Hypothesis:
The Pathogenesis of AIDS.
Activation of the T- and B-Cell Cascades

ALFRED S. EVANS, M.D., M.P.H.

John Rodman Paul Professor of Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut

Received September 7, 1983

The hypothesis is presented that a human T-cell leukemia virus (HTLV) or a related agent produces a lytic response of T cells manifested by the acquired immunodeficiency syndrome (AIDS) and a proliferative response represented by the adult leukemia/lymphoma (ATL) syndromes. The sequence or cascade of T-cell events following loss of T4 helper cells in AIDS includes reactivation of Epstein-Barr virus and a B-cell cascade of cytomegalovirus, resulting in Kaposi sarcoma in genetically susceptible persons, and of other intracellular agents (CNS viruses, M. avium intracellulare, T. gondii); opportunistic infections also occur. A comparison of AIDS and ATL syndromes is presented and the details of the B-cell cascade are outlined.

The usefulness of prospective serological/immunological studies is discussed in an effort to determine the temporal sequence of infection by the candidate agents and their relation to the appearance of T4/T8 reversal and of the clinical features of AIDS.

A total of 3,000 cases and 1,283 deaths (43 percent) from the acquired immune deficiency syndrome (AIDS) have been reported from 42 states, the District of Columbia, and Puerto Rico from June 1981 to December 19, 1983 [1] that meet the Centers for Disease Control definition. This does not include 42 children under five years with an AIDS-like syndrome. Figure 1 presents the sequence of events as recorded in periodic reports from the Centers for Disease Control up to June 1983. The cause or causes of this syndrome are currently unknown, as is its pathogenesis and the sequence of immunological events. This paper proposes that a human T-cell leukemia-like virus is one cause of AIDS. The general concept is advanced that HTLV infection of T4 lymphocytes and EBV infection of B lymphocytes can lead to a proliferative or lytic response depending on the circumstances of infection, each of which may lead to a cascade of secondary events. The possible consequences of B-cell infection by EBV have been presented previously [2-5].

THE T-CELL CASCADE

The possibility of a virus capable of inducing a proliferative sequence in T lymphocytes in humans was suggested by the lymphatic tumors produced in non-human primates by Herpes atelis and H. saimiri viruses and in herpes infections of other animals [6]. Two new developments suggest a T-cell retrovirus may cause

317

The concepts in this paper have arisen while working on EBV under research grants from the National Institutes of Health, the most current of which is CA 30433.

Address reprint requests to A.S. Evans, M.D., 60 College Street, Box 3333, New Haven, CT 06510

Copyright ©1984 by The Yale Journal of Biology and Medicine, Inc.

All rights of reproduction in any form reserved.
null
homosexual practices. Fortunately, no spread to hospital personnel or casual contacts of AIDS patients has been reported. Probably the agent is not as contagious as HBV in these circumstances. Immunologically, AIDS is characterized by a reversal of the helper (OKT4): suppressor (OKT8) ratio [13]. Whether the primary event is a decrease in helper cells, as might occur from the direct lytic effect of a virus, or an early increase in suppressor and cytotoxic T cells which then leads to decreased helper T cells is under study. Asymptomatic reversal of the helper: suppressor ratio is common in homosexuals [13] but clinically severe and often fatal manifestations appear which include *Pneumocystis carinii*, cerebral toxoplasmosis, Kaposi sarcomas and B-cell lymphomas, and a wide variety of other opportunistic infections. B lymphocytes are also involved in AIDS, as shown by an increased number of cells secreting immunoglobulins and decreased B-cell proliferative responses to T-cell-independent B-cell mitogens; this evidence is suggestive of an *in vitro* polyclonal activation of B cells [14].

There is increasing interest in the possibility that some cases of AIDS are due to a "new" virus or viruses capable of infecting T cells and possibly imported from the Caribbean or Haiti. HTLV or a related agent is one good biological and geographic candidate for the causative virus in AIDS; other causative agents may also exist. Given a specific virus capable of infecting T cells, especially helper T cells, one can imagine a sequence of events that could lead to the various manifestations of AIDS and predict new ones. Figure 2 represents a hypothetical T-cell cascade. The concept of a T-cell cascade was suggested by Pagano [15] and HTLV as a possible cause proposed by Gellman and Gallo [16] at a recent meeting in New York City. HTLV apparently infects helper cells preferentially [7]. As this essay is being completed, scientific evidence supporting the possible role of HTLV in AIDS has appeared from the National Cancer Institute and other centers [17] as well as possible evidence of person-to-person [18-19] and perinatal transmission [19]. The details of this relationship to HTLV have just been published in a series of five papers in *Science* [20-24].
They document the presence of antibody to cell membrane antigens of HTLV in sera from 19 of 75 AIDS patients (25.3 percent) and in 6 of 23 (26 percent) of patients with the lymphadenopathy syndrome (LAS) as compared with only 1 of 71 matched and 0/118 unmatched homosexual controls and in none of 139 blood donors [21]; HTLV-DNA or viral isolates have been found in 3/35 AIDS patients, one of which has been identified as HTLV-1 [23]; a French group has isolated another distinct type of HTLV from the lymph node of a patient with LAS which cross-reacted serologically with HTLV-1 antigens [24]. These results suggest a possible pathogenic role of HTLV-like retroviruses in AIDS but don't exclude the possibility that HTLV-like agents are secondary invaders. The presence of antibody to HTLV in only 25.3 percent of AIDS patients could be due to lack of sensitivity of the test, to HTLV-like agents that don't react to the antigen used, or to the existence of other causative agents. The low isolation rate of only 8.6 percent could be due to lack of sensitivity to the test system, to loss or destruction of T4 infected cells, or to other causes. Confirmation and extension of the data by others will be needed as well as prospective, incidence studies as discussed later in this paper.

The following discussion is based on the hypothesis that HTLV or related agent is one of the causes of AIDS. Infection of T4 (helper) cells by such a virus might initiate either a proliferative T-cell response resulting in the adult leukemia/lymphoma (ATL) syndrome [8] or a lytic response leading to AIDS. The ATL syndrome is seen primarily in adults of both sexes, in Japanese in southern Japan, and in the Caribbean islands and southern U.S. [8,9]. AIDS has been recognized primarily in young and middle-aged adult males in the U.S., Haiti, and some foreign countries. No outbreak of the AIDS syndrome has been reported from southern Japan where up to 30 percent of healthy adults including both males and females have HTLV antibody [8,9] although one case has recently been noted [25]. The factors that lead to a lytic or proliferative response to HTLV are unknown, as are the different geographic and ethnic differences. Certainly, behavioral and sexual practices differ, as could the portal of entry of the agent in the leukemia/lymphoma syndrome and in AIDS, or a different strain of HTLV is involved that is lytic.

The factors resulting in a direct lytic effect of HTLV-like virus in AIDS could be due to antigenic bombardment with diverse infectious agents as seen in many active urban homosexuals, to an unusual portal of entry of HTLV, or to large dosage of the virus (many and multiple partners). The trauma and bleeding associated with active anal intercourse in the passive partner could lead to viral entry into the blood stream. The occurrence of AIDS in hemophiliacs might be related to repeated administrations of Factor VIII or blood transfusions which might contain HTLV; in Haitians the factors are unclear but are probably behavioral rather than ethnic in character. The lytic effect could also be a secondary event resulting from an initial increase in suppressor and cytotoxic T-cell activity, as seen in infectious mononucleosis [1-5,26-27] and due to neo-antigens induced on T cells by HTLV, or to other agents. Whatever its genesis, the lytic effect on helper T cells impairs a key link in our cell-mediated immune system. This could lead to (1) impaired surveillance of malignant cells, (2) reactivation of latent viruses, especially herpes viruses and latent CNS viruses, (3) reactivation of certain intracellular agents (M. avium intracellulari, T. gondii) and other opportunistic infections (Pneumocystis carinii, candida, and the like), and (4) impairment of the primary immune response to these agents. This latter problem is of major importance in homosexuals who are exposed to multiple partners, multiple antigens, and multiple portals of entry. The reactivation of EBV
and cytomegalovirus (CMV) is of special interest. EBV reactivation in B lymphocytes could lead to polyclonal B-cell proliferation [14], high EBV antibody titers, and the whole cascade of EBV events as discussed below. CMV reactivation, or the lack of control of a primary infection, might be manifested as an acute CMV mononucleosis syndrome, as lymphadenitis, or, in a more chronic phase, as Kaposi's sarcoma [14]. Like T. gondii, latent viruses in the central nervous systems also might reactivate such pathogens as papova and measles viruses, leading to progressive multifocal leukoencephalopathy (PML) and subacute sclerosing panencephalitis (SSPE). The potential spectrum of the acute and chronic consequences of AIDS is not yet fully known and as more persons with T4/T8 disturbances are followed longer, new manifestations may be recognized. The current status of HTLV in leukemia/lymphoma and in AIDS has been well summarized in a recent editorial [26].

THE B-CELL CASCADE

Re-activation of Epstein-Barr virus (EBV) present in infected B cells may occur in patients with AIDS as manifested by an increase in EBV antibody titer, by polyclonal expansion of B cells, immunoglobulin production, and by the appearance of B-cell lymphomas. The cascade of events following primary EBV infection can be of proliferative or, less commonly, of a lytic nature. These possible outcomes are presented in Fig. 3 as derived from previous work [2–4].

The proliferative events include the transformation and “immortalization” of B lymphocytes and a polyclonal B-cell expansion. A wide spectrum of antibodies are produced by B cells, including antibodies to various EBV antigens, the heterophile antibody, and a variety of auto-antibodies [2]. The induction of new antigens on the surface of B cells by EBV evokes a vigorous T-cell response in older children and young adults that is manifested as infectious mononucleosis. These proliferative events are usually brought under control through suppressor and cytotoxic T-lymphocyte activity as well as non-specific “killer” T lymphocytes early in disease. This makes infectious mononucleosis usually a benign and self-limited disease [2,27,28].

THE B CELL CASCADE

![Diagram of the B-cell cascade](image)

FIG. 3. Hypothetical sequence of events following infection of B lymphocytes by Epstein-Barr virus (EBV)
When B-cell proliferation is left unchecked as a result of a genetic (X-linked) or an acquired defect in T-cell responsiveness, then acute lymphoblastic sarcoma may result [29-31]. When EBV infection occurs early in infancy in Africa there may be impairment of an appropriate cytotoxic and suppressor T-cell response and an augmentation of B-cell proliferation from the polyclonal B-cell mitogenic effect of holendemic malaria [32]. This leads to a chromosomal change in the rapidly proliferating B cells, usually a translocation of a piece of chromosome 8 to chromosome 14 (14q+ translocation) which renders one B cell malignant, and the monoclonal tumor known as African Burkitt lymphoma (ABL) arises from this event, with a peak around age seven to nine [33]. There is also strong virologic association of EBV to nasopharyngeal cancer manifested by high antibody titers and the presence of EBV genome in tumor cells [34]. The tumor occurs in adults with tenfold higher incidence in Chinese. High EBV antibodies also occur in 30-40 percent of Hodgkin's disease (HD) [35-36] even prior to diagnoses [37], but the genome has not been demonstrated in HD tissue [38]. The proliferating B cells also produce increased immunoglobulins of various types, EBV and heterophile antibodies, and a plethora of connective tissue and other autoantibodies [39]. The lytic effect may occur in the X-linked lymphoproliferative syndrome [29] and result in B-cell loss, hypogammaglobulinemia, or aplastic anemia.

PROOF OF HYPOTHESIS

The role of HTLV and of other candidate agents (CMV, HBV, and so on) in the causation of AIDS can only be established, in the author's view, by prospective serological/immunological studies as proposed at a recent National Institutes of Health Workshop on the Epidemiology of AIDS [40], or by a suitable laboratory model, if one can be found.

The advantages of prospective (cohort) serological/immunological studies are (1) the incidence of infection, disease, and death can be measured in a defined group of persons, (2) susceptibility can often be determined at the start of the study by the presence or absence of antibody or other markers, (3) the sequence and temporal relation of serologic and immunologic events can be ascertained, (4) the risk of developing a disease can be calculated in relation to seroconversion to various microbial agents as well as to other risk factors, (5) both clues to the etiology and to pathogenesis can be uncovered, (6) given a known etiologic agent the biologic spectrum of response can be measured both quantitatively in terms of severity and qualitatively in terms of the various clinical syndromes manifested, (7) the ratio of inapparent to apparent infection (subclinical:clinical) is determinable, and (8) serum, secretions, and other materials can be obtained serially, frozen away, and tested later. The possible methods of analysis include (1) analysis and testing of the entire cohort at the start, during, and at the end of a defined period, (2) analysis and follow-up of the susceptible group alone, or (3) a case/control analysis based on retrospective analysis and testing of those who developed the disease as compared to persons shown to be susceptible at the start but who did not develop the disease [46].

In the understanding of the etiology of AIDS the most critical issue is the temporal relationship of infection by various candidate agents to the inversion of the T4/T8 ratio and of other immunologic markers (beta 2 microglobulin, alpha interferon, thymosin), and to the development of the clinical symptoms of AIDS. It must be shown that infection with the candidate agent precedes these events, and that the incidence of infection (manifested by viral isolation and/or antibody seroconversion) is significantly higher in those that develop AIDS than in those who do not.
Similar epidemiological techniques have been very useful in establishing the causal role of Epstein-Barr virus (EBV) in infectious mononucleosis [40,41] and in African Burkitt lymphoma [34].

In the study of AIDS, I suggest selection of exposed (homosexual, intravenous drug users, hemophiliacs) and unexposed persons to the known risk factors of AIDS. At the start, one should obtain detailed questionnaire data related to various possible risk factors and appropriate specimens. Next, identify those who are "susceptible" as determined by: (1) no clinical feature of AIDS or its prodrome, (2) normal immune system (normal T4/T8 ratio and/or normal alpha thymosin or acid labile interferon), and (3) absence of antibody to HTLV and normal EBV and CMV antibody levels (if possible to test). This susceptible group should be serially followed for evidence of changes in the immune system and seroconversion or for a rise in titer to candidate agents; of greatest interest are the serologic changes that accompany or precede a detectable change in an immunologic marker, especially T4/T8 alteration. The initial screening for "susceptibility" may be expensive and time-consuming but attention directed at this group alone, rather than the whole cohort, may save money and effort in the end. The need for inclusion of a non-exposed group in the cohort is that serologic and immunologic events unrelated to the etiology of AIDS or antibody increases may occur that play no role in the pathogenesis of AIDS. The endpoints to be determined are the occurrence of infection, of immunologic changes or other markers, and of the clinical manifestations of AIDS. The size of the cohort needed to identify the risk factors and etiologic agent(s) of AIDS is not clear. My estimate is that of 1,000 active urban homosexuals only about 50 percent or 500 would be "susceptible" (with a normal T4/T8 and alpha thymosin level) and that 10 percent of these (50) might be "infected" per year, of whom perhaps 2-10 percent (one to five persons) would develop clinical manifestations of AIDS. For comparison, a prospective study of 1,400 West Point cadets for the role of EBV in infectious mononucleosis showed 437 were susceptible at the start (lacked EBV antibody), 54 were infected during the first year, and there were 15 clinical cases of infectious mononucleosis [42]. Thus, a cohort of considerable size may be required to yield many cases of AIDS. Concentrating on a high-risk, susceptible population and a susceptible heterosexual control group would seem to be the most efficient approach. If AIDS is due to a single transmissible agent then great geographical differences might exist in these estimates, depending upon whether or not the agent has been introduced, the prevalence of infected persons in the community, and the probability of an infected person and a susceptible coming into appropriate contact. As of this writing, five prospective studies with approximately 1,000 homosexuals in each have been funded by NIH in five urban centers. Sera already collected in the hepatitis B vaccine trial in homosexuals in New York City [43] could also be tested to determine if the incidence of HTLV (or other) infection was higher in those persons later developing AIDS than in those remaining normal. Unfortunately, lymphocytes were not collected and frozen away in that study so that the relationship of infection to T4/T8 conversion can not be measured. The study of hemophiliacs who subsequently developed AIDS and of the donors to the pool of Factor VIII, as recently reported [44], provides another opportunity for testing antibody levels in donors and patients as compared with controls. Investigation of high-risk groups other than homosexuals has the advantage of freedom from multiple infections but the disadvantage of a lower risk. Recommendations of the NIH workshop [45] for epidemiological approaches are scheduled for publication in the Journal of Infectious Diseases.
DISCUSSION

In the classical sequence of investigating an epidemic there comes a time when a hypothesis that best fits the assembled facts is made. Then one sets out to prove or disprove the hypothesis. Several other authors have presented theirs on AIDS [46-48]. In general, most investigators feel that the concept of a transmissible agent is the most likely. Among the leading candidate agents and their proponents are cytomegalovirus [48-49], Epstein-Barr virus [46], hepatitis B virus and/or its associated Delta agent [50-51], and a human T-cell leukemia or related retrovirus [21-24]. The hypothesis presented in this paper is that an HTLV-like virus, or related retrovirus, best meets the biological characteristics of the cause of AIDS. In this concept infection of T4 cells leads to the lysis and/or suppression by T8 cells which initiates the reactivation of EBV, CMV, and other latent viral, bacterial, and fungal agents. The major limitation to the current evidence for this, or any other candidate agent, is that only prevalence data for antibody are available. As emphasized at a recent NIH workshop on AIDS [40] and in this paper we need careful, prospective, serologic and immunological studies of susceptible persons (with a normal T4/T8 ratio) who are at high risk in order to ascertain the temporal sequence of infection of various candidate agents in relation to the appearance of changes in the immune system, to various markers (acid labile interferon, beta-2-microglobulin, thymosin), and to the prodromata and early clinical features of AIDS.

There are critics with arguments against the role of HTLV as a cause of AIDS [52]: there is no direct evidence that HTLV is cytopathogenic, that a normal T4/T8 ratio was found in a patient with lymphadenopathy from whom an HTLV virus was isolated, and that the tropism for T cells does not directly explain Kaposi sarcoma, the undifferentiated non-Hodgkin's type of lymphoma, or the Burkitt type of lymphoma reported in AIDS patients (which I think are the result of reactivation of CMV and EBV, respectively). Other critiques state that the antibody has been detected in only 25 percent of AIDS patients, that it may be a cross-reacting, non-HTLV-induced membrane component, and that antibody titers are usually very low, perhaps representing a latent, reactivated virus. These problems may relate to (1) the sensitivity of the test procedure, (2) the use of a HTLV antigen not closely enough related to the retrovirus causing AIDS, and (3) that primary infection leads to a poor humoral response in an immunocompromised homosexual host. It is also true that only a few isolations (about 3 of 33) of HTLV-like viruses have been made from AIDS patients. These poor results may relate to low sensitivity of the isolation techniques for the virus or to the low number of infected T4 cells available when sampled. In my view, the evidence of transmission of AIDS via blood or blood products, even though rare, gives strong support to the concept that an infectious agent in the blood can transmit AIDS even to relatively healthy recipients [43]. If the subclinical: clinical ratio of infection to disease is high, then we must be concerned about the prevalence of unrecognized infection and the duration of an unrecognized infectious state in high-risk populations. I feel that the agent responsible is probably newly introduced into the U.S. and that a HTLV-like agent is a strong candidate for causation.

ADDENDUM

Strong evidence implicating a HTLV-like virus, one termed HTLV-III, has been presented by Gallo and his group at the National Cancer Institute (NCI) in a series of four papers in the May 4, 1984, issue of Science [53-56]. Similar data for a virus
called lymphadenopathy virus (LAV) are emerging from Vilmer et al. at the Pasteur Institute [57,58]. It is probable that HTLV-III and LAV are closely related, if not identical. The NCI group has isolated HTLV from 18/25 (72 percent) of pre-AIDS patients, 22/26 (85 percent) of AIDS patients, 0/115 heterosexuals, and one of 22 healthy homosexuals (the one positive later developed AIDS); the French have 12 isolates. Serologically 43/49 (88 percent) of AIDS patients have antibody to HTLV-III as well as 11/14 (79 percent) of mild AIDS, 7/17 (41.2 percent) healthy homosexuals, and only one of 186 (0.5 percent) normal controls. HTLV produces lysis of T4 helper cells and shows serological cross-reactions with membrane tests for HTLV-I and HTLV-II.

REFERENCES

1. Centers for Disease Control: Update: Acquired immuno-deficiency syndrome (AIDS). United States. MMWR 32:689–691, 1984
2. Evans AS, Niederman JC: Epstein-Barr Virus. In Viral Infections of Humans. Epidemiology and Control. Edited by AS Evans. New York, Plenum Press, 2nd Edition, 1982, pp 253–281
3. Evans AS: The spectrum of infections and Epstein-Barr virus. J Inf Dis 124:330–337, 1971
4. Carter RL: Infectious mononucleosis: model for self-limiting lymphoproliferation. Lancet i:846–855, 1975
5. Epstein MA, Achong BG: Pathogenesis of infectious mononucleosis. Lancet ii:1270–1278, 1977
6. Deinhardt F, Deinhardt J: Comparative aspects: oncogenic animal herpes-viruses. In The Epstein-Barr Virus. Edited by MA Epstein, BG Achong. New York, Springer-Verlag, 1979, pp 374–415
7. Reitz MS Jr, Kalyanaraman VS, Robert-Guroff M, et al: Human T-cell leukemia/lymphoma virus: the retroviruses of adult T-cell leukemia/lymphoma. J Inf Dis 147:299–305, 1983
8. Blattner WA, Blayney DW, Robert-Guroff M, et al: Epidemiology of human T-cell leukemia/lymphoma virus. J Inf Dis 147:406–416, 1983
9. Hinuma Y, Nagata K, Hanako K, et al: Adult T-cell leukemia antigen in an ATL cell line and detection of antibodies in human sera. Proc Natl Acad Sci USA 78:6476–6480, 1981
10. Miyoshi I, Kobayashi M, Yoshimoto S, et al: Type C virus particles in a cord T-cell line derived by cocultivating normal human cord leukocytes and human leukemia T-cells. Nature 294:770–771, 1981
11. CDC: Update on acquired immune deficiency syndrome (AIDS). United States. MMWR 31:507–508, 1982
12. CDC: Prevention of acquired immune deficiency syndrome: Report of interagency recommendations. MMWR 32:101–103, 1983
13. Kornfield H, Vade Stouwe RA, Lange M, et al: T-lymphocyte subpopulations in homosexual men. New Eng J Med 307:729–730, 1982
14. Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. New Eng J Med 309:453–458, 1983
15. Pagano J: Consideration on viral etiology: Causes and effects. Presented at Conference on Epidemic Kaposis's sarcoma and opportunistic infections in homosexual men: expression of an acquired immunoregulatory disorder. New York University, New York. March 17–19, 1983
16. Goldmann E, Gallo R: A search for retroviruses in patients with diseases associated with acquired immunodeficiency. Presented at Conference on Epidemic Kaposis's sarcoma and opportunistic infections in homosexual men: expression of an acquired immunoregulatory disorder. New York University, New York. March 17–19, 1983
17. CDC: Human T-cell leukemia virus infections in patients with acquired immune-deficiency syndrome: preliminary observations. MMWR 32:233–234, 1983
18. Oleske J, Minnefor A, Cooper R Jr, Thomas K, dela Cruz A, et al: Immune-deficiency syndrome in children. JAMA 249:2345–2349, 1983
19. Rubinstein A, Sicklick M, Gupta A, Bernstein L, Klein N, Rubinstein E: Acquired immunodeficiency with reserved T4/T8 ratios in infants born to promiscuous and drug-addicted mothers. JAMA 249:2350–2353, 1983
20. Research News: Human T-cell leukemia virus linked to AIDS. Science 220:806–807, 1983
21. Essex M, McLane MF, Lee TH, Falk L, Howe CWS, Mullins JI, Cabrardilla C, Francis DP: Antibodies to cell membrane antigens associated with human T-cell leukemia virus in patients with AIDS. Science 220:859–862, 1983
22. Gellmann EP, Povic M, Blayney D, Masur H, Sidhu G, Stahl RE, Gallo RC: Proviral DNA of a retrovirus, human T-cell leukemia virus, in two patients with AIDS. Science 220:862–865, 1983
23. Gallo R, Sarin PS, Gellmann EP, Robert-Guroff M, Richardson E, Kalyanaraman VS, Mann D, Sidhu G, Stahl RE, Zolla-Pazner S, Leibowitch J, Popovic M: Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science 220:865–866, 1983
24. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L: Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220:868–871, 1983
25. Miyoshi I, Kobayashi M, Yoshimoto S, et al: ATLV in Japanese patients with AIDS. Lancet ii:275, 1983
26. Editorial: HTLV-related disease. Lancet ii:319–321, 1983
27. Thorley-Lawson DA, Chess L, Strominger JL: Suppression of in-vitro Epstein-Barr virus infection. A new role for adult human T lymphocytes. J Exp Med 146:495–507, 1977
28. Tosato G, McGrath I, Koski I, et al: Activation of suppressor T cells during Epstein-Barr-virus-induced infectious mononucleosis. New Eng J Med 301:1133–1137, 1979
29. Pursilto DT, Hutt L, Bhawan J, et al: Immunodeficiency to the Epstein-Barr viruses in the X-linked lymphoproliferative syndrome. Clin Immunol Immunopath 9:147–156, 1978
30. Robinson JE, Brown N, Andiman W, et al: Diffuse polyclonal B-cell lymphoma during primary infection with Epstein-Barr virus. New Eng J Med 320:1293–1296, 1989
31. Snyderman DR, Rudders RA, Daoust P, et al: Infectious mononucleosis in an adult progressing to fatal immunoblastic sarcoma. Ann Int Med 96:737–742, 1982
32. de-Thé G, Geser A, Day NE, et al: Epidemiological evidence for causal relationship between Epstein-Barr virus and Burkitt's lymphoma from Ugandan prospective study. Nature 274:756–761, 1978
33. Miller G: Burkitt lymphoma. In Viral Infections of Humans. Epidemiology and Control. Edited by AS Evans. New York, Plenum Press, 2nd Edition, 1982, pp. 599–619
34. de-Thé G, Ho JHC, Muir CS: Nasopharyngeal carcinoma. In Viral Infections of Humans. Epidemiology and Control. Edited by AS Evans. New York, Plenum Press, 2nd Edition, 1982, pp 621–652
35. Evans AS, Kirchhoff LV, Pannuti CS, Carvalho RPS, McClelland KE: A case-control study of Hodgkin's disease in Brazil. II. Seroepidemiologic studies in cases and family members. Amer J Epid 112:609–618, 1980
36. Henle W, Henle G: Epstein-Barr virus related serology in Hodgkin's disease. In International Symposium on Hodgkin's disease. Int J Cancer 16:323–328, 1975
37. Evans AS, Comstock GW: Presence of elevated antibody titers to Epstein-Barr virus before Hodgkin's disease. Lancet i:1183–1186, 1981
38. Pagano JS, Huang CH, Levine P: Absence of Epstein-Barr viral DNA in American Burkitt's lymphoma. New Eng J Med 289:1395–1399, 1973
39. Kano K, Milgrom F: Heterophile antigens and antibodies in medicine. Curr Topics in Microbiol Immunol 77:43–69, 1979
40. Evans AS: Prospective seroepidemiological studies: Application to studies of AIDS. Presented at NIH Workshop on the Epidemiology of AIDS, September 12–13, 1983
41. Hallee TJ, Evans AS, Niederman JC, Brooks CM, Voegtlly JH: Infectious mononucleosis at the U.S. Military Academy: A prospective study of a single class over four years. Yale J Biol Med 47:182–195, 1974
42. Sawyer RN, Evans AS, Niederman JC, McCollum RW: Prospective studies of a group of Yale University freshmen. I. Occurrence of infectious mononucleosis. J Infect Dis 123:263–269, 1971
43. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, Sadowsky R, Morrison JM, Kellner A: Hepatitis B Vaccine. Demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. New Eng J Med 303:833–841, 1980
44. Curran JW, Lawrence DN, Jaffe H, et al: Acquired immunodeficiency disease (AIDS) associated with transfusions. New Eng J Med 310:69–75, 1984
45. National Institutes of Health Workshop on Epidemiology of AIDS. Rockville, MD, September 12–13, 1983
46. Sonnabend J, Witkin SS, Pursilto DT: Acquired immunodeficiency syndrome, opportunistic infections, and malignancies in male homosexuals. A hypothesis of etiologic factors in pathogenesis. JAMA 249:2370–2374, 1983
47. Levy JA, Zregler JL: Hypothesis. Acquired immunodeficiency syndrome is an opportunistic infection and Kaposi's sarcoma results from secondary immune stimulation. Lancet ii:78–80, 1983
48. Mintz L, Drew WL, Miner RC, Braff EH: Cytomegalovirus infections in homosexual men, an epidemiological study. Ann Int Med 326–329, 1983
49. Macher AM, Reichert CM, Straus SE, Longo DL, Parrillo J, Lane C, Fauci AS, Rook AH, Manischewitz JF, Quinnan GV: Death in the AIDS patient: role of cytomegalovirus. New Eng J Med 1454, 1983
50. McDonald MI, Hamilton JD, Curack DT: Hepatitis B surface antigen could harbour the infective agent of AIDS. Lancet ii:882-885, 1983
51. Ravenholt RT: Role of hepatitis B virus in acquired immunodeficiency syndrome. Lancet ii:885-887, 1983
52. Black DH, Levy EM: The human T-cell leukemia virus and AIDS. New Eng J Med 309:856, 1983
53. Popovic M, Sarngadharan MG, Read E, et al: Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and Pre-AIDS. Science 224:497-500, 1984
54. Gallo RC, Salahuddin SZ, Popovic M, et al: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 224:500-502, 1984
55. Schüpbach J, Popovic M, Gilden RV, et al: Serological analysis of a subgroup of human T-lymphotropic retroviruses (HTLV-III) associated with AIDS. Science 224:503-505, 1984
56. Sarngadharan MG, Popovic M, Bruch L, et al: Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. Science 224:506-508, 1984
57. Marx JL: Strong new candidate for AIDS agent. A newly discovered member of the human T-cell leukemia virus family is very closely linked to the immunodeficiency disease. Science 224:475-477, 1984
58. Vilmer E, Barré-Sinoussi F, Rouzioux C, et al: Isolation of new lymphotropic retrovirus from two siblings with haemophilia B, one with AIDS. Lancet i:753-757, 1984