Leukemia Virus Linked to Nerve Disease

The linkage of HTLV-I to nerve diseases in the tropics and Japan extends the range of retroviruses implicated as causes of human neurological conditions

A recent flurry of reports has linked human T-cell lymphotropic virus I (HTLV-I) to a common paralytic disease of the tropics and to a similar, if not identical, condition in Japan. The virus, which is best known for its connection to certain leukemias and lymphomas, thus becomes the second retrovirus to be linked to degenerative nerve disease in humans. The first was the AIDS virus, which frequently causes brain degeneration and a consequent dementia in addition to the profound immune suppression for which AIDS—acquired immune deficiency syndrome—was originally named.

In addition, work by Hilary Koprowski of the Wistar Institute in Philadelphia and his colleagues has raised the possibility that a virus that is related to HTLV-I may cause at least some cases of multiple sclerosis. The results of the Koprowski group have been challenged by others, however, and the final word on a possible retrovirus–multiple sclerosis link is not yet in. Nevertheless, the new findings are beginning to suggest a possible widespread involvement of retroviruses in chronic neurological diseases, many of which, including multiple sclerosis, are currently of unknown origin. "We are now opening a new era in the study of neurological diseases," predicts Koprowski.

The tropical paralysis to which HTLV-I has been linked goes by the jaw-breaking name of tropical spastic paraparesis (TSP). The primary clinical feature of the disease is the development of a progressive weakness of the legs and lower body. The upper body is less affected and the patient's mental facilities remain intact. As Guy de Thé of the Faculté de Médecine Alexis Carrel in Lyon, France, describes TSP, "It is of the same magnitude and importance in the tropics as the multiple sclerosis syndrome is in the Western world." Multiple sclerosis, which is much more common in northern climes than in the tropics, affects approximately 250,000 people in the United States.

De Thé and his colleagues made the first connection between TSP and HTLV-I in 1985. The discovery came, as discoveries often do, by chance. The researchers were studying patients with adult T-cell leukemia, which is caused by HTLV-I, on the Caribbean island of Martinique. They happened to look for antibodies to the retrovirus in two TSP patients, and both turned out to give positive tests, which indicates that they had been infected with the virus.

Pursuing this lead, the French workers went on to show that nearly 60% of 17 TSP patients on Martinique had antibodies to HTLV-I, compared to only 4% of the 303 controls. Since then the French workers have confirmed and extended their findings in Martinique and have also found evidence for a link between the virus and TSP in West Africa.

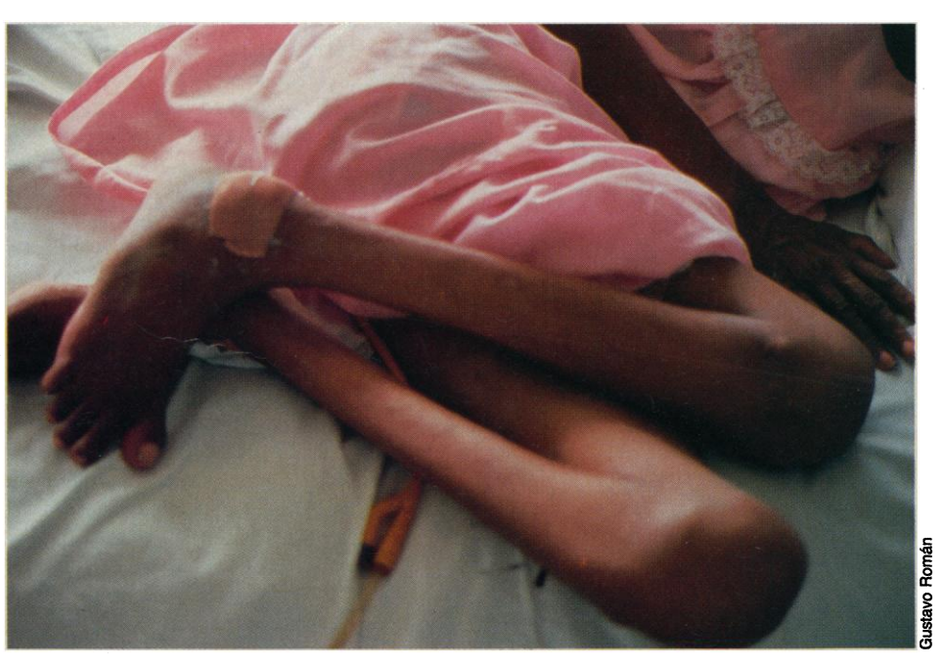
Meanwhile, other investigators have made the connection in several additional locations. For example, at a recent meeting on "Retroviruses in the Nervous System,"* Pamela Rodgers-Johnson of D. Carleton Gajdusek's group at the National Institute of Neurological and Communicative Diseases and Stroke (NINCDS) reported that about 75% of 35 TSP patients on Jamaica, another Caribbean island, show evidence of HTLV-I infection, compared to only 12% of 100 individuals with other neurological diseases who were serving as "neurological controls."

The "controls" provided another surprise, however. They included six individuals with polymyositis, a disease characterized by diffuse muscle inflammation. All six turned out to be in the positive-testing group. Infection with HTLV-I may therefore be associated with at least some cases of polymyositis.

Other countries where a link has been found between HTLV-I infection and TSP include Colombia and Trinidad. Lastly, data presented at the meeting by Gustavo Román of Texas Tech Health Sciences Center in Lubbock show that TSP patients on the island of Mahé in the Seychelles, off the east coast of Africa, also have high incidences of HTLV-I infection.

The link between HTLV-I and TSP is consistent with the known geographic distribution of the virus, which is endemic in all the regions where the association has been found. In the Caribbean, for example, some 2 to 3% of the normal population has

*The meeting was sponsored by the National Institute of Neurological Diseases and Stroke and was held in Bethesda, Maryland, on 4 and 5 May.



Gustavo Román

Colombian TSP patient. *The photo shows the deterioration of the legs in the advanced stages of the disease.*

been infected by HTLV-I. But the region of the world where the virus is most prevalent is the island of Kyushu in southern Japan, where about 15% of the population has been infected.

Recently, Mitsuhiro Osame, Akihiro Igata, and their colleagues at Kagoshima University on Kyushu, identified a group of patients with symptoms similar to those of TSP who also have HTLV-I antibodies. Although the researchers called the syndrome they identified "HTLV-I–associated myelopathy" (HAM), it may be the Japanese version of TSP. "There is a remarkable concordance of the occurrence of adult T-cell leukemia, the occurrence of the virus, and the occurrence of TSP," says William Blattner of the National Cancer Institute (NCI).

The discovery that HTLV-I apparently causes TSP clears up a long-standing mystery about the origins of the disease. "We are all very excited now about HTLV-I playing a role in its etiology," Rodgers-Johnson says. A number of the other possible causes that had been suggested over the years had fallen by the wayside. One prime candidate, for example, was the organism that causes yaws, a tropical disease very similar to syphilis, but that link became suspect when the incidence of yaws declined markedly as a result of efforts by the World Health Organization to eliminate the disease while the incidence of TSP did not decline.

Diet has also been suggested as a cause of TSP and does play a role in some circumstances. Certain of the common foods of the tropics are high in compounds that can cause TSP-like symptoms. Cassava, for example, has high concentrations of cyanide compounds. When such foods form the major portion of diets that are otherwise deficient in essential nutrients, as may happen in the drought-stricken regions of Africa, TSP epidemics can result.

But diet has been largely eliminated as the cause of the TSP cases that have now been linked to HTLV-I. As Vladimir Zaninovic of the Hospital Universitario del Valle in Cali points out, the epidemiological picture of the disease in Colombia militates against a dietary cause. TSP in that country is largely localized to the southern half of the Pacific Coast. It rarely occurs along the northern coast, even though conditions there, including the climate, diet, and genetic background of the people, are all very similar to those of the south. Moreover, Zaninovic notes, "The people are poor, but not undernourished." An infectious agent spread primarily by close contact, as HTLV-I is, would be a more likely cause than diet of TSP in Colombia. And in the Seychelles, Román says, "The cases and the controls have the same diets."

A great deal still remains to be learned about how HTLV-I might produce the symptoms of TSP. One particularly intriguing question concerns whether the virus that is linked to the neurological conditions is genetically and molecularly identical to the one that causes leukemia. So far at least, the two outcomes of infection appear to be almost mutually exclusive. Only two or three individuals have been found to have both TSP or HAM and leukemia. Efforts to isolate and clone the virus from TSP and HAM patients so that it can be compared with leukemia-causing isolates are now under way.

If the link between HTLV-I infection and TSP is now considered to be firmly established, the same cannot be said for Koprowski's suggestion that HTLV-I or an HTLV-I relative might cause multiple sclerosis. The suggestion is based on findings made about 18 months ago by Koprowski and his colleagues at the Wistar Institute in collaboration with Robert Gallo's group at NCI.

The researchers found antibodies that react with an HTLV-I protein in about 30% of the multiple sclerosis patients they examined. In addition, Mary Harper of the Gallo group detected gene sequences in some of the patients' cells that are related to HTLV-I gene sequences.

The researchers were careful to state that they may not have been detecting evidence of infection by HTLV-I itself, but possibly by an as yet unidentified relative of the virus. The specific HTLV-I antibody that they detected is to one of the proteins of the viral core, and this protein, which is designated p24, is likely to be preserved in different, but related, viruses.

The patients in the study conducted by the Koprowski-Gallo group were from Sweden and Key West, Florida. Since then, Takahiro Saida and his colleagues at Utano National Hospital in Kyoto have detected antibodies to the HTLV-I core protein in roughly one-third of a group of Japanese multiple sclerosis patients, and Annamarie Ranki of the University of Helsinki, Finland, has evidence for the antibodies in Finnish patients.

Other researchers have failed to find antibodies to HTLV-I or genetic traces of the virus in multiple sclerosis patients, however. These include de Thé, S. L. Hauser of the Pasteur Institute in Paris, and their colleagues who examined patients from Paris and Martinique. Studies of patients in England, Sweden, Japan, Italy, and the United States have also produced negative results. For example, at the retrovirus meeting, David Madden of NINCDS reported that he and his colleagues had not found the antibodies to HTLV-I in any of 62 multiple sclerosis patients from Milwaukee, Wisconsin, and Richmond, Virginia.

Koprowski points out that attempts to detect antibodies to HTLV-I proteins may be confounded by the variability shown by multiple sclerosis patients. The Wistar workers find that they cannot detect antibodies to HTLV-I proteins in some patients even though these patients show other indications of infection by an HTLV-I–like virus. Moreover, individual patients may have the antibodies at some times and not at others.

But Koprowski's strongest criticism of the negative studies is based on their use of commercial kits for detecting HTLV-I antibodies, rather than the specific test for p24 antibodies used by the Wistar and NCI workers. The kits, which were designed primarily for detecting large amounts of HTLV-I antibodies in leukemia patients, contain only very small amounts of p24 and may not be sufficiently sensitive to pick up small quantities of antibodies to the protein, especially if the virus that originally triggered the antibody production is an HTLV-I relative. In fact, Elaine DeFretais of the Wistar group obtained negative results with the kits on samples previously shown to test positive for the p24 antibodies.

The discrepancy in methods nonetheless led several participants at the retrovirus meeting to suggest that the Koprowski group exchange blood and spinal fluid samples from patients with TSP, multiple sclerosis, and other neurological diseases with groups that had had the negative antibody findings. Each group would use its own

Hilary Koprowski *is studying the involvement of retroviruses in chronic neurological diseases such as multiple sclerosis.*

methods to analyze the samples, the identities of which would not be revealed until the tests were completed. The results of such a study could help to resolve the issue of whether an HTLV-I relative does contribute to the genesis of multiple sclerosis. "It is an important and interesting finding," says meeting cochairman John Sever of NINCDS about the Koprowski-Gallo findings, "and we need to nail it down."

Koprowski is opposed to the suggested trial, however, partly on practical grounds. He notes that p24 is costly and difficult to obtain in quantities sufficient for such a large-scale study. Moreover, he is concerned that the diagnoses of the patients from whom the samples would be taken may not be accurate because "They are all based on subjective diagnostic criteria by clinical examination."

The clinical features of TSP and multiple sclerosis, for example, show several similarities that make distinguishing the two conditions difficult. Although the brains of multiple sclerosis patients show certain characteristic pathologic changes that can be detected by magnetic resonance imaging, such high-technology diagnostic procedures are not likely to be available in the typically poor regions of the tropics where TSP is endemic. Consequently, Koprowski suggests, many "TSP" patients may actually have multiple sclerosis.

Conversely, the apparent high incidence of multiple sclerosis on Key West is unusual for such a southerly location, and other investigators have suggested that the "multiple sclerosis" there may be misdiagnosed TSP. However, Román, who has reviewed the clinical features of multiple sclerosis patients on Key West, concludes, "From the clinical point of view, the patients on Key West are not TSP by any stretch of the imagination."

In any event, because of the general difficulty of diagnosing chronic neurological diseases, Koprowski proposes that a better way of pinpointing a retroviral involvement in the conditions would be to have a large number of investigators survey patients for evidence of infection. In the current absence of a specific viral probe, a very sensitive test for the p24 core protein would be needed.

The diseases surveyed should not be limited to multiple sclerosis and TSP, Koprowski says, but should also include other degenerative nerve conditions of unknown cause, such as Guillain-Barré syndrome, Alzheimer's disease, and amyotrophic lateral sclerosis (more commonly known as Lou Gehrig's disease). Then if viral traces in any of the patients were found, attempts to correlate them with particular clinical entities could be made.

Another approach that could help clarify matters would be to isolate the putative retrovirus itself, or if that is not possible, to clone the retroviral gene sequences present in cells. If either can be done, it would make available specific probes for detecting evidence of infection by the virus and would thus be another route to determining whether it plays a role in the etiology of multiple sclerosis or other neurological diseases.

The situation with regard to the putative new retrovirus and multiple sclerosis parallels that seen just 4 years ago when Luc Montagnier and his colleagues at the Pasteur Institute were first detecting evidence of infection by a new retrovirus in AIDS patients. At the time, no one knew what the Pasteur findings meant. Only when the virus was isolated by the Gallo and Montagnier groups and specific probes became available could it be confirmed as the cause of the AIDS. It will be interesting to see what the outcome of the current situation will be. ■

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The Earliest "Humans" Were More Like Apes

The discovery at Olduvai Gorge of arm and leg bones of the first member of the genus Homo *shows that the creature was much more primitive than had been expected*

"I laughed when I saw it," says Henry McHenry. "It is so tiny." McHenry, an anthropologist at the University of California, Davis, was telling of his initial impressions of a newly discovered "partial skeleton" of a 1.8-million-year-old human ancestor from Olduvai Gorge, Tanzania. "Now we have to go back to the fossil collections and fish out the hominid limb bones that have been misclassified as monkeys."

The new Olduvai fossils, which were discovered last year by Tim White of the University of California, Berkeley, are especially important because in addition to the entire right arm bones, and some leg bones of a single individual, they also include diagnostic parts of the head that allow its species to be identified. "There's no doubt that it is *Homo habilis*," says Donald Johanson of the Institute of Human Origins (IHO), Berkeley, who organized the expedition to Olduvai Gorge in conjunction with the National Museums of Tanzania. "This is the first time that limb bones and cranial material of *Homo habilis* have been found in definite association," he says. "The result is a big surprise."

The surprise is that this *Homo habilis* individual was, as McHenry noted, tiny, standing just 3 feet tall. The famous Lucy skeleton, which was discovered 13 years ago in Ethiopia by Johanson and is over 3 million years old, is about the same size as the new fossil. Lucy belongs to a species called *Australopithecus afarensis*. Both Lucy and the new Olduvai hominid are thought to be females of their species.

"Because *Homo habilis* is considered to be an evolutionary intermediate between the relatively small *Australopithecus afarensis* and the relatively large *Homo erectus*, everyone assumed *habilis* would be of intermediate size," says White. "People have viewed human evolution through the glasses of gradualistic change. Well, this fossil has smashed those glasses. The change was obviously abrupt, with a big modification in body form between *habilis* and *erectus*." Details of the recovery and interpretation of OH 62 are published in the current issue of *Nature*.

A widely accepted picture of human evolution places *Australopithecus afarensis* as the first known hominid, which is dated from between 3.75 to 3.00 million years ago. *Homo habilis* is thought to be a descendant of *afarensis*, and probably arose a little more