AIDS Research in New Phase

Paris. *Two strong messages emerged from the second International Conference on AIDS (acquired immune deficiency syndrome), which was held here at the end of June. First, there remain clear differences of scientific opinion on the basic biology of the disease and the virus that causes it. Resolution of these issues should facilitate the development of both a vaccine to prevent someone from getting AIDS and also drugs to treat people who are already infected with the AIDS virus.*

Second, whatever their discipline, conference participants came to realize that AIDS can no longer be regarded as a disease restricted to certain populations. Data from surveys in the United States, including a military study, and on the massive spread of the disease in Africa, indicate that AIDS is passed as easily from women to men as from men to their sexual partners. In its pattern of transmission, AIDS is typical of other sexually transmitted diseases.

The 3-day meeting included six areas of AIDS research—virology, immunology, epidemiology, clinical medicine, psychiatry, and public health. Researchers who investigate the technical aspects of AIDS agree that no astonishing scientific breakthroughs in terms of vaccine or drug development were revealed. Nevertheless, they cite important advances, but no general consensus, in understanding the nature of the virus itself and how it infects or kills cells.

The Complexity of the AIDS Virus

"The genome of the AIDS virus has a complex structure," says Luc Montagnier of the Pasteur Institute in Paris. In contrast to most other retroviruses, which have only three genes, each of which is necessary for replication, the AIDS retrovirus has at least seven. Three of these code for proteins directly involved in replication, and the other four code for regulatory or accessory proteins.

There is a growing list of cell types the AIDS virus can infect. The virus binds to T4 receptors and infects cell types that carry T4 receptors (or perhaps a similar molecule) on their surface. In addition to the well-characterized T4 lymphocytes, the AIDS virus also infects cells of the monocyte/macrophage lineage. These include blood monocytes and macrophages, Langerhans cells in the skin, lung macrophages, brain macrophages, and follicular dendritic cells in lymph nodes. It is also possible the the virus infects some B lymphocytes, brain astrocytes and microglia, and T8 cells that have been transformed by a different human retrovirus, HTLV-I.

Some of these cells may actually be killed by the AIDS virus, perhaps those with a high concentration of T4 receptors, as Jeffrey Lifson of Stanford University and his colleagues recently reported (*Science*, 30 May, p. 1123) and as William Haseltine of the Dana-Farber Cancer Institute at Harvard suggested at the Paris meeting. Some cell types may be infected but not killed, the latter group possibly serving as reservoirs for the virus. Robert Gallo of the National Cancer Institute (NCI) and his collaborators propose that the AIDS virus may infect cells of the monocyte/macrophage lineage first, and then go on to infect T lymphocytes (*Science*, 11 July, p. 215).

Clinical researchers are studying not only patterns of infection in the population but also how the disease progresses within individuals. For instance, it is apparent that some people who are infected remain free of clinical symptoms for long periods of time while others succumb quickly. One possible explanation for this difference may be due to variations in the immune response to the AIDS virus.

In general, AIDS patients tend to make antibodies against both envelope and core proteins of the virus early in the disease when they are free of clinical symptoms. As the disease progresses, symptoms appear, including swollen lymph nodes, multiple bacterial, viral or fungal infections, secondary cancers, and dementia. By the time they develop such symptoms, many patients' antibodies to core proteins have declined while anti-envelope protein antibodies remain.

Unsuspected Prevalence of AIDS in Africa

"Today we know that AIDS is present almost everywhere in Africa," says Bila Kapita of Mama Yeno Hospital in Kinshasa, Zaire. "But the question remains, how many AIDS cases are there in Africa? The entire scope of the AIDS problem is not yet known."

Part of the reason for uncertainty about the extent of the disease in Africa is "willful silence, refusal to recognize a problem, and misplaced pride among some governments of African countries," according to Kapita. This has made a true count of the number of AIDS cases impossible. Now, several African researchers are collaborating with American and Belgian scientists in an effort to detect and report cases of AIDS in Africa. Nevertheless, Kapita estimates that the number of people who carry the AIDS virus is much higher in Africa than in Europe or the United States, where the number of infected persons is believed to be 1 to 1.5 million.

Of all the cases of AIDS in Africa that have been reported, 80% are from central and east Africa, 6% from southern Africa, and 14% from other areas.

Using counts of people with antibodies to the AIDS virus, Kapita reports that, even within central Africa, the virus is unequally distributed. For instance, among prostitutes who come to clinics for treatment, 27% in Zaire carry AIDS virus antibodies, 59% in Kenya, and 88% in Rwanda. These percentages are much higher than the prevalence of the virus among the general population, but they do indicate regional variability. Also, young, sexually active city dwellers tend to carry the virus more often than people who live in the country. For example, 18% of tested people in the capital of Rwanda have antibodies, but only 3% in rural areas.

Kapita estimates that 1 to 2% of the entire African population carries the AIDS virus. "We wonder, if in Africa, there are certain environmental factors that promote the disease," he says. "In Africa, we have a hidden epidemic."

Lethal Actions of the AIDS Virus Debated

One of the most competitive areas in AIDS research is the development of a safe and effective vaccine. In order to design the best strategy for making a vaccine, researchers are trying to identify exactly how the virus kills cells. Equipped with this information, they hope to be able to induce the production of antibodies that block some critical stage of the cell-killing process and thus protect against the real AIDS virus.

William Haseltine of the Dana-Farber Cancer Institute at Harvard said, "We must be clever in the way that we make vaccines. When you listen to the vaccine data at this meeting and at future meetings, ask yourself

'Have these vaccine preparations done any better than the virus itself does?' "

His point is that, although people produce antibodies to the AIDS virus when they are infected, their natural antibodies do not protect them from the devastating effects of the virus. Thus, any vaccine that does protect may need to improve upon this "unfortunate trick of nature." If a vaccine does no better than the natural virus, then Haseltine thinks its chances of working are "very slight."

Laurence Lasky and his co-workers at Genentech in South San Francisco demurred. "In spite of Haseltine's relatively pessimistic assessment about the production of an AIDS retrovirus vaccine, our experience with the production of other vaccines led us to attempt to develop a subunit vaccine against AIDS infection," said Lasky (*Science*, 11 July, p. 209).

Lasky went on to describe how the Genentech group induces a line of mammalian cells growing in culture "to secrete a glycosylated form of the AIDS virus envelope protein." Their recombinant protein, gp130, has many carbohydrate residues, thus making it a glycoprotein very similar to the one that surrounds the AIDS virus and the kind of immunogen Haseltine doubts will be effective.

Nevertheless, the Genentech group finds that both guinea pigs and rabbits make antibodies against gp130, and that some of these antibodies prevent replication of the AIDS virus in vitro. These steps are preliminary to testing gp130 in primates, research that Lasky will not say is being done now but indicates is the next obvious thing to try.

Haseltine thinks that although the anti-gp130 antibodies seem to bind well to the AIDS virus, their ability to block viral replication is relatively weak. Lasky acknowledges that the neutralizing power of anti-gp130 antibodies is less than optimal, but thinks the key to protecting an animal or a person against AIDS is to induce antibody production before they are exposed to the real virus. This objective, Lasky thinks, may be met through Genentech's recent efforts.

Entering the fray, Robert Gallo of the National Cancer Institute explained his theory of how the AIDS virus kills cells, remarking that "this is going to be partly in contrast to what my friend Haseltine said in an earlier session of this meeting." Gallo emphasizes that a T4 lymphocyte infected with the AIDS virus may remain alive until it receives another immunological stimulus. At that point the cell begins to make proteins coded for by the AIDS virus that has infected it (*Science*, 11 July, p. 850).

Haseltine, on the other hand, believes that the two most critical steps in killing human cells are binding of the envelope proteins from the AIDS virus and fusion of infected cells. A critical element in his theory is that the infected cell expresses envelope protein from the AIDS virus and that this protein binds to T4 receptors on other cells, whether they are infected or not. Haseltine's data show that cells meeting these criteria fuse with each other to form giant multinucleated cells, and he hypothesizes that an individual cell may undergo a similar process of autofusion.

Thus, if a cell has a high enough density of T4 receptors and it expresses enough of the envelope protein coded for by the virus, then the cell will die. Any vaccine designed to raise antibodies that fail to prevent these processes may not be effective, Haseltine suggests.

Both Haseltine and Gallo agree that if a cell infected with the AIDS virus begins to express viral proteins, it is in trouble. Haseltine proposes that a primary mechanism of cell death is a membrane fusion process, and that infected cells often fuse with each other. Gallo agrees that fusion is part of the cell-killing process, but thinks that many single T4 cells die because they differentiate prematurely in the presence of a second immunological stimulus.

Military Statistics on AIDS in the U.S.

As a result of their program to screen all potential recruits for antibodies to the AIDS virus, U.S. military doctors have compiled an impressive and sobering group of statistics about the prevalence and patterns of AIDS infection in this country. "These military data are important because they express the first cross-sectional look at the epidemiology of the AIDS virus in this country," says Robert Redfield of the Walter Reed Army Medical Center in Washington, D.C.

They find that the ratio of infected men to infected women in their study is about 2.5 to 1, a great contrast to the estimated national average of about 13 infected men for every 1 infected woman. Donald Burke, also of Walter Reed, and Redfield believe the major reason why the two ratios are so different is that the AIDS virus is transmitted very efficiently through normal heterosexual contact.

In support of this concept, the military researchers point to their studies of 34 married couples currently in military service. They find that if one partner in a married couple is infected with the AIDS virus, there is a 40% to 50% chance that the spouse will also become infected. This is true whether the husband or the wife is the first to have the AIDS virus. These data confirm ideas that were resisted for a long time in this country, "that the risk of becoming infected with the AIDS virus is having sex with someone who is infected, male or female," says Redfield.

Another unexpected statistic in this study involves the great degree of geographical variation in the number of people infected with the AIDS virus in the United States. For instance, 1 in 50 people in Manhattan between the ages of 18 and 25 who apply for military service are infected by the AIDS virus. Or expressed in another way, the AIDS virus infects 200 of 10,000 people in Manhattan in this age group, in contrast to the national estimate of 4 infected people per 10,000. The latter statistic is based on data from blood banks.

In the entire New York metropolitan area, 6 of 1000 women and 8 of 1000 men who applied for military service were infected with the AIDS virus. These numbers are 15 to 20 times higher than the national prevalence for the AIDS virus and they also reflect a ratio of females to males that is nearly 1 to 1. Redfield thinks these data indicate that, when the AIDS virus is common in a given area, such as New York City, the number of infected females and males is likely to be very similar.

In general, major cities—New York, San Francisco, Los Angeles, and Washington, D.C., for example—seem to have a high prevalence of infected people. The military survey encompassed the entire country, including many more rural areas such as Idaho, Montana, North and South Dakota, in which very few or no potential recruits were infected.

The new data come from a screening program that began in October of 1985. Since that time, military doctors have tested over 300,000 people, about 261,000 men and 42,000 women, many of whom are between the ages of 18 and 25.

Although the military "has no data on whether their figures include people who are intravenous drug users, they can probably exclude homosexual transmission of the AIDS virus as a major mode among those tested," says Burke. At the very least, the new data from screening potential military recruits and personnel for antibodies to the AIDS virus indicate that the disease is likely be transmitted at an increasing rate within the general population in the United States. ■ **DEBORAH M. BARNES**