

UPDATE

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TITLE The Biology of HIV-1 and its Relationship to Other Human Retroviruses

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STOCKHOLM--All human retroviruses, not just HIV-1, appear to be spreading and by the same mode of transmission as HIV-1, said Robert C. Gallo, M.D., of the U.S. National Cancer Institute (NCI) today at the 4th International Conference on AIDS in Stockholm. A second AIDS virus, HIV-2, appears to be spreading with far less efficiency and probably less pathogenicity than HIV-1.

The first human retrovirus HTLV-I was isolated in 1978 by Dr. Gallo and colleagues. The retrovirus causes T-cell leukemia and central nervous system disease. It is far more prevalent than HIV-2, and testing of blood for HTLV-I prior to transfusion will soon be routine in the United States as it is in some areas of Japan. A new retrovirus, HTLV-V, recently described by scientists in Rome, is related to HTLV-I, and may be linked to a subset of cutaneous T-cell lymphoma.

The pathogenesis of HIV-1 is clearly related to T4 cell and macrophage infection and T4 cell depletion, Dr. Gallo said. (T4 cells and macrophages

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are types of human immune system cells.) Cells related to macrophages such as Langerhans, microglial, and follicular dendritic cells have been confirmed as additional targets of HIV infection.

Dr. Gallo said there are new indications from studies in Italy and the U.S. National Institutes of Health that some small animals may be susceptible to infection, thereby opening up the possibility of new, important animal models for studies of antiviral therapy and vaccines.

Depletion of T4 cells and subsequent profound immunodeficiency remain principal effects of HIV-1 infection. At the present time, Dr. Gallo explained, scientists know that HIV-1 expression is required for cell killing (neither entry nor integration seem sufficient), that expression of the virus requires immune stimulation, and that the envelope of HIV-1 and the CD4 molecule on the cell surface also are required for the killing effect.

Some years ago Dr. Gallo and his co-workers Flossie Wong-Staal, Ph.D., and Mary Harper, Ph.D., showed that only a small number of T4 cells express HIV at any one time (usually less than 1 in 10^4). Now, several indirect mechanisms that may be possible contributing factors to T4 cell depletion have been identified. Last year, Dani Bolognesi, M.D., Duke University, Raleigh, N.C., and his co-workers described antibody-dependent cell killing of uninfected T4 cells due to complex formation of their CD4 and the gp120 envelope, separate from virus particles.

Another mechanism by which T4 cells are depleted has now been found and is being reported by scientists from Dr. Gallo's laboratory at the AIDS Conference.* Recently, Dr. Gallo and co-workers discovered that a new human herpesvirus HBLV, also called HHV-6, is T4 lympholytic. The findings indicate, Dr. Gallo said, that immune suppression resulting from HIV-1 could lead to enhanced replication of HBLV and further T4 killing. In in vitro

studies, he said, HBLV and HTLV-I transactivate the HIV-1 LTR and can infect the same T4 cell as HIV-1. The dual infection of T4 cell may be very crucial for cell killing.

Another after effect of HIV infection is a marked increase in Kaposi's sarcoma. Dr. Gallo said that he and his colleagues and collaborators, especially Shuji Nakamura, M.D., and S. Zaki Salahuddin of NCI, and Peter Biberfeld, M.D., of the Karolinska Institute in Stockholm, have developed exciting new in vitro and in vivo systems for the study of this remarkable multifocal tumor of a mixed-cell population. The results from these studies, Dr. Gallo said, have given new insights into the origin of this tumor as dependent on several growth factors for proliferation of abnormal but probably not initially fully malignant cells. Presentations are being made on these studies at the AIDS conference.**

Since last year, significant advances have occurred in efforts for control of HIV-1 by antiviral therapy, Dr. Gallo said. In this respect, use of the CD4 molecule in soluble form and dextran sulfate to block virus binding and systems for the study of inhibitors of viral reverse transcriptase, protease, and tat function have been rapidly developed, and may offer unique opportunities to interfere with disease progression. A number of papers on these studies are being presented at the AIDS Conference by scientists at the U.S. National Cancer Institute and collaborators.

An international collaborative program (called HIVAC) to develop a vaccine against AIDS was initiated in 1984. Dr. Gallo said that despite the fact that HIV presents one of the most formidable challenges to a successful vaccine (e.g., we now know of biologically significant intrastain variations as well as the well-known interstrain heterogeneity), studies from members of this group have defined one neutralizing epitope (Putney et al., 1986-1988); and three T-cell epitopes (Berzofsky et al., 1988); while other studies

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(Zagury et al., 1988) have made the first attempts to define the immune response in humans to a candidate vaccine. These studies in humans are important, he said, because they have given the most impressive response yet reported in animals or in humans, including broadly reactive neutralization antibodies, broad T-cell response, and in vivo delayed type hypersensitivity.

The two truly major problems are the spread of HIV-1 in Central Africa and among intravenous addicts in the West, Dr Gallo said. For these problems, public education by our governments is the only weapon we have today, though very insufficient. In addition to technical training and resources, more help is needed from concerned individuals, government leaders, and scientists.

* HBLV Infection of T Lymphocytes in vitro: Implications for Involvement in T-Cell Disorders Including AIDS by P. Lusso, E. Tschachler, and R.C. Gallo, National Cancer Institute, Bethesda, Md.; P.D. Markham and F. di Marzo Veronese, Bionetics Research Inc., Rockville, Md.

Elevated HBLV (Human Herpesvirus-6) Antibody in HIV-1 Antibody-Positive Symptomatic and Asymptomatic Individuals by D.V. Ablashi, S.Z. Salahuddin, H.Z. Streicher, G.M. Shearer, and R.C. Gallo, National Cancer Institute, Bethesda, Md.; M. Kaplan, North Shore University Hospital, Long Island, N.Y.; and G.R.F. Krueger, Institute of Pathology, University of Cologne, West Germany.

** Possible Role of Growth Factors and Cytokines in the Pathogenesis of Kaposi's Sarcoma by B. Ensoli, S. Nakamura, S.Z. Salahuddin, F. Wong-Staal, and R.C. Gallo, National Cancer Institute, Bethesda, Md.; and P. Biberfeld, Karolinska Institute, Stockholm, Sweden.

Novel Growth Factor Capable of Inducing in vitro Long-Term Growth of Kaposi's Sarcoma-Derived Endothelial Cells by S. Nakamura, S.Z. Salahuddin, and R.C. Gallo, National Cancer Institute, Bethesda, Md.; and P. Biberfeld, Karolinska Institute, Stockholm, Sweden.

Development of Cloned Endothelial Cells in Long-Term Culture and Their Biological Properties by S.Z. Salahuddin, S. Nakamura, and R.C. Gallo, National Cancer Institute, Bethesda, Md.; and P. Biberfeld, Karolinska Institute, Stockholm, Sweden.

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