Human T-Cell Leukemia Virus Linked to AIDS

Patients with the new immune disease show evidence of infection by human T-cell leukemia virus. Does the virus cause the disease?

Five reports in this issue of *Science* suggest a possible link between the serious new disease, acquired immune deficiency syndrome (AIDS) and human T-cell leukemia virus (HTLV), which has been associated with a rare type of human cancer. Investigators at the Harvard University School of Public Health, the National Cancer Institute, and the Pasteur Institute have found evidence of HTLV infection in patients with AIDS or at high risk of developing the syndrome. The evidence includes isolation of the virus itself from a few patients, detection of the viral DNA in T cells from two cases, and also a much higher incidence of antibodies against HTLV in AIDS patients than in controls.

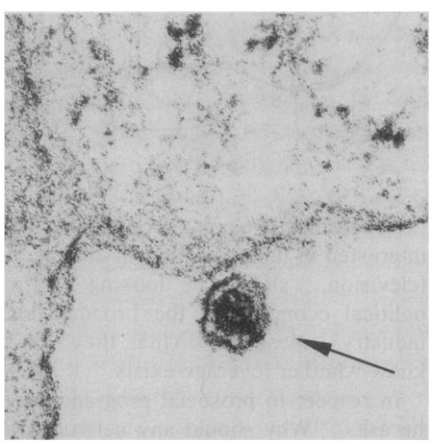
It is still too early to tell whether HTLV actually causes AIDS. The disease is characterized by immune suppression, which results in high susceptibility to opportunistic infections by agents that do not usually cause serious illnesses in healthy people but can prove devastating to individuals with defective immune responses. HTLV may be just another of these opportunistic pathogens, a consequence rather than a cause of AIDS. Max Essex of the Harvard group says, "I definitely do not want anyone to get the impression that we have proof of cause. What we do have is a good lead."

A good lead is much needed. Since AIDS first became manifest in 1981, more than 1350 cases have been reported to the Centers for Disease Control (CDC). The mortality rate may be 70 percent or higher, and the number of cases continues to grow by four to five per day. Epidemiological studies strongly suggest that AIDS is caused by an infectious agent, although other possibilities have not been conclusively ruled out. Efforts to identify the infectious agent have proved frustrating.

According to Robert Gallo of the National Cancer Institute (NCI), there are a number of reasons for taking a close look at HTLV as a possible cause of AIDS. First is the prevalence of HTLV in the Caribbean area and in Africa. The Caribbean area, especially Haiti, and equatorial Africa have been suggested as possible sources of the putative AIDS agent.

In the United States, Haitian immigrants constitute the third largest group of AIDS patients. The largest group consists of homosexual and bisexual men who have been extremely active sexually, and the second largest includes users of illegal intravenous drugs. Hemophiliacs are a fourth group with increased risk of AIDS.

AIDS has apparently spread among homosexuals by sexual contact and among drug users by contaminated needles. It is believed to have been transmitted to hemophiliacs by way of the blood clotting factor preparations that they must take. But the Haitians have always been a puzzle, because the vast majority deny both homosexual practices and drug use and they have not been exposed to clotting factor preparations. The identification of a causative virus in the Haitian population could help clear up this mystery.



Human T-cell leukemia virus

But does it cause AIDS?

Secondly, HTLV primarily infects T cells. As Gallo puts it, "HTLV is extraordinarily T-cell tropic." The primary AIDS defect also seems to be in the T lymphocytes, which are reduced in number in the patients and abnormal in composition. The helper T cells, which are needed to activate certain immune responses, including antibody production by the B lymphocytes, are very low in number, whereas the killer-suppressor cells are much less affected. The loss of helpers, while the activities of suppressor T cells remain more or less intact, could produce the profound suppression of the immune response that is characteristic of AIDS.

A third point of similarity is mode of transmission. As noted previously, AIDS spreads by intimate contact and through blood products. "Everything we know about HTLV suggests that intimate contact is needed for transmission," Gallo remarks. He points out that the viral envelope, which is required for infectivity, is very fragile. It tends to come off when the virus buds from infected cells, thus rendering the particles incapable of infecting new cells. Gallo speculates that direct cell-to-cell contact may be required for the spread of HTLV.

Finally, there are precedents for a virus causing both a leukemia and immunosuppression. This is true for feline leukemia virus, which has been studied for many years in the Essex laboratory. "More cats are killed as a result of feline leukemia virus causing immunosuppression than by feline leukemia virus causing leukemia," Essex says.

The virus generally impairs T-cell responses in the animals. Previous attempts to demonstrate an effect on antibody production had failed, but the Essex group now finds that natural infection by feline leukemia virus suppresses the antibody response to an antigen that normally requires the cooperation of helper T cells to elicit antibody production. Feline leukemia virus also has a preference for infecting T cells and produces primarily T cell leukemias. The antibody response may be deficient, Essex speculates, because of a problem with the helper T cells.

Previous failures to demonstrate a viral effect on antibody production may be attributable to the differing responses of cats to naturally occurring and laboratory-induced infections. The natural infections are more effective at suppressing the immune response of cats than infections induced by such laboratory methods as directly injecting the virus.

HTLV is one of the retroviruses, which have RNA as their genetic material. In infected cells, the RNA is copied into DNA, which may then become integrated into the DNA genome of the host

cell and bring about the cell's cancerous transformation. To determine whether AIDS patients showed signs of infection by HTLV the Gallo group looked for viral DNA in the patients' T cells.

They detected the viral DNA in the cells of two of 33 patients, but did not find it in T cells from any of 25 healthy homosexual males. They were able to isolate infectious HTLV particles from the T cells of one of the two individuals who were positive for viral DNA and also from two additional patients. This is from a total of about 20 patients whose T cells were used in attempts to isolate HTLV. In addition, a French group, under the direction of Luc Montagnier of the Pasteur Institute in Paris, has isolated a related virus from the T cells of a homosexual male with lymphadenopathy, a condition that may be a mild form of AIDS or a forerunner of the full-blown disease.

There is more than one type of HTLV. About 35 isolates of the virus have been made throughout the world. Roughly 25 of these have been characterized and most are of the type designated HTLV-I, which was originally isolated by the Gallo group. A second type of the virus, which is designated HTLV-II, has been isolated from the cells of a patient with hairy cell leukemia.

The NCI workers have characterized one of their three HTLV isolates from AIDS patients and it is HTLV-I. The virus isolated by the French group is neither HTLV-I nor -II, but represents a third variant of the virus. Although the members of the HTLV family are distinguished on the basis of structural variations in one of the internal proteins of the viral particle, they have other features in common, including their preference for infecting T cells and the rather unusual properties of their enzyme for copying RNA into DNA.

Gallo suggests that logistical problems might explain why viral DNA could be detected in the cells of so few AIDS patients. "If infection leads to a decline in the population of infected cells, you may not be able to find them by the time you get frank disease," he explains. In fact, the NCI workers could not detect integrated viral DNA in T cells from blood samples taken at a later date from the two patients who had earlier given positive results. The same problem might affect attempts to isolate the virus itself. Lymphocytes from the spleen or lymph nodes might be a better source of virus than the peripheral blood cells used for the NCI studies. The French workers isolated their virus from lymph node cells.

Early Climate Data Questioned

Some geochemists are questioning whether paleoceanographers have convincingly verified the fidelity of their climate record for the time between the demise of the dinosaurs 65 million years ago and the first appearance of a major ice cap on Antarctica about 15 million years ago. The oxygen isotope composition of marine microfossils, especially the calcium carbonate shells of the amoeba-like Foraminifera, has been used for 25 years to estimate ancient seawater temperatures and the amount of glacial ice in the world. There have been complications, but nevertheless most paleoceanographers concluded that surface waters have cooled during the past 65 million years, mainly near the poles, and bottom waters have gradually if somewhat jerkily cooled to present near-freezing temperatures.

John Killingley, a geochemist at Scripps Institution of Oceanography, has recently questioned how much of these isotopically determined temperature trends is due to climate change and how much could have been caused by chemical alteration of the sediment during its burial beneath the sea floor. Even before carbonate sediments turn into limestone under the pressure and heat of burial, forams can gradually dissolve and recrystallize, exchanging oxygen isotopes with the pore water in the sediment as they do.

Killingley simulated this recrystallization process in a mathematical model, his critical assumption being that recrystallization would be 80 percent complete after 60 million years. He took this figure from a recent study of sediment alteration by Paul Baker of Duke University, Joris Gieskes of Scripps, and Harry Elderfield of Leeds University. The model duplicated the direction of observed isotopic trends, which was no surprise, but the assumed 80 percent recrystallization also produced the same size isotopic shifts as observed or ones of similar size. "I don't believe it explains all of the observed trends," says Killingley, "but the model is so similar, we have to be careful. It's a warning flag."

Paleoceanographers generally believe that the warning is unnecessary. Visual inspection of forams and the consistent results obtained from sediments of the same age buried at varying depths has reassured them that they have avoided recrystallization extensive enough to affect their results significantly. In addition, recrystallization should also produce similar trends in the carbon isotopic composition of forams, says Samuel Savin of Case Western Reserve University, but no such trend has been found. While paleoceanographers have been careful to choose the best preserved forams, others argue, geochemists have studied bulk sediment properties.

Baker, for one, sees potential problems with all of these checks on the extent of recrystallization. Intersite comparisons could be flawed if recrystallization is more dependent on time than temperature, a question not yet fully resolved, he says. The carbon isotopes could be misleading, he adds, because unlike the case of oxygen, most of the carbon in sediment is in the carbonate and little is in the pore water. And at the one spot, Deep-Sea Drilling site 289 in the equatorial Pacific, where geochemists analyzed selected forams they found more alteration than had been assumed.

Paleoceanographers had selected the site 289 sediment core to study changes in glacial ice during the past 20 million years, in part because of its well-preserved forams. Comparing strontium isotope ratios of carbonate, pore water, and ancient seawater, Elderfield, Gieskes, and their colleagues concluded that alteration was minimal in 15-million-year-old sediments, but 20-million-year-old sediments were about 60 percent recrystallized. Savin responds that new, more accurate strontium isotope values for ancient seawater render the geochemists' arguments inconclusive.

A resolution of these differences may be in the offing. Some paleoceanographers want to take a serious geochemical look at sediments older than 60 million years, and some geochemists are now applying their techniques to the same samples being studied by paleoceanographers.—**RICHARD A. KERR**

Additional Readings

1. P. A. Baker, J. M. Gieskes, H. Elderfield, *J. Sediment. Petrol.* **52**, 71 (1982).
2. J. S. Killingley, *Nature (London)* **301**, 594 (1983).
3. H. Elderfield *et al.*, *Geochim. Cosmochim. Acta* **46**, 2259 (1982).

The Uses of a Large Array

Sometimes a tool has more than one use—witness the Very Long Baseline Array (VLBA), a proposed network of radio telescopes that would stretch from Europe to Hawaii and from Alaska to the Caribbean.

If and when the VLBA is completed, its individual antennas will be able to combine their signals into astronomical images having an angular resolution of 0.3 milliarcsecond—100 times better than any other telescope at any wavelength, and good enough to see a dime in New York from the distance of Los Angeles. The likely targets of the array include x-ray stars, the cores of quasars, the nuclei of galaxies (including our own galaxy), and star-forming regions within the interstellar molecular clouds. The technology required, although sophisticated, is essentially off-the-shelf; the VLBA could be built within a few years for a relatively modest $50 million.

Thus, it is not surprising that the VLBA won a strong endorsement last year from the National Academy of Science's Astronomy Survey Committee (the "Field Committee," *Science*, 16 April 1982, p. 282), and more recently, from presidential science adviser George A. Keyworth. Indeed, Keyworth saw to it that the President's fiscal 1984 budget for the National Science Foundation included funds for a VLBA design study, and he has pledged to push for full-scale funding in fiscal 1985.

Not the least of the VLBA's charms, however, is its potential for nonastrophysical spin-offs, particularly in geophysics and geodesy. To remind people of that, and to give the wider community some input into the array's design—and not incidentally, to help turn potential funding rivals into allies—astronomer Herbert Friedman, co-chairman of the National Research Council's Commission on Physical Sciences, Mathematics, and Resources, organized a multidisciplinary VLBA workshop on 8–9 April.

"The results were everything we expected," says Friedman. "The geophysics community was impressed with the power of the instrument, and the astronomers were impressed with the quality of the geophysical science that could be done." Some highlights:

- *Geodesy*. As the VLBA antennas record the signals from distant quasars, they will also be establishing their positions relative to one another with extraordinary precision. Experiments with existing antennas have already achieved accuracies of a few centimeters over thousands of kilometers. The VLBA could thus be important in determining deformations and large-scale motions in the earth's crustal plates; in monitoring the motion of the polar axis and variations in the earth's rotation; and, for mapping purposes, in providing a terrestrial reference system far more accurate than any now in existence.
- *Astrometry*. Measuring the positions and motions of the stars and planets is an unglamorous, meat-and-potatoes kind of science. But it is fundamentally important in deriving the distance to the stars and clusters, and thus in understanding their masses, luminosities, and general state of evolution. Moreover, observing tiny, cyclic shifts in a star's position could be the most straightforward way of detecting planets in other solar systems. The VLBA would help by relating its own coordinate system, which is fixed to the rotating earth, to a coordinate system pegged to the quasars, which is probably the closest approximation possible to an inertial reference frame.
- *Satellite orbits*. A higher precision determination of satellite orbits would be useful both in geodesy and in studying irregularities in the earth's gravitational field.
- *Timekeeping*. Astronomical signals from the individual VLBA antennas will be correlated by means of very accurate maser clocks, which will have to be very precisely synchronized. Thus, almost by accident, the array will provide the standards for an improved, worldwide master clock.

"The idea was to let people articulate their needs early on," says workshop co-chairman Bernard F. Burke of the Massachusetts Institute of Technology. "At this point in the process we can easily make accommodations [in the software, electronics, and antenna placement] that will cost the astrophysics nothing, yet will yield big payoffs for the geophysicists. Six months from now, it would have been too late."—**M. Mitchell Waldrop**

If HTLV does cause AIDS then there must be a way of maintaining the immunosuppressed state even after the virus is no longer detectable. The immune systems of the patients do not appear to recover.

Simply finding HTLV or the DNA in AIDS patients does not mean that the virus caused the disease. "From our data it could be an opportunistic infection," Gallo concedes. "But Essex's data argue that it is more than opportunistic."

Essex and his Harvard and CDC collaborators detected antibodies against membrane-associated antigens of HTLV in at least 25 percent of 75 AIDS and 23 lymphadenopathy patients. Another 10 percent or so would be positive if the investigators used a somewhat less stringent criterion for a positive antibody test.

In contrast, only one of 81 homosexual controls who had been matched for age, race, and place of residence with 36 of the AIDS patients had the antibodies. The one positive individual was a friend, but not a sex partner, of one of the patients. Only two of an additional 305 controls, including homosexuals who had visited a venereal disease clinic, healthy blood donors, kidney dialysis and chronic hepatitis patients, had the antibodies. "The message is that 25 to 40 percent of AIDS cases have the antibodies and 1 percent or less of control groups do," Essex says.

Other attempts to identify differences in viral exposures between AIDS patients and controls have not turned up such a large discrepancy between the two groups. Nevertheless, some 50 percent of the patients did not have the antibodies, either because the test was not sensitive enough to detect them or because their immune systems failed to make the antibodies—or because they had not been infected by HTLV.

Militating against the possibility that HTLV causes AIDS, Gallo says, is the relatively short period of time required for the immune deficiency disease to develop. CDC officials have reported the latency period of AIDS to be several months to a year. The T-cell leukemia caused by HTLV may require years, if not decades, to develop after infection by the virus.

Perhaps more disconcerting than the discrepancies in the latency periods of the two conditions is the apparent lack of AIDS in southern Japan, an area where the rate of HTLV infection is very high. Some 25 percent of the population there have antibodies against the virus, compared to 4 to 5 percent in Haiti and 1 percent in the United States.

Either AIDS exists in that part of Japan but has not been diagnosed, which seems unlikely especially in view of the publicity AIDS has received during the past year, or the Japanese may respond differently to the infection. Another possibility, Gallo points out, is that a change occurred in the HTLV family in Africa or Haiti that conferred a new capability for immune suppression on the virus. Comparison of the nucleotide sequences of the DNA of viral isolates from the various sources may help to clarify this issue.

Why some people might develop AIDS as a consequence of HTLV infection while others get leukemia is unclear. It might be an as yet undetermined difference in the infecting HTLV or in the host response to the infection. It might depend on the site at which the viral DNA integrates in the genome of infected cells.

In any event, there are now a number of approaches that may be taken to clarify the relation between HTLV and AIDS. A prospective study of high-risk individuals to see whether HTLV infection precedes or follows development of AIDS is a possibility. Another is to look at people who have other types of immune suppression, children with congenital immunodeficiency diseases or kidney transplant patients, for example, to see if they too have an increased number of HTLV infections.

If HTLV does eventually prove to be the cause of AIDS, then a specific test for the early diagnosis of the condition may be feasible. Especially desirable is an assay for the AIDS agent in blood. The possibility that the condition may be transmitted in blood products has naturally generated a great deal of concern. Ultimately a vaccine may be developed to protect high-risk individuals. But that all awaits firm proof of the cause of AIDS.—**JEAN L. MARX**

High Energy Physics Looks to the Future

Physicists meet this June in Woods Hole to ponder new accelerators; most contentious is the fate of the CBA, née Isabelle

Every 2 years or so, the Department of Energy (DOE) asks its High Energy Physics Advisory Panel (HEPAP) to convene a subpanel on long-range planning for new accelerator facilities. There is always a certain drama to these exercises—after all, the recommendations involve the futures of whole national laboratories and hundreds of millions of dollars, not to mention the course of particle physics—but this year there seems to be a special sense of urgency:

- The recent discovery of the W boson at CERN, the European Laboratory for Particle Physics in Geneva, underscores an American sense of having fallen behind in high energy physics, of missing out on the truly exciting discoveries.
- At the same time (and partly as a result), the Reagan Administration has already begun to boost its funding for high energy physics; moreover, accelerator technology has now evolved to the point where the HEPAP subpanel can begin to make serious recommendations on an Ultra High Energy Accelerator, a 20-trillion-electron-volt-(TeV) device that would represent an order-of-magnitude advance in energy over current machines, and which could once again put the United States solidly in the forefront.
- Most importantly, however, the subpanel must once and for all decide the fate of Brookhaven National Laboratory's proposed Colliding Beam Accelerator (CBA), the reincarnation of troubled, controversial Isabelle (*Science*, 13 November 1981, p. 769).

"The committee's got a tough job," says William A. Wallenmeyer, director of DOE's high energy physics program. "Usually with these things I have a pretty clear idea beforehand what the obvious decision is. Not on this one."

Under chairman Stanley G. Wojcicki, the HEPAP subpanel holds its final meeting at Woods Hole, Massachusetts, during the week of 5 June, which is about the last date its recommendations can affect the fiscal year 1985 budget. The European challenge will be very much on people's minds.

It is only a slight oversimplification to say that high energy physics today is a worldwide effort to test the so-called standard model of particle interactions, in which the Weinberg-Salam theory describes the unified electromagnetic and weak interactions, and quantum chromodynamics (QCD) describes the strong, or nuclear, force. Every new accelerator is planned with this goal in mind. In recent years, however, the standard model has sometimes seemed to be a special province of Europe.

"They have had two major successes," recalls Wojcicki. First, the electron-positron colliding beam machine PETRA came on line at West Germany's DESY laboratory in 1978, about a year before the equivalent American machine, PEP, started operation at the Stanford Linear Accelerator Center. "They were able to skim the cream," he says. A prime example was the first empirical evidence for gluons, the quanta that are thought to hold the quarks together in the proton and neutron and that are an essential feature of QCD.

Second, of course, was the recent discovery of the W boson at CERN's new proton-antiproton collider, the SPS. The W is a central prediction of the Weinberg-Salam model; another, the Z boson, should appear at the SPS soon. Meanwhile, the accelerator has also produced hints of the long-sought top quark. "Once again, they are walking off with the most exciting physics," says Wojcicki.

Europe is also building up considerable momentum for the future. CERN has gotten the go-ahead for its enormous LEP, a billion-dollar, 9-kilometer-wide electron-positron ring that will operate at 50 billion electron volts (GeV) per beam, with the possibility of 100 GeV later. [Electron-positron annihilation at these energies is a particularly clean way to produce and study the W's, Z's, and new quarks (*Science*, 31 July 1981, p. 528)]. And it now appears that DESY will get its high energy electron-proton collider.

In the United States, by contrast, the high energy program has suffered through the budgetary uncertainties of the first two Reagan years—to save money the big American accelerators are currently being operated only part time—and the fiasco of Isabelle. The latter was to have been the major new facility for the late 1980's. Instead it was thrown into limbo as project scientists struggled to master their recalcitrant new superconducting magnets. The result has