response of hamsters to intracerebral injection with virus derived from an SSPE patient depends on the age of the animal. Newborn animals died of encephalitis within a few days of the injection. Adult animals, although they displayed no out-

or a Serious Intellectual Endeavor?

ideas about possible "intellectual mechanisms." Even the process of developing these devices and the computer programs that control them is leading, in his view, to deep insights into the nature of learning.

John McCarthy of Stanford puts it somewhat differently—nobody knows any mechanism that can carry out the coordination of vision and manipulation, that can distinguish objects against a background, and that can perform a number of tasks as effectively as humans and animals routinely do. Investigation of these mechanisms, he believes, is a valid intellectual goal. And it is not a trivial problem, in his view, to try to formalize a description of the intellectual structure of the world.

Researchers on AI do not claim to have made much progress in understanding the details of specifically human thought processes, but they do believe that they have made a start on discovering how intelligence might work. They point to a new interest among cognitive psychologists in the vocabulary for discussing thought processes and in a variety of simple cognitive phenomena developed by AI researchers. More concrete, if preliminary, results include a computer-directed hand-eye machine developed at Stanford which can assemble a simple pump from parts randomly placed on a table. Researchers at Bolt Beranek and Newman Inc. in Boston have developed a natural language question-answering program which, when combined with a data bank of information on moon rocks (as a demonstration), proved so irresistible and accessible to geophysicists that they soon forgot it was the program, not the data base, that was being demonstrated. In contrast to earlier presuppositions that the use of computer languages to describe cognitive phenomena would result in oversimplification, there is growing recognition that work on artificial intelligence has provided a lot of new ideas.

Even granting that AI is an intellectually important area for research, it is fair to ask whether the field is using its resources wisely. The Lighthill report suggests that, in the United States especially, little attention has been given to this question, in part because there has been a relatively assured source of funding. As is true for computer science in general, research on AI is predominantly supported by the Defense Advanced Research Projects Agency (ARPA), which provides about $4.5 million a year. Another $1.5 million comes from the National Science Foundation (NSF). The bulk of the ARPA money goes for work on robots and natural language programming at a few large centers, while smaller, more widespread research projects on pattern recognition, pattern processing, and automation make up the core of the NSF funding. There has been no overall evaluation of the field for some years, researchers admit, and there are substantial disagreements as to which of several lines of research will prove most fruitful. But while conceding the need for some reexamination, what concerns many AI researchers is that the Lighthill report will be used as ammunition by budget-conscious administrators looking for reasons to eliminate funding entirely. They report that ARPA is getting nervous about supporting basic research, and also point to a lack of U.S. research on automated manufacturing techniques comparable to the $115 million effort launched by Japan in 1971.

The term artificial intelligence was initially chosen by Minsky and McCarthy so that they and their colleagues could work on the nature of problem-solving processes without competition from psychologists. The field has outlived the excess optimism that characterized its early years, although it continues to be judged, unfairly many believe, in the light of promises made during that period. Even ardent proponents of AI admit that it still does not have any well-agreed-upon theoretical basis. Nonetheless, they are optimistic. Work on natural language programming alone, one admittedly partisan research administrator told *Science*, will greatly affect how people interact with computers. "We are looking," he said, "at a science in its infancy which will have an enormous impact." But as the Lighthill report makes clear, that impact is not yet obvious to everyone.

—ALLEN L. HAMMOND

ward symptoms, had a brain inflammation of short duration; no virus could be recovered from their brains after approximately 2 weeks. Weanling hamsters (14 to 28 days old) developed a persistent inflammation of the brain which had many of the characteristics of SSPE in humans.

These characteristics included the clinical symptoms, pathological changes in the brain, high concentrations of antibody to measles virus, and presence in brain tissue of virus that could be recovered by the same techniques used for recovery of SSPE virus from human brain. Byington and Johnson also think that a specific defect in the cellular immune system is responsible for the persistence of the SSPE infection. If this theory is correct, restoration of cell-mediated immunity against measles virus may be of therapeutic value in the treatment of SSPE.

While the development of PML and SSPE apparently depend on an impaired immune response by the host, other persistent viruses may collaborate with the host's immune system to produce cell and organ damage. Lymphocytic choriomeningitis (LCM) is a viral disease of mice. In adults the virus produces a transient but severe infection that results either in death or in recovery with immunity. However, if the mice acquire the virus before birth or are injected with it shortly after birth, they develop a persistent infection even though they continue to make antibodies against the LCM virus. The clinical symptoms, which do not appear for several months, include glomerulonephritis, an inflammation of the kidney. The pathological changes in the mouse kidneys resemble those in human glomerulonephritis.

According to Frank Dixon and Michael Oldstone at the Scripps Clinic and Research Foundation, La Jolla, California, the LCM virus exists in the blood as an infectious complex with antibody. Glomerulonephritis occurs when these complexes are deposited in the kidney. Presumably, these trapped complexes activate other components of the immune system that can cause cell destruction and inflammation. Similar changes also occur in blood vessels and other tissues during infection with LCM virus.

Diseases that are elicited by such complexes of antigen with antibody are called "immune-complex" diseases. Lactate dehydrogenase virus (LDV) is another virus that produces this type of disease. Abner L. Notkins and his associates at the National Institute of Dental Research, Bethesda, Maryland, found that LDV produces a large increase in the concentration of several plasma enzymes, including lactate dehydrogenase, in mice. The animals suffer only mild symptoms or none at all, even though the viral infection persists for long periods of time.

During the early stages of the infection, LDV enhances antibody production but decreases cellular immunity. Notkins found that this virus circulates in the blood as an infectious complex with antibody. Dixon and Oldstone demonstrated that the virus-antibody complexes are also deposited in the kidney where they cause glomerulonephritis, but of a much milder form than the glomerulonephritis of LCM. Thus, these viruses remain infectious even when combined with antibody, and the complexes themselves are responsible for organ damage. Notkins points out that this situation would present serious difficulties for vaccine development if similar persistent viruses trigger immune-complex diseases in the human.

Etiology of Autoimmune Diseases

Several investigators are also considering the possibility that slow viruses are implicated in the etiology of certain autoimmune diseases. An autoimmune disease is one in which the body's immune system directs its attack, not at some invading foreign substance, but rather at the body's own tissue. There are several hypotheses to explain how a virus could cause autoimmune disease: For example, it could damage the host's cells, releasing an antigen that is normally hidden; or the virus or a viral component, incorporated into the host's cells, could trigger an attack by elements of the immune system. Rheumatoid arthritis and MS are degenerative diseases thought by many to be autoimmune diseases. The precise causes of both are unknown.

Multiple sclerosis, the most common demyelinating disease of the human, afflicts about 100,000 people in the United States. It is variously thought to be an autoimmune disease, or a viral disease, or an autoimmune disease provoked by a virus. Epidemiological studies of the geographic distribution of MS cases support the possibility that a virus is involved in the etiology of the disease. If that is the case, these studies indicate that from 3 to 23 years may elapse between the time of exposure to the virus and the onset of symptoms. The incubation periods of known slow virus infections provide an adequate precedent for a time lapse of that magnitude.

Evidence is accumulating to indicate that if a virus is indeed involved in MS, that virus may be a myxovirus. Myxoviruses contain RNA as their genetic material; they have a lipoprotein envelope. The measles virus belongs to this group. Investigators in several laboratories, including that of John Sever, have found that MS patients have more measles antibody in their blood serum than do controls. Moreover, three groups of researchers have found myxovirus-like particles in the brains of MS patients. Hilary Koprowski, of the Wistar Institute, Philadelphia, Pennsylvania, together with V. ter Meulen and Dieter Müller of the University of Göttingen, Germany, isolated a parainfluenza virus (a member of the myxovirus family) from the brains of two MS patients. Ephraim Field, at Newcastle-upon-Tyne General Hospital in England, and John Prineas, at the University of Sydney, Australia, found virus particles resembling myxoviruses in the brains of MS patients. Field was able to isolate measles virus from the brain tissue. The function—if any—of these viruses in the etiology of MS is not yet known.

Except for the fact that the conventional viruses discussed in this article do fulfill the definition of "slow virus," they do not appear to be closely related. The PML and SSPE viruses, for example, belong to distinctly different groups. Moreover, they may produce their pathological effects by different mechanisms. Some take advantage of a defective host immune response, while others collaborate with the immune system to produce organ damage. However, the conventional viruses, unlike the unconventional ones, are antigenic—they can provoke antibody formation.

Although most slow viruses, whether conventional or unconventional, cause severe neurological disorders, their activity may not be restricted to the CNS, as evidenced by the effects of LCM virus on the kidney. Consequently, their involvement in numerous degenerative diseases is now under consideration.—JEAN L. MARX

Additional Readings

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3. L. P. Weiner, R. T. Johnson, R. M. Herndon, *N. Engl. J. Med.* **288**, 1103 (1973).