Causation of AIDS revealed

Secretary of Health Margaret Heckler announced in Washington this week that the retrovirus responsible for AIDS has been identified by Gallo's group at NIH; Montagnier's group in Paris has helped.

THE greatest obstacle in the study of the acquired immunodeficiency syndrome (AIDS) has been the inability to identify the responsible aetiologic agent. The initial stage of the epidemic has been one of recognition and description[1-5]. The publication of four papers this week in *Science* (dated 4 May) by Dr Robert Gallo (National Cancer Institute) and co-workers on a novel human T-cell lymphotropic retrovirus, HTLV-III, provides compelling evidence for a primary association of this virus with the disease. Preliminary seroepidemologic data indicate that nearly all AIDS patients and patients with AIDS-related disorders such as unexplained generalized lymphadenopathy have antibody to HTLV-III antigens. The prevalence of seropositivity among asymptomatic persons at high risk for AIDS is currently being determined. HTLV-III was readily recovered from a significant number of patients with AIDS and the lymphadenopathy syndrome.

The hypothesis that AIDS is caused by an immunosuppressive retrovirus tropic for helper T-cells has been advanced by Essex and colleagues[6-8]. They showed an increased prevalence of seropositivity among AIDS patients and certain high risk groups, such as haemophiliacs, for antibody which recognized envelope antigens of HTLV-I and HTLV-II. Similarly, Chermann, Montagnier and co-workers at the Pasteur Institute in Paris have reported isolation of lymphadenopathy-associated retrovirus (LAV) from AIDS patients[9,10].

LAV is tropic for helper T-cells. Subsequent characterization will define its relationship to HTLV-III. Proving that HTLV III is the cause of AIDS cannot be readily done in accord with Koch's postulates. Nonetheless, such evidence can be obtained in cases of transfusion-associated AIDS, wherein a person lacking lifestyle risk factors for AIDS contracts the disease after receiving blood from a person who either has AIDS or is at risk for the disorder[11,12]. Demonstration of seropositivity and/or recovery of HTLV III from such donor and recipient pairs will provide further data for causation. Similarly, prospective studies proving that seroconversion, particularly with recovery of HTLV-III, is both a necessary and sufficient event for development of AIDS will allow us to state definitively that this virus is responsible for the syndrome. Based on other viral diseases transmitted by sexual, blood and needle routes, such as hepatitis-B, we can expect a spectrum of clinical manifestations following HTLV III infection. Host or environmental factors may well modulate susceptibility and severity of clinical disease. Indeed, HTLV I is isolated from seropositive persons in endemic areas of Japan and the Caribbean who do not develop adult T-cell leukaemia.

The geographic distribution of AIDS is an unusual one, particularly the occurrence of the disease in Haiti and Central Africa[13]. Identification of a region with high seropositivity among the general population should provide circumstantial evidence regarding the geographic origin of the virus. Although HTLV I and HTLV II have been recovered from homosexual men with AIDS in the United States it is unlikely that the seropositivity reported by Essex and co-workers among such high-risk persons using an indirect fluorescence assay was acutally measuring antibody cross-reactivity to HTLV III.

AIDS research can now shift from studying indirect manifestations of the AIDS agent to a direct examination of the interaction of HTLV III with T-lymphocyte subpopulations, B-cells, monocyte-macrophages and haematopoietic stem cells. All of these cell types have been noted to be dysfunctional in AIDS, and understanding how this virus disrupts so many immune responses should provide important insights into the murky web of interacting cell populations. We can also now ask whether infection with HTLV III is permanent or transient, and whether persistent infection is a requirement for development of clinical disease. Epidemiologically, data have been accumulated indicating a hierarchy of risk for AIDS upon exposure to body secretions and excretions with semen, stool and blood thought to be the most contagious substances. With direct identification of the causative virus, we can now verify how the disease is transmitted and whether surface fluids such as sweat, saliva and tears could be infectious.

It has often been said that AIDS offers a unique opportunity to understand basic mechanisms of the interaction of the cellular immune system with infectious agents and in the pathogenesis of certain neoplasms. Is there a direct role for HTLV III in the genesis of Kaposi's sarcoma or B-cell lymphomas, frequent tumours in these patients? These neoplasms are epidemiologically related to cytomegalovirus and Epstein–Barr virus respectively. Is there a direct interaction between DNA viruses and retroviruses such as HTLV III? Will therapy directed against HTLV III, with improvement or restoration of immune status, result in the body's own defence mechanisms limiting such neoplasms?

At present, there is no effective therapy for AIDS. Determining the effects of various therapeutic agents, such as alpha and gamma interferons and interleukin-2, on HTLV III infected lymphocytes may provide direction for development of rational therapy for the syndrome. Furthermore, studying whether antibody is protective against HTLV-III infection will determine the utility of vaccination. Certain monkeys may be amenable to HTLV-III infection and serve as models for vaccination in man. But given the apparently long incubation period of AIDS[12], it will be difficult to determine whether seropositive individuals who do not have recoverable virus are indeed protected.

The psychological, economic and logistical impact of identification of the cause of AIDS is formidable[14]. It is estimated that there are now 10–20 million sexually active homosexual men, 15,000 haemophiliacs, 500,000 Haitians, and 4 million blood donors in the United States. Screening such populations is a staggering enterprise. Not yet fully knowing the ultimate clinical significance of seropositivity and/or recoverable virus in such populations will compound the complexities of testing. Difficult lifestyle questions concerning continued sexual activity will certainly arise for seropositive persons.

AIDS is a tragic disease with considerable morbidity and mortality. The work by Gallo and colleagues constitutes a turning point in the struggle with this epidemic. Identification of its cause should rapidly provide accurate information on the extent and pathogenesis of the disorder; prevention and therapy will require long-term efforts.

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