The Slow, Insidious Natures of the HTLV's

The scope of the viruses that cause AIDS and certain leukemias and lymphomas is broadening in terms of number of people affected and range of clinical syndromes

Trois Ilets, Martinique.

WHEN some 60 researchers gathered recently on the French island of Martinique for a meeting on "Viruses and Cancers,"* the program reflected the great interest that has been generated by the human T-cell lymphotropic viruses (HTLV's). Roughly half the presentations were devoted to HTLV-I and -II, which cause human leukemias or lymphomas, and to a third virus, which causes acquired immune deficiency syndrome (AIDS) and has been variously designated as HTLV-III, LAV (for lymphadenopathy-associated virus), or ARV (for AIDS-associated retrovirus).

Progress in understanding the molecular biology and mechanisms of action of these viruses has been rapid. In particular, data presented at the meeting pointed up the insidious nature of infection by the agents. They seem to have been almost diabolically designed by nature to allow them to elude detection and elimination. Moreover, the scope of the HTLV's is broadening. The number of people affected is increasing, and the viruses may be associated with a growing number of clinical syndromes. However, there are some indications—although the results are highly preliminary the investigators stressed—that drugs might be found to counteract the AIDS virus.

The AIDS epidemic may be even more serious than has been thought, according to epidemiological data presented by William Blattner of the National Cancer Institute. Current estimates from the Centers for Disease Control (CDC) in Atlanta put the number of people in the United States who have been infected by HTLV-III at between 500,000 and 1,000,000. From 5 to 20 percent of them are expected to develop AIDS, the CDC says. However, Blattner and his colleagues find that this estimate may be too low. They have been following 80 homosexual men who were infected by the AIDS virus by 1982. So far about 35 percent have come down with AIDS.

The number of persons studied is small, Blattner cautions, and they are extremely active sexually and may not be representative of the total population of infected people. Nevertheless, the results suggest that given enough time an increasing proportion of the people who have been infected with HTLV-III will develop AIDS.

"As latent viruses, they are much more hidden from the immune system. They are much more likely to result in long-term disease."

Additional indications of the growing scope of HTLV-III infections comes from the less-developed countries. In the developed countries, roughly three-quarters of AIDS victims are homo- or bisexual men, whereas in Africa about half are women. A similar situation may be developing in Haiti, according to Haitian physician Jean Pape, who reports that the number of Haitian women who have AIDS has been steadily increasing. They are expected to constitute nearly 50 percent of the total by 1988.

Moreover, Pape and Lurhuma Z. of the Cliniques Universitaires de Mont Alba in Kinshasa, Zaire, both pointed out that AIDS may be underreported in the developing countries because the patients there rarely fit the CDC definition. In particular, they have a spectrum of diseases that is quite different from what is seen in AIDS patients in the United States and Western Europe.

The drugs that are now being tested for AIDS therapy include agents that inhibit infection or reproduction of the AIDS virus or help to restore immune functions. For example, Alain Pompidou of the Hôpital Saint-Vincent de Paul in Paris, Jean-Marie Lang of the Centre Hospitalo-Université in Strasbourg, and their colleagues are now using the drug Imuthiol (diethyldithiocarbamate) to treat 12 patients with AIDS-related complex (ARC), which may be an early or mild form of AIDS.

HTLV-III preferentially infects and kills lymphocytes of the T4 subclass, which includes the helper cells needed for mounting many immune responses. Imuthiol is an immunomodulator, Pompidou says, that fosters the maturation of T4 cells without stimulating them to divide, which might activate reproduction of the AIDS virus, and also inhibits T-cell infection by the virus. Such a drug might help prevent patients in the early stages of AIDS from developing the advanced disease.

Pompidou told the meeting participants that eight of the ARC patients who are being treated with Imuthiol experienced clinical improvements, including reduced fever, return to more normal weight, and increased numbers of T4 cells. The patients have been taking the drug for from 3 months to 2 years and thus far have not had significant side effects, although long-term toxicities have not been ruled out. How long the beneficial effects of the drug will be maintained is unknown.

Samuel Broder and his colleagues at the NCI also have early results suggesting that drug therapy may improve the immune status of AIDS patients. They are using 3′-azido-3′-deoxythymidine, which acts by interrupting the synthesis of viral DNA, thereby interfering with the HTLV-III life cycle. According to Broder, some of the 15 patients who were given the drug showed increased numbers of T4 cells and one individual had a remission of an oral yeast infection. "The drug is tolerated rather well; we haven't seen significant toxicities," Broder says, while stressing that any claims of therapeutic efficacy would be premature.

A third drug under investigation for its possible use in AIDS therapy is HPA-23, which is the agent with which Rock Hudson was reported to have been treated in Paris. HPA-23 prevents HTLV-III replication in cultured cells by inhibiting the enzyme reverse transcriptase. According to Jean-Claude Chermann of the Pasteur Institute, a phase 1 clinical trial is now under way to

*The meeting was cosponsored by the French Association pour la Recherche sur le Cancer, the National Institutes of Health, and the National Cancer Institute and held on 8 to 10 January.

determine how effectively the drug inhibits viral reproduction in AIDS patients. The results are expected in March.

Although limited experience with HPA-23 in the United States and Europe has raised questions about whether the drug produces immunological or clinical improvements in AIDS patients, the goal is to reduce the amount of virus carried by infected individuals, Chermann explains. When the virus burden has been eliminated or reduced, then other therapies, such as bone marrow transplants or treatment with immunomodulatory agents, may be tried to restore the patients' immune systems.

Presentations at the Martinique meeting indicate that a clearer picture of how all the HTLV's work is beginning to develop. Their course of action is usually slow. HTLV-I and -II also preferentially infect T4 cells, but eventually lead to uncontrolled growth of the cells and malignancy, rather than the cell death caused by HTLV-III. But many months or years may elapse before any disease becomes apparent.

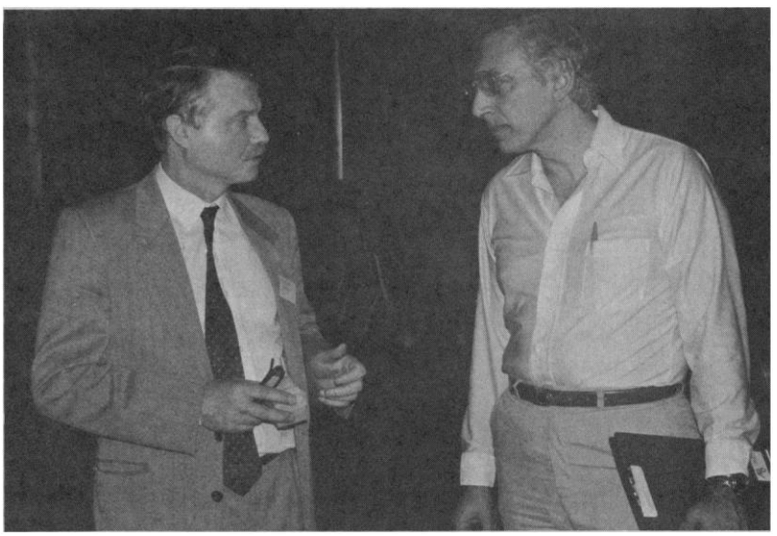
The HTLV's are retroviruses. They have RNA as their genetic material and their life cycles include the copying of the RNA into DNA by reverse transcriptase. Whether or not the DNA's are integrated into the genomes of infected cells they can remain there without the genes being expressed, provided that the cells are not dividing. Consequently, viral proteins are not made and the immune system does not recognize and eliminate infected cells. "As latent viruses, they are much more hidden from the immune system," says William Haseltine of Harvard's Dana-Farber Cancer Institute. "They are much more likely to result in long-term disease."

The trigger for expression of the viral genes and consequent reproduction of the viruses appears to be the normal antigenic activation of infected lymphocytes, at least for HTLV-III. Daniel Zagury of the Université Pierre et Marie Curie in Paris, Robert Gallo of the NCI, and their colleagues have found that HTLV-III–infected cells, when grown in culture, begin producing the virus and then die when the cells are stimulated to divide.

All the individuals at greatest risk for developing AIDS, including homo- or bisexual men who have many sex partners, drug addicts, and hemophiliacs, have high exposures to foreign antigens. Estimates are that only about 10 percent of the T4 cells of infected individuals contain HTLV-III, but as these cells respond to foreign antigens, the virus will reproduce, thereby leading not only to the death of already infected cells but also to the spread of the virus to new cells. Ultimately the immune system will be crippled by the loss of T4 cells.

Luc Montagnier (left) and Robert Gallo

Discussing the AIDS virus while on Martinique.



Analysis of the nucleotide sequences of the HTLV-III genome suggests a possible way in which T-cell activation and initiation of viral replication may be linked. The control regions for expression of the viral genes are located at the ends of the genome in the long terminal repeats (LTR's). An early consequence of T-cell activation is the turning on of the gene coding for interleukin-2, a protein that stimulates T-cell division. As Gallo points out, the LTR control regions of HTLV-III contain nucleotide sequences that are similar to sequences in the control region of the interleukin-2 gene and also that of the gamma-interferon gene. Conceivably then, the same factors that turn on interleukin-2 production when T cells are activated also activate the HTLV-III genomes. Less is known about what might activate the HTLV-I and -II genomes, although replication of these viruses is also turned on in dividing lymphocytes

All three HTLV's contain genes that code for proteins that further stimulate the expression of the viral genomes after the initial activation. According to Haseltine, these genes (designated *tat* for "*trans*-activation of transcription") represent an adaptation that permits the viruses to replicate very rapidly once they get the opportunity.

The *tat* genes may also underlie the pathogenic actions of the viruses. Haseltine, NCI's Warner Greene, and their colleagues have recently found that the HTLV-II *tat* product induces the expression of the genes both for interleukin-2 and its receptor. Continuous production of these proteins would provide the T cells with a powerful, built-in stimulus for growth. Additional factors are presumably involved. "It doesn't happen to everyone infected," Haseltine says. "Most have ways of shutting down the genes. Only when this fails do people get sick."

How HTLV-III kills T4 cells is unclear, although the Haseltine group has shown that the *tat* gene is necessary for cell death. However, a direct action of the virus may not be necessary for all the cell-killing. Luc Montagnier of the Pasteur Institute postulates that an abnormal immune attack may also contribute.

Flossie Wong-Staal of the NCI described another aspect of HTLV-III molecular biology that may help it escape immune surveillance. Analysis of several isolates from different individuals shows that the genomes vary in their nucleotide sequences. "The picture that emerges is one of a virus that evolves with time," Wong-Staal explains. She and her colleagues now have evidence that the HTLV-III genome can even change over time within a given individual. Moreover, the patient's antibodies reacted more readily with the original isolate than with later ones, a result which suggests that the immune system is helping to select for viral change.

Finally, there are indications of a broadening role for the leukemia-causing HTLV's as well as for HTLV-III. HTLV-I is best known as the cause of adult T-cell leukemia, which is a very aggressive cancer. However, Blattner presented data indicating that the virus may also be linked to a B-cell leukemia, although it apparently acts indirectly and not directly as it does in the T-cell disease. Moreover, until recently, only one or two isolates of HTLV-II had been found. Now Gallo and his colleagues have obtained several more, and work by both Gallo's group and that of Robin Weiss at the Institute for Cancer Research in London indicates that HTLV-II might be spreading in the same way as HTLV-I and -III. HTLV-II is associated with a much milder form of cancer than is HTLV-I, however. The more people look for these retroviruses, the more it seems they find. ■ JEAN L. MARX