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Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome: Correlation But Not Causation

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Abstract

AIDS is an acquired immunodeficiency syndrome defined by a severe depletion of T cells and over 20 conventional degenerative and neoplastic diseases. In the U.S. and Europe, AIDS correlates to 95% with risk factors, such as about 8 years of promiscuous male homosexuality, intravenous drug use, or hemophilia. Since AIDS also correlates with antibody to a retrovirus, confirmed in about 40% of American cases, it has been hypothesized that this virus causes AIDS by killing T cells. Consequently, the virus was termed human immunodeficiency virus (HIV), and antibody to HIV became part of the definition of AIDS. The hypothesis that HIV causes AIDS is examined in terms of Koch's postulates and epidemiological, biochemical, genetic, and evolutionary conditions of viral pathology. HIV does not fulfill Koch's postulates: (*i*) free virus is not detectable in most cases of AIDS; (*ii*) virus can only be isolated by reactivating virus *in vitro* from a few latently infected lymphocytes among millions of uninfected ones; (*iii*) pure HIV does not cause AIDS upon experimental infection of chimpanzees or accidental infection of healthy humans. Further, HIV violates classical conditions of viral pathology. (*i*) Epidemiological surveys indicate that the annual incidence of AIDS among antibody-positive persons varies from nearly 0 to over 10%, depending critically on nonviral risk factors. (*ii*) HIV is expressed in ²1 of every 104 T cells it supposedly kills in AIDS, whereas about 5% of all T cells are regenerated during the 2 days it takes the virus to infect a cell. (*ii*) If HIV were the cause of AIDS, it would be the first virus to cause a disease only after the onset of antiviral immunity, as detected by a positive "AIDS test." (*iv*) AIDS follows the onset of antiviral immunity only after long and unpredictable asymptomatic intervals averaging 8 years, although HIV replicates within 1 to 2 days and induces immunity within 1 to 2 months. (*v*) HIV supposedly causes AIDS by killing T cells, although retroviruses can only replicate in viable cells. In fact, infected T cells grown in culture continue to divide. (*vi*) HIV is isogenic with all other retroviruses and does not express a late, AIDS-specific gene. (*vii*) If HIV were to cause AIDS, it would have a paradoxical, country-specific pathology, causing over 90% *Pneumocystis* pneumonia and Kaposi sarcoma in the U.S. but over 90% slim disease, fever, and diarrhea in Africa. (*viii*) It is highly improbable that within the last few years two viruses (HIV-I and HIV-2) that are only 40% sequence-related would have evolved that could both cause the newly defined syndrome AIDS. Also, viruses are improbable that kill their only natural host with efficiencies of 50-100%, as is claimed for HIVs. It is concluded that HIV is not sufficient for AIDS and that it may not even be necessary for AIDS because its activity is just as low in symptomatic carriers as in asymptomatic carriers. The correlation between antibody to HIV and AIDS does not prove causation, because otherwise indistinguishable diseases are now set apart only on the basis of this antibody. I propose that AIDS is not a contagious syndrome caused by one conventional virus or microbe. No such virus or microbe would require almost a decade to cause primary disease, nor could it cause the diverse collection of AIDS diseases. Neither would its host range be as selective as that of AIDS, nor could it survive if it were as inefficiently transmitted as AIDS. Since AIDS is defined by new combinations of conventional diseases, it may be caused by new combinations of conventional pathogens, including acute viral or microbial infections and chronic drug use and malnutrition. The long and unpredictable intervals between infection with HIV and AIDS would then reflect the thresholds for these pathogenic factors to cause AIDS diseases, instead of an unlikely mechanism of HIV pathogenesis.

Introduction

The important thing is to not stop questioning.
-Albert Einstein

In 1981, acquired immunodeficiency was proposed to be the common denominator of a newly defined syndrome (AIDS) of diseases that were on the rise in promiscuous male homosexuals and intravenous drug users, referred to as "AIDS risk groups" (1, 2). Since then, about 70,000 persons have developed AIDS in the U.S., of whom over 90% are still from these same risk groups (3, 4). The hallmark of AIDS is a severe depletion of T cells (3, 5-7). By definition, this immunodeficiency manifests itself in over 20 previously known degenerative and neoplastic diseases, including Kaposi sarcoma, Burkitt and other lymphomas, *Pneumocystis* pneumonia, diarrhea, dementia, candidiasis, tuberculosis, lymphadenopathy, slim disease, fever, herpes, and many others (5, 7-11). The frequent reference to AIDS as a new disease (12-14), instead of a new syndrome composed of old diseases, has inspired a search for a single new pathogen (12). However, it is debatable whether a single pathogen can explain over 20 diseases, whether a clustering of old diseases in risk groups that only recently became visible signals a new pathogen, and whether an AIDS pathogen must be infectious. Indeed, compared to conventional infectious diseases, AIDS is very difficult to acquire and has a very selective host range, usually manifesting only in individuals who have taken AIDS risks for an average of 8 years (see below).

The Virus-AIDS Hypothesis. About 40% of the AIDS patients in the U.S. (5), and many of those who are at risk for AIDS, have been confirmed to have neutralizing antibodies to a retrovirus (3, 7) that was discovered in 1983 (15). These antibodies are detected by the "AIDS test" (3). Less than a year later, in 1984, this virus was adopted as the cause of AIDS by the U.S. Department of Health and Human Services and the AIDS test was registered as a patent, even before the first American study on the virus was published (16). The epidemiological correlation between these antibodies and AIDS is the primary basis for the hypothesis that AIDS is caused by this virus (3, 7, 12, 14, 17, 18). AIDS is also believed to be caused by this virus because AIDS diseases appear in a small percentage (see below) of recipients of blood transfusions that have antibodies to this virus (3, 12, 19-22). In view of this the virus has been named human immunodeficiency virus (HIV) by an international committee of retrovirologists (18) and antibody to HIV became part of the definition of AIDS (3, 5, 7). "... Patients are excluded as AIDS cases if they have a negative result(s) on testing for serum antibody to HIV, do not have a positive culture for HIV" (3). If confirmed, HIV would be the first clinically relevant retrovirus since the Virus-Cancer Program called for viral carcinogens in 1971 (23, 24).

The virus-AIDS hypothesis holds that the retrovirus HIV causes AIDS by killing T cells in the manner of a cytocidal virus (3, 6, 7, 12, 18) and is transmitted by sex and parenteral exposure (3, 7, 12, 19, 22). Early evidence for a T cell-specific HIV receptor lent support to this hypothesis (25). Recently, however, the presumed T cell specificity of HIV has lost ground, as HIV is only barely detectable in T cells and often is detectable only in monocytes (26-28) and other body cells (23, 29-32), displaying the same lack of virulence and broad host range toward differentiated cells as all other human and animal retroviruses (17, 23). In about 50% of those who habitually practice risk behavior or regularly receive transfusions, AIDS is estimated to occur after an average asymptomatic period of about 8 years from the onset of antiviral immunity, and in up to 100% after about 15 years (5-7, 20-22, 33-38). Therefore, HIV is called a "slow" virus, or lentivirus (40). It is on the basis of the relatively high conversion rates of these risk groups that every asymptomatic infection by HIV is now being called "HIV disease" (7), and that some are subjected to chemotherapy (39). Nevertheless, individual asymptomatic periods are unpredictable, ranging from <1 to >15 years (22, 33-38). Once AIDS is diagnosed, the mean life expectancy is about 1 year (35).

The early adoption of the virus-AIDS hypothesis by the U.S. Department of Health and Human Services (16) and by retrovirologists (17, 18) is the probable reason that the hypothesis was generally accepted without scrutiny. For instance, the virus is typically referred to as deadly by the popular press (41, 42) and public enemy number 1 by the U.S. Department of Health and Human Services (43). In view of this, it is surprising that the virus has yet to cause the first AIDS case among hundreds of unvaccinated scientists who have propagated it for the past 5 years at titers that exceed those in AIDS patients by up to 6 orders of magnitude (see below) with no more containment than is required for marginally pathogenic animal viruses (44). It is also surprising that despite 2000 recorded (and probably many more unrecorded) parenteral exposures to HIV-infected materials, unvaccinated health care workers have exactly the same incidence of AIDS as the rest of the U.S. labor force (19, 22, 45, 186). Further, it is difficult to believe that a sexually transmitted virus (7, 12) would not have caused more than 1649 sex-linked AIDS cases among the 125 million American women in 8 years (4)-and this number is not even corrected for the antibody-negative women who might have developed such diseases over an 8-year period. Moreover, it is paradoxical for a supposedly new viral epidemic (12-14) that the estimates of infected persons in the U.S. have remained constant at 0.5 to 1.5 million (46, 47) or even declined to <1 million (7, 38) since the "AIDS test" became available in 1985.

About 2 years ago I proposed that HIV is not likely to be the cause of AIDS (23, 48-50, 180). This proposal has since been fiercely challenged or defended at meetings and in publications (14, 32, 51-65, 180). Here I respond to these challenges.

HIV Does Not Meet Koch's Postulates

HIV Cannot Account for the Loss of T Cells and the Clinical Course of AIDS. The causative agent of an infectious disease is classically defined by the postulates of Robert Koch and Jacob Henle (66, 67). They were originally formulated *a priori* by Henle about 50 years before bacteria and viruses were discovered to be pathogens (67). However, their definitive text was formulated by Koch to distinguish causative from other bacteria at a time when bacteriologists applying newly developed tools in the search for pathogenic microbes found all sorts of bacteria in humans. This situation was quite similar to our current increasing proficiency in demonstrating viruses (68). The first of these postulates states that "the parasite must be present in every single case of the disease, under conditions that can account for the pathological lesions and the clinical course of the disease" (67). However, there is no free virus in most-and very little in some-persons with AIDS, or in asymptomatic carriers (69, 70). Virus titers range from 0 to 10 infectious units per milliliter of blood (69, 70). Viral RNA is found in a very low percentage (see below) of blood cells of 50-80% of antibody-positive persons (71-74, 187). Further, no provirus is detectable in blood cells of 70-100% of symptomatic or asymptomatic antibody-positive persons, if tested by direct hybridization of cellular DNA with cloned proviral DNA (73, 75, 187) at the limit of detection by this method (76). Antibody to HIV is confirmed in only about 40% of the U.S. cases and in only 7% of the AIDS cases from New York and San Francisco, which represent one-third of all U.S. cases (5). In some cases, even the antibody to HIV disappears, due to chronic dormancy or loss of the HIV provirus (77, 78)-analogous to the loss of antibody to other viruses long after infection. Indeed, the Centers for Disease Control publishes specific guidelines for AIDS cases in which laboratory evidence for HIV is totally negative (5). Thus, although viral elements can be traced in many AIDS

patients, and antibody to HIV is, at least by definition, present in all of them, HIV violates Koch's first postulate in terms of a tangible presence, of being "under conditions that can account for" the loss of T cells, and of the "clinical course of the disease" that lags 8 years behind infection.

The absence of free virus in most AIDS cases and in antibody-positive asymptomatic carriers explains why HIV is not casually transmitted (19, 22, 23, 35). For example, the probability of transmission of the virus from an antibody-positive to an antibody-negative person by heterosexual intercourse is estimated to be 1 in 500 (79, 80).

Due to Extremely Low Titers, HIV Can Be Isolated Only with Great Difficulty from AIDS Patients. Koch further postulated that it must be possible to isolate and propagate the etiological agent from all cases of the disease. However, virus isolation, although possible in up to 80% of AIDS cases, is technically very difficult and is perhaps best described as maieutic (23, 69, 70, 81-84). It depends on reactivation of dormant proviruses from one or a few latently infected lymphocytes among millions of uninfected lymphocytes from AIDS patients. This is only possible by culturing these cells for several weeks *in vitro,* away from the suppressive, virus-neutralizing immune system of the host (23, 48-50). Even then success sometimes comes only after 15 (!) trials (85). These difficulties and the often over 20% failure rate (84) in isolation of HIV from AIDS patients are consistent with the extremely low titers of HIV in such patients. Thus, HIV does not meet Koch's second postulate.

In vitro reactivation of latent HIV from antibody-positive persons is exactly analogous to the *in vitro* reactivation of latent Epstein-Barr virus (EBV) from healthy persons with antibody to EBV (86). As in the case of HIV (see below), acute EBV infections occasionally cause mononucleosis (86-88). Subsequent antiviral immunity restricts EBV to chronic latency (86). Since latent EBV, again like latent HIV, is present in only 1 of 107 lymphocytes, millions of these cells must be cultivated *in vitro* to reactivate the virus (86).

HIV Does Not Reproduce AIDS When Inoculated into Animals or Humans. *Animal infections.* Koch's third postulate calls for inducing the disease by experimental infection of a suitable host with pure pathogen. Chimpanzees infected with pure HIV develop antibodies, indicating that they are susceptible to HIV. However, all attempts to cause AIDS in chimpanzees have been unsuccessful, even after they have been antibody-positive for 4 to 5 years (23). Thus, Koch's third postulate has not been fulfilled in animals.

Accidental human infections. Due to the extremely low titers of HIV in all antibody-positive materials, very few infections have occurred. Four women who received infected donor semen in 1984 developed antibody to HIV. Yet none of them developed AIDS or transmitted the virus to their husbands, although insufficient time has elapsed for the average latent period that the virus is thought to require to cause AIDS (see below). Moreover, three of these women subsequently became pregnant and gave birth to healthy infants (89). Further, 15 to 20 accidental infections of health care workers and scientists propagating HIV were identified during the last 4 years on the basis of antiviral antibodies, and none of these people have developed AIDS (19, 22, 23, 45, 85, 90, 186).

Recently, a single conversion to AIDS of such an antibody-positive health care worker was reported anonymously without data on gender, latent period, or AIDS symptoms (45). This case was claimed to prove Koch's third postulate (14). However, 2586 health care workers got AIDS without occupational infection. About 95% of these fall into the conventional risk groups and 5% are without verifiable AIDS risks (4, 45)-which are notoriously difficult to verify (91, 92). From the 135 (5% of 2586) health care workers who developed AIDS without verifiable risks, the one who contracted an occupational infection was selected to prove that such infections, rather than other risks, caused AIDS. It is arbitrary to base a hypothesis on 1 case when 134 cases do not support the hypothesis. To prove the hypothesis, it is necessary to show that the percentage of health care workers with AIDS who do not belong to the known risk groups exceeds that of the rest of the population and reflects their sexual distribution. However, the incidence and even the sexual distribution of AIDS cases among health care workers are exactly the same as that of AIDS in the general population (4), namely 92% males, although 75% of the health care workers are female (45). Moreover, a subsequent study (186) that included this case described only transient, mononucleosis-like symptoms but not one AIDS case among occupationally infected health care workers.

Blood transfusions are another source of iatrogenic infections. The best-documented cases are the 10,000 to 14,000 U.S. hemophiliacs with antibody to HIV (19, 38, 47, 93, 94), of whom only 646 developed symptoms of AIDS between 1981 and August 1988 (4). During the year that ended in August 1988, 290 developed AIDS, whereas 178 developed AIDS in the previous year (4). This corresponds to annual conversion rates of about 1-3%. Higher rates, of up to 25%, have been observed in certain groups of hemophiliacs (20, 21, 35, 36, 38). However, the view that AIDS in recipients of transfusions is due to HIV transmission is presumptive on several grounds. (*i*) Blood transfusion does not distinguish between HIV and other undetected viruses, microbes, and blood-borne toxins. This is particularly true since HIV-positive blood was never knowingly transfused. (*ii*) It is presumed that the recipients had no AIDS risks other than HIV during the average of 8 years between HIV infection and AIDS symptoms (20, 21). The transfusion evidence would be more convincing if AIDS appeared in step with virus replication (see below) soon after a singular transfusion. (*iii*) Transfusion-related AIDS cases occur primarily in persons with other health risks, such as hemophilia, that are not representative of healthy individuals. (*iv*) Above all, the transfusion cases are all anecdotal (95, 96). There are no controlled studies to show that recipients of transfusions with antibody to HIV have more of the diseases now called AIDS than those without antibody to HIV.

The assertion that HIV causes AIDS is also contained in the erroneous claims that new cases of transfusion AIDS have virtually ceased appearing since the AIDS test became available in 1985 (12, 14), due to a factor-of-40 reduction of transfusions with antibody-positive blood (95). In fact, adult transfusion AIDS cases have doubled and pediatric cases have tripled in the year ending August 8, compared to the previous year (4, 49). The increase in adult cases could be expected if one were to accept the assumptions that HIV requires 8 years to cause AIDS (see

below) and that there was a rapid increase in unconfirmed HIV transfusions 8 years ago, which stopped 3 years ago. However, the increase in pediatric cases in the face of a 40-fold reduction of antibody-positive transfusions argues directly against HIV as the cause of AIDS, because the average latent period in children is only 2 years (21, 36).

HIV Does Not Meet Established Epidemiological, Biochemical, Genetic, and Evolutionary Criteria of a Viral Pathogen

Epidemiologies of AIDS and HIV Are Not Consistent. Epidemiology has been proposed as adequate to identify causative agents, particularly in human diseases where Koch's postulates are difficult to meet (67), as in the case of HIV (12, 14, 32). Nevertheless, even a consistent correlation with virus-not with antibody-would fulfill only the first postulate. However, the epidemiologies of AIDS and HIV are not consistent in different risk groups and countries.

About 10% of the 30 million people in Zaire have been reported since 1985 to be antibody-positive (46, 98, 184). However, only 335 AIDS cases have been reported in Zaire as of 1988 (97, 99). This corresponds to an annual conversion rate of 0.004%. Also, since 1985, 6% of the 6 million Haitians have been reported to be antibody-positive (46,100), but only 912 had developed AIDS by 1988 (97). This corresponds to an annual conversion rate of 0.1%. of 0.5 to 1.5 million antibody-positive Americans, about 29,000 [including 9000 who meet only the 1987 definition for AIDS (5)] developed AIDS in the year ending August 1988, and, according to earlier definitions, 16,000 to 17,000 developed AIDS in each of the previous 2 years (4). This corresponds to an annual conversion rate of about 1.5% for the average antibody-positive American. Thus, the AIDS risk of an antibody-positive person varies with the country of residence. These calculations all assume that the pools of short- and long-term HIV carriers in each of these countries are comparable. This assumption is based on the claims that HIV was newly introduced into all countries with AIDS about 10 to 20 years ago (3, 7, 12-14).

Moreover, the AIDS risk of an antibody-positive American varies a great deal with his or her risk group. For example, 3-25% of antibody-positive Americans who habitually practice risk behavior or are hemophiliacs develop AIDS annually (7, 21, 22, 33-38). Thus, the 1.5% annual conversion rate of antibody-positive Americans is an average of minorities with high conversion rates of 3-25% and a majority with a conversion rate close to 0%.

Since the incidence of AIDS among antibody-positive persons varies from 0 to over 10% depending on factors defined by lifestyle, health, and country of residence (35), it follows that HIV is not sufficient to cause AIDS.

AIDS Occurs Despite Minimal Viral Activity. During replication, viruses are biochemically very active in the host cell. If they replicate in more cells than the host can spare or regenerate, they typically cause a disease (48, 86).

Paradoxically, HIV is very inactive even when it is said to cause fatal immunodeficiency. Viral RNA synthesis is detectable in only 1 of 104 to 106 mononuclear lymphocytes, including T cells (71-74). Frequently, virus can only be found in monocytes, and not in T cells (26-28). Virus expression recorded in monocyte-macrophages is at the same low levels as in other lymphocytes (72). Thus, there is as yet no experimental proof for the suggestion, based on experiments in cell culture, that monocyte-macrophages may be the reservoirs of the virus *in vivo* (6, 12, 28). Also, very few lung and brain cells ever express HIV (101, 102, 187). At this level of infiltration HIV cannot account by any known mechanism for the loss of T cells that is the hallmark of AIDS (3, 5, 6, 12), even if all actively infected T cells died. During the 2 days it takes for a retrovirus to replicate, the body regenerates about 5% of T cells (23, 103), more than enough to compensate for presumptive losses due to the virus. Hence, HIV cannot be sufficient to cause AIDS.

Although there is virtually no free virus, and HIV RNA synthesis is extremely low, both in AIDS patients and in asymptomatic carriers (71-74), it has been argued that the viral core protein p24 is produced at higher levels in AIDS patients than in asymptomatic carriers (83, 84, 104-108, 183). However, all studies on p24 report AIDS cases that occur without p24 antigenemia, indicating that p24 is not necessary for AIDS (83, 84, 104-108, 183). They also report antigenemia without AIDS, indicating that p24 is not sufficient for AIDS (72, 84, 104-108, 183). Moreover, antigenemic carriers are not viremic because they always maintain an excess of virus-neutralizing antibodies directed against the viral envelope, a positive AIDS test (72, 83, 84, 104-108, 183). In addition, the colorimetric antibody test used to measure p24 protein raises unresolved questions. Reportedly, the assay's detection limit is 50 pg/ml, and up to 100 times more p24 than that is found in some HIV carriers (83, 84, 104-109). Five hundred picograms of p24 is the protein equivalent of 106 HIV particles, given 10-3 pg per retrovirus, half of which is core protein (110). Yet such high concentrations of p24 cannot be reconciled with the extremely low numbers of cells in AIDS patients that are engaged in viral RNA synthesis (6, 71-74, 101, 102), nor can the failure to isolate virus from 20-50% of p24-antigenemic patients (83, 84). Based on my 24-year experience with retroviruses, only large numbers of infected cells growing in the absence of antiviral immunity *in vivo* or *in vitro* produce such high titers of virus or viral protein. Thus, the assertions that HIV becomes activated during AIDS or that p24 antigenemia is necessary for the syndrome (6, 7, 12, 31, 35) are without experimental support.

AIDS Occurs Despite Antiviral Immunity. Viruses typically cause disease before virus-neutralizing antibodies and cellular immunity appear. Antiviral antibodies signal a successful rejection of the virus and a lasting protection (vaccination) against diseases by the same or related viruses. Immunity is the only weapon against viral disease.

Paradoxically, HIV is said to cause AIDS, by definition, only years after inducing very active antiviral immunity (3, 5). If this assertion were correct, HIV would be the first virus to cause a disease only after antiviral immunity. Yet the effectiveness of this immunity is the reason that provirus remains dormant and that free HIV cannot be found in AIDS patients (69). In view of this, vaccination of antibody-positive persons would appear to be completely superfluous, even if HIV were the cause of AIDS (3, 7, 12, 111-113). The claims of some scientists that antiviral

antibodies fail to neutralize HIV (3, 32, 55, 56, 59, 113-115) are incompatible with the efficient immunity *in vivo* and with experimental evidence for virus-neutralizing activity *in vitro* (23, 115-119).

Although most viruses are eliminated by immunity, some, such as the retroviruses and the herpes viruses, may persist-severely restricted by antiviral immunity-as latent infections (23, 86, 87). Such viruses can again become pathogenic, but only when they are reactivated. For example, upon reactivation, the herpes viruses cause fever blisters or zoster even in the presence of serum antibody (120). Reactivation may follow a decline of cellular immunity in response to other parasitic infections, radiation, or immunosuppressive therapy (23, 86). Further, it has been claimed that 8 years after primary infection and immunity, latent measles virus may cause subacute sclerosing panencephalitis (121) in about 1 case per million (86) and that another latent paramyxovirus may cause multiple sclerosis (121). However, these viruses could be isolated from each system in only 2 of 8 cases after cultivating millions of patient cells *in vitro* (121). Moreover, multiple sclerosis has since been suggested to be caused by a latent retrovirus closely related to HIV (122) and subacute encephalitis by HIV (28, 187). Thus, there is no proven precedent for the hypothesis that HIV causes AIDS only years after the onset of antiviral immunity and yet remains as inactive as it is in asymptomatic infections.

It has been proposed that pathogenic HIV mutants arise during the long intervals between infection and AIDS and that these mutants might escape antiviral immunity by losing specific epitopes (28, 31, 82, 90, 112, 113, 123, 124) or even by changing their host range from T cells to macrophages (44). However, there is no report of a mutant HIV present at high titer in AIDS. Further, it is very unlikely that a mutant could escape an existing immunity, because it would share most variable and, of necessity, all constant determinants with the parent virus. Even though all retroviruses, including HIV (125-128), mutate at a frequency of 1 in 104 nucleotides per replicative cycle, they have never been observed to escape an existing antiviral immunity. It has also been proposed that HIV escapes immunity by spreading via cell-to-cell transmission (28, 32, 115, 117, 129). However, consistent with the syncytium-blocking function of natural antibodies (23, 115, 119), there is no spread of HIV *in vivo.*

Intervals of 2 to 15 Years Between Infection and AIDS Are Incompatible with HIV Replication. If cytocidal viruses or retroviruses cause disease, they do so within 1 to 2 months of infection (23, 86). By that time, the host's immune system either eliminates the virus or restricts it to latency, or the virus overcomes the immune system and kills the host. Indeed, clinicians have reported that, in rare cases, HIV causes a disease like mononucleosis prior to immunity, presumably due to an acute infection (23, 69, 130, 186). Since this disease correlates with viral activity (69) and disappears within weeks as the body develops antiviral immunity, it may reflect the true pathogenic potential of HIV.

Considering that HIV replicates within 2 days in tissue culture and induces antiviral immunity within 1 to 2 months (19, 23, 69, 130), the inevitably long and seemingly unpredictable intervals, ranging from 1 to 15 years (20, 35, 37), between the onset of antiviral immunity and AIDS are bizarre. The average latent period is reported to be 8 years in adults (21, 33-38) and 2 years in children (21, 36). Indeed, at least 2 years of immunity is required before AIDS appears in adults (7, 38). If one accepts that 50-100% of antibody-positive Americans eventually develop AIDS (7, 20-22, 33-37), the average 1.5% annual conversion corresponds to grotesque viral latent periods of 30 to 65 years. These intervals between HIV infection and AIDS clearly indicate that HIV by itself is not sufficient to initiate AIDS. Because all genes of HIV are expressed during the early immunogenic phase of the infection, AIDS should occur at that time, rather than years later when it is latent (23).

In an effort to rationalize the long intervals between infection and AIDS, HIV has been classified as a slow virus, or lentivirus (40), a type of retrovirus that is thought to cause disease only after long incubation periods (129). Yet there are no "slow" viruses. Since viral nucleic acids and proteins are synthesized by the cell, viruses must replicate as fast or faster than cells (i.e., within hours or days) to survive (86, 87).

Nevertheless, as pathogens, viruses may be (*i*) fast in acute infections that involve many actively infected cells, (*ii*) slow in subacute infections that involve moderate numbers of actively infected cells, or (*iii*) asymptomatic and latent. Retroviruses provide examples of each different pathogenic role. Acute infections with the "slow" Visna/Maedi retrovirus of sheep, a lentivirus, rapidly cause pneumonia (131), and those with equine anemia lentivirus cause fever and anemia within days or weeks of infection (132). Such infections typically generate titers of 104 to 105 infectious units per milliliter or gram of tissue (132, 133). The caprine arthritis-encephalitis lentivirus is also pathogenic within 2 months of inoculation (134). Acute infections with other retroviruses also rapidly cause debilitating diseases or cancers (23). This includes retrovirus infections that are now considered to be animal models of AIDS, termed simian or feline AIDS (12, 23, 30, 111, 135). Unlike HIV in AIDS, these viruses are all very active when they cause diseases, and the respective diseases appear shortly after infection (23). In rare cases, when antiviral immunity fails to restrict Visna/Maedi or other retroviruses, they persist as subacute symptomatic infections (3, 86, 129, 133). Under these conditions, Visna/Maedi virus causes a slow, progressive pulmonary disease (129, 133, 136) by chronically infecting a moderate number of cells that produce moderate titers of 102 to 105 virus particles per gram of tissue (136). However, in over 99% of all Visna/Maedi or caprine arthritis-encephalitis virus infections, and in most equine anemia virus infections, the retrovirus is either eliminated or restricted to latency by immunity, and hence asymptomatic, exactly like almost all other retroviruses in mice, chickens, cats, and other animals (23). For instance, 30-50% of all healthy sheep in the U.S., Holland, and Germany have asymptomatic Visna/Maedi virus infections (129, 137, 138), and 80% of healthy goats in the U.S. have asymptomatic caprine arthritis-encephalitis virus infections (133) in the presence of antiviral immunity.

Thus, the progressive diseases induced by active retroviruses depend on relative tolerance to the virus due to rare native or acquired immunodeficiency or congenital infection prior to immune competence. Since tolerance to HIV

that would result in active chronic infection has never been observed and is certainly not to be expected for 50-100% of infections [the percentage of infections said to develop into AIDS (ref. 7 and above)], the rare retrovirus infections of animals that cause slow, progressive diseases are not models for how HIV might cause AIDS. Indeed, not one acute retrovirus infection has ever been described in humans (23).

The Paradox of How HIV, a Noncytocidal Retrovirus, Is to Cause the Degenerative Disease AIDS. Unlike cytocidal viruses, which replicate by killing cells, retroviruses need viable cells for replication (139). During retroviral infection, proviral DNA becomes a cellular gene as it is integrated into the DNA of the cell. Such a mechanism is superfluous for a cytocidal virus. Virus reproduction from then on is essentially gene expression in viable cells, often stimulating hyperplastic growth (17, 23). Alternatively, retroviruses survive as latent proviruses, like latent cellular genes. The very distinction of not killing the host cell is the reason that scientists have for so long considered retroviruses to be the most plausible viral carcinogens (17, 23, 140).

Yet HIV, a retrovirus, is said to behave like a cytocidal virus, causing AIDS by killing billions of T cells (3, 5, 6, 12, 31). This is said even though some infected T-cell lines remain immortal (12, 23), and primary umbilical-cord blood cells may continue to divide in culture while propagating up to 106 infectious units per milliliter (82), much more than in AIDS patients. Also, there are no cytopathic changes or cell death in cultures of HIV-infected monocytes and macrophages (28, 141-146) and B cells (17, 23, 147). As is typical of retroviruses, HIV does not kill its host cells.

The cytocidal effects that are occasionally observed in HIV-infected cultures (but as yet, never in humans) soon after infection do not break this rule (23). These early effects result from fusions of HIV-infected and uninfected cells that depend on virus isolates and cell culture conditions (23, 82, 146, 147), and are completely inhibited by antiviral antibody (23, 115, 119). They are not HIV-specific, because many animal and human retroviruses show conditional, but never absolute, cytocidal effects in cell culture (23). Thus, the fusion effect in culture might be relevant for the mononucleosis observed in some patients soon after infection, when free virus (but no fusion-inhibitory antibody) is present. However, the effect cannot be relevant to AIDS because there is plenty of fusion-inhibitory antibody and because the virus isolates from some patients fuse, and those from others don't (23, 82, 146, 147). Thus, HIV is not sufficient to kill even the few T cells it infects in AIDS.

HIV Is a Conventional Retrovirus, Without an AIDS Gene. The virus-AIDS hypothesis proposes that HIV is an unorthodox retrovirus (6, 12, 14, 31, 32) containing specific suppressor and activator genes that control the 2- to 15-year intervals between infection and AIDS (12, 37,188). However, the two known HIVs (see below) are profoundly conventional retroviruses. They have the same genetic complexity of about 9150 nucleotides, the same genetic structure, including the three major essential retrovirus genes linked in the order *gag-pol-env,* the same mechanism of replication, and the same mutation frequency (3, 7, 17, 90, 125, 126, 148) as all other retroviruses (17, 127, 128, 149, 150). Humans carry between 50 and 100 such retroviruses in their germ line, mostly as latent proviruses (151). The presumably specific genes of the HIVs (12, 188) are alternative reading frames of essential genes shared by all retroviruses (3, 7, 12, 23, 90, 148). Their apparent novelty is more likely to reflect new techniques of gene analysis than to represent HIV-specific retroviral functions. Indeed, analogous genes have recently been found in other retroviruses, including one bovine and at least three other human retroviruses that do not cause AIDS (23, 152, 188). Because HIV and all other retroviruses are isogenic, the newly discovered genes cannot be AIDS-specific. Moreover, it is unlikely that these genes even control virus replication. *In vivo,* HIV lies chronically dormant, although the presumed suppressor genes are not expressed. *In vitro,* HIV is propagated at titers of about 106 per ml in the same human cells in which it is dormant *in vivo,* although the presumed suppressor genes are highly expressed (23, 188). Therefore, I propose that antiviral immunity rather than viral genes suppress HIV *in vivo,* as is the case with essentially all retroviruses in wild animals (23). Further, I propose that the multiplicity of AIDS diseases are caused by a multiplicity of risk factors (see below), rather than by one or a few viral activator genes, since viral gene expression in AIDS is just as low as in asymptomatic carriers. Also, the extremely low genetic complexity of HIV can hardly be sufficient to control the inevitably long times between infection and AIDS, and the great diversity of AIDS diseases. Thus, there is neither biochemical nor genetic evidence that HIV genes initiate or maintain AIDS.

The Paradoxes of an AIDS Virus with Country- and Risk-Specific Pathologies and Host Ranges. It is yet another paradox of the virus-AIDS hypothesis that HIV is said to cause very different diseases in different risk groups and countries. For example, in the U.S. over 90% of AIDS patients have *Pneumocystis* pneumonia or Kaposi sarcoma. However, Kaposi sarcoma is found almost exclusively in homosexuals (8, 191). By contrast, in Africa over 90% of the AIDS cases are manifested by slim disease, fever, and diarrhea (9, 10, 64). Moreover, it is paradoxical that the prevalence of Kaposi sarcoma among U.S. AIDS cases has shifted down from 35% in 1983 (156) to 6% in 1988 (4) (see below and refs. 190 and 191), and *Pneumocystis* pneumonia has shifted up from 42% to 64% (8), while the alleged cause, HIV, has remained the same.

One explanation of these facts is that HIV is not sufficient to cause AIDS but depends critically on country- and risk-specific cofactors. However, the simplest explanation proposes that HIV is a harmless, idle retrovirus that is not the cause of AIDS.

In view of the claims that AIDS is a sexually transmitted viral syndrome (3, 7, 12), it is surprising (47, 64, 65, 91, 92, 154, 155) that, in the U.S., about 90% of all HIV carriers and AIDS patients are male (4, 7, 22, 38, 47). Even if one assumes that the virus was originally introduced into the U.S. through homosexual men (7), this epidemiology is hard to reconcile with the spread of a sexually transmitted virus 8 years later. In order to survive, a virus must infect new hosts, which it does most readily when it is at the highest titer (153). In the case of HIV, this would be before

antiviral immunity, or 1 to 2 months after infection (69). Thus, the 8 years of AIDS in the U.S. represent about 50 to 100 human passages of HIV, enough time for the virus to equilibrate between the sexes. By contrast, the uniform sexual distribution of HIV in Africa appears consistent with a sexually transmissible virus, underscoring the paradox of the U.S. epidemiology, particularly since the viruses (12) and the epidemics (12-14, 90, 113) of both countries are thought to be equally new.

A solution of the paradox is that HIV is not new but is endemic in Africa and, like most retroviruses (23), is transmitted perinatally rather than sexually. Accordingly, 10% of healthy Zairians are antibody-positive (46, 98,184), and not more than 30% of the Kaposi sarcoma patients in Africa are infected with HIV (157, 158). Indeed, perinatal transmission between mother and child occurs with an efficiency of 30-50% (7, 22, 39), while sexual transmission is extremely inefficient (65, 79, 80, 154, 155). Since the virus is not endemic in the U.S., it is transmitted more often by parenteral exposures associated with risk behavior (see below) than perinatally.

Evolutionary Arguments Against AIDS Viruses. It is now claimed that there are at least two new retroviruses capable of causing AIDS, HIV-1 and HIV-2 (3, 7, 12-14), which differ about 60% in their nucleic acid sequences (148). Both allegedly evolved only 20 to <100 years ago (12). Since viruses, like cells, are the products of gradual evolution, the proposition that, within a very short evolutionary time, two different viruses capable of causing AIDS would have evolved or crossed over from another species is highly improbable (56, 64, 159). It is also improbable that viruses evolved that kill their only natural host with efficiencies of 50-100% as is claimed for the HIVs (7, 33-38).

Conclusions and Perspectives

It is concluded that HIV is not sufficient to cause AIDS because HIV meets neither Koch's postulates nor established epidemiological, biochemical, genetic, and evolutionary criteria of a viral pathogen. Further, it is concluded that HIV may not even be necessary for AIDS because there is neither biochemical nor genetic evidence that it initiates or maintains AIDS. HIV infiltration and activity are just as low in symptomatic carriers as in asymptomatic carriers, and HIV lacks an AIDS gene. The association between AIDS and antibody to HIV-now part of the definition of AIDS-does not prove causation because otherwise indistinguishable diseases are now set apart only on the basis of this antibody. According to this view, HIV is an ordinary harmless retrovirus that, in rare acute infections, may cause a mononucleosis-like disease before immunity.

Antibody to HIV Is a Surrogate Marker for Risk of AIDS. Although HIV does not appear to cause AIDS, it may serve in the U.S. and Europe as a surrogate marker for the risk of AIDS for the following reasons. (*i*) In these countries, HIV is not widespread but is one of the most specific occupational infections of persons at risk for AIDS (3, 7, 38, 47, 61, 94, 160). (*ii*) Since HIV is extremely difficult to transmit, like all latent viruses, it would specifically identify those who habitually receive transfusions or intravenous drugs or are promiscuous. Indeed, the probability of being antibody-positive correlates directly with the frequency of drug use (38, 47, 160), transfusions (94, 161), and male homosexual activity (38, 160). (*iii*) Since HIV is not cytocidal, it persists as a minimally active virus in a small number of cells, which will chronically boost antiviral immunity to produce a positive AIDS test. Latent EBV, cytomegalovirus, or other herpes virus infections will likewise maintain a chronic immunity (86, 120), although less specific for AIDS risk. By contrast, antibodies against viruses and microbes, which cannot persist at subclinical levels, tend to disappear after primary infection.

Epidemiology Is Not Sufficient to Prove Etiology. It has been argued that Koch's postulates can be abandoned as proof for etiology in favor of epidemiological correlations (67, 68, 162), most recently in the case of HIV (14, 32). However, adherence to this epidemiological concept (68, 162) as a substitute for biochemical and genetic proof of etiology has resulted in some of the most spectacular misdiagnoses in virology. (*a*) Based on epidemiological correlations, EBV was thought to be the cause of Burkitt lymphoma-until Burkitt lymphomas free of the virus were discovered (163). [It is ironic that HIV is currently a proposed cause of Burkitt lymphoma (5).] (*b*) Also on the basis of seroepidemiological evidence, retroviruses were thought to cause human and bovine leukemias after bizarre latent periods of up to 40 years in humans (164), until the discovery of these viruses in billions of normal cells of millions of asymptomatic carriers cast doubt on this hypothesis (23). It is scarcely surprising that the particular T cell from which a rare clonal leukemia originated was also infected. It is consistent with this view that these tumors are clonal and not contagious, like virus-negative leukemias, and that the presumably causative viruses are biochemically inactive in the human and bovine leukemias (23). Instead of viruses, the only specific markers of such tumors are clonal chromosomal abnormalities (23). (*c*) Likewise, slow viruses have gained acceptance as causes for such diseases as kuru, Creutzfeld-Jacob disease, and Alzheimer disease on the basis of epidemiological evidence (165), although these viruses have never been detected.

Proof of Etiology Depends on Evidence for Activity. Regrettably, the hasty acceptance of the virus as the cause of AIDS (16), signaled by naming it HIV (18), has created an orthodoxy whose adherents prefer to discuss "how" rather than "whether" HIV causes AIDS. They argue that it is not necessary to understand HIV pathology, or how a latent virus kills, in order to claim etiology (7, 14, 32, 51). Therefore, many different mechanisms, including ones in which HIV is said to depend on cofactors to cause AIDS, have been discussed (6, 12, 31, 32, 35, 61, 91) to explain how the virus supposedly kills at least 104 times more Tcells than it actively infects (26-28, 71-74). Yet all speculations that HIV causes AIDS through cofactors cast doubt on HIV as a cause of AIDS, until such factors are proven to depend on HIV.

In contrast to what is claimed for HIV, there is unambiguous genetic evidence that biochemical activity in or on more cells than the body can spare or regenerate is absolutely necessary for viral or microbial pathogenicity. Examples are transformation-defective mutants of Rous sarcoma virus (166) and replication-defective mutants of cytocidal viruses (87). If latent viruses or microbes were pathogenic at the level of activity of HIV, most of us would have *Pneumocystis* pneumonia (80-100%) (167), cytomegalovirus disease (50%) (88), mononucleosis from EBV (50-100%) (see above; ref. 88), and herpes (25-50%) (88) all at once, and 5-10% also would have tuberculosis (168), because the respective pathogens are latent, immunosuppressed passengers in the U.S. population at the percentages indicated. Since we can now, through molecularly cloned radioactive probes, detect latent viruses or microbes at concentrations that are far below those required for clinical detectability and relevance, it is necessary to reexamine the claims that HIV is the cause of AIDS.

In response to this, it has been argued that a biochemically inactive HIV may cause AIDS indirectly by a mechanism(s) involving new biological phenomena (12, 14, 31, 32). This is argued even though HIV is like numerous other retroviruses studied under the Virus-Cancer Program during the last 20 years (17, 140), which are only pathogenic when they are biochemically active (23). Nevertheless, some retroviruses (23) and DNA viruses [e.g., hepatitis virus in hepatomas (169)] are thought to cause tumors indirectly by converting, by means of site-specific integration, a specific gene of a rare infected cell to a cancer gene. Such a cell would then grow autonomously to form a monoclonal tumor, in which the virus may be inactive and often defective (17, 23, 140, 169). However, such highly specific, and hence rare, virus-cell interactions cannot explain the loss of billions of cells during a degenerative disease like AIDS. It is also hard to accept that HIV could cause AIDS through a T cell autoimmunity (12, 31, 32, 170), because it reaches far too few cells to function as a direct immunogen and because it is unlikely to function as an indirect immunogen since it is not homologous with human cells (73, 75, 77). Further, it is extremely unlikely that any virus could induce autoimmunity, which is a rare consequence of viral infection, as efficiently as HIV is thought to cause AIDS, namely in 50-100% of all infections.

Not All AIDS Diseases Can Be Explained by Immunodeficiency. Clearly, immunodeficiency is a plausible explanation for the microbial and viral AIDS diseases (5) and *Pneumocystis* pneumonia. However, the effective immunity against HIV, which defines AIDS, together with those against cytomegalovirus, herpes simplex virus, hepatitis virus, and other viruses (3, 23, 61, 94), is hard to reconcile with acquired immunodeficiency. One would have to argue that T cell depletion in AIDS is highly selective in order to allow *Pneumocystis* but not HIV or other viruses to become active. If HIV were able to induce T cell immunodeficiency against itself, its titer during AIDS should be as high as it is in cultures of infected human monocytes-namely, up to 10^6 infectious units per milliliter (see above), just as high as the titers of all other retroviruses when they are pathogenic in animals (23).

Moreover, immunodeficiency does not explain AIDS neoplasias such as lymphomas or Kaposi sarcoma, which may be a hyperplasia (175, 178). The hypothesis that cancers reflect a defective immune system, the immune-surveillance hypothesis (176), has been disproven through athymic (nude) mice, which develop no more cancers than other laboratory mice (177). In fact, no immunodeficiency was observed in HIV-infected African patients who had Kaposi sarcomas (157, 158). In addition, Kaposi sarcoma tissue does not contain any HIV (23, 178, 179). Immunodeficiency also cannot explain dementia; nor can dementia be explained by HIV infection of neurons, because retroviruses are dependent on mitosis for infection (17, 23, 139, 140) and neurons do not divide (169). HIV would indeed be a mysterious virus (31) to kill T cells and neurons that are not infected and, at the same time, to induce hyperplastic or neoplastic growth of other cells that are also not infected.

HIV Is Not a Rational Basis for AIDS Therapy. Since there is no proven mechanism of HIV pathogenesis, HIV is not a rational basis for the control of AIDS. Thus the treatment of symptomatic and even asymptomatic HIV carriers with azidothymidine (AZT) (7, 39) cannot be justified in terms of its original design, which is to inhibit HIV DNA synthesis by chain termination (171). Even if HIV were to cause AIDS, it would hardly be a legitimate target for AZT therapy, because in 70-100% of antibody-positive persons proviral DNA is not detectable (73, 75, 187) without amplification (77), and its biosynthesis has never been observed.

Nevertheless, AZT has been claimed to have beneficial effects for AIDS patients on the basis of a 16- to 24-week double-blind trial (194). However, AZT, originally developed for chemotherapy by terminating cellular DNA synthesis, efficiently kills dividing blood cells and other cells (39, 84, 172-174, 189, 193, 195) and is thus directly immunosuppressive. Moreover, the immediate toxicity of AZT (174, 189, 193, 195) suggests that this trial could hardly have been double-blind and hence unbiased.

What Are the Causes of AIDS? I propose that AIDS is not a contagious syndrome caused by one conventional virus or microbe, because no such virus or microbe would average 8 years to cause a primary disease, or would selectively affect only those who habitually practice risk behavior, or would be able to cause the diverse collection of over 20 degenerative and neoplastic AIDS diseases. Neither could a conventional virus or microbe survive if it were as inefficiently transmitted as AIDS, and killed its host in the process. Conventional viruses either are highly pathogenic and easy to transmit or are nonpathogenic and latent and hence very difficult to transmit (153). Conventional viruses or microbes also exist that cause secondary-or even primary-diseases long after infection, but only when they are activated from dormancy by rare acquired deficiencies of the immune system (86). Such opportunistic infections are the consequence rather than the cause of immunodeficiency.

Since AIDS is defined by new combinations of conventional diseases, it may be caused by new combinations of conventional pathogenic factors. The habitual administration of factor VIII or blood transfusions (94, 161) or of drugs (47, 64, 160, 190-192), chronic promiscuous male homosexual activity that is associated with drugs (64, 160, 191), numerous acute parasitic infections, and chronic malnutrition (159, 160)-each for an average of 8 years-are

factors that appear to provide biochemically more tangible and plausible bases for AIDS than an idle retrovirus. Indeed, the correlation between AIDS and such factors is 95% (4, 5). Among these factors, EBV, cytomegalovirus, herpes simplex virus, and administration of blood components and factor VIII have all been identified as causes of immunodeficiency not only in HIV-positive, but also in HIV-negative, hemophiliacs (11, 61, 94, 161). In fact, the dose of factor VIII received was found to be directly proportional to subsequent immunodeficiencies (94, 161). The habitual admission of narcotic toxins appears to play a major immunosuppressive role in the U.S. and Europe (11, 64). About 30% of the American AIDS patients are confirmed users of injected drugs (4, 47). Because of the difficulties in assessing drug data (47, 91, 92), it is probable that the percentage who use injected and/or noninjected drugs is even higher (64, 155, 185, 190-192). For example, nine different drugs were used in combination by a cohort of antibody-positive homosexuals in San Francisco (160). Again there are quantitative drug-AIDS correlations. For example, the decreased use of nitrite inhalants was shown to correlate with the decreased incidence of Kaposi sarcoma in homosexuals (190, 191). Moreover, that the Kaposi sarcoma cases decreased exactly with the use of nitrites, rather than lagging behind it by 8 years as would be expected from the presumed 8-year latent period of HIV, argues directly against a role of HIV in Kaposi sarcoma. Further, it has been documented that protein malnutrition and parasitic infections are the most common causes of T cell immunodeficiency worldwide, particularly in developing countries (181). Unlike HIV, the specifics of these risk factors provide a plausible explanation for the risk specificity of AIDS diseases. The long and unpredictable intervals between the appearance of antibody to HIV and the onset of AIDS would then reflect the thresholds for these factors to cause AIDS diseases, rather than an unlikely mechanism of HIV pathogenesis.

In response to this view it is often pointed out that AIDS risks have existed for a long time (55, 59), whereas AIDS is said to be a new syndrome (3, 7, 12-14). However, this argument fails to consider that the major risk groups-male homosexuals and intravenous drug users-have only become visible and acceptable in the U.S. and in Europe during the last 10 to 15 years, about the same time that AIDS became visible. Acceptability facilitated and probably enhanced risk behavior, and thus the incidence of the many diseases now called AIDS. Increased consumption of drugs was reported to have increased the number of drug-related deaths, although unconfirmed HIV infections were the prefered interpretation (190, 192). Moreover, the particular permissiveness toward these risk groups in metropolitan centers encouraged the clustering of cases that was necessary to detect AIDS. Further, it has been pointed out that slim disease, fever, and diarrhea in Africa are not a new epidemic, but old diseases under a new name, caused by previously known infectious agents and malnutrition (11, 64, 98, 182).

This analysis offers several benefits. It ends the fear of infection by HIV, and particularly of immunity to HIV, because it proves that HIV alone is not sufficient to cause AIDS. To determine whether HIV is necessary for AIDS, controlled, randomized analyses (196) either of risk takers who differ only by the presence of antibody to HIV or of antibody-positive individuals who differ only in taking AIDS risks must be carried out. Moreover, assessment of a pathogenic potential of HIV would depend on evidence that the life-span of antibody-positive risk takers is shorter than that of antibody-free controls. In addition, it should be determined whether, prior to 1981, AIDS-risk takers ever developed what are now called AIDS diseases. This analysis also suggests studies on how the nature, frequency, and duration of AIDS risks generate risk-specific diseases. Such studies should include persons treated with AZT before or after AIDS symptoms to assess the AIDS risks of AZT. To this end, diseases should be reported by their original names (8-10), rather than as AIDS (4) because of their association with antibody to HIV. Finally, this analysis suggests that AIDS prevention efforts be concentrated on AIDS risks rather than on transmission of HIV (43).

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References

1. Gottlieb, M.S., Schroff, R., Schamber, H.M., Weisman, J.D., Fan, P.T., Wolf, R.A. & Saxon, A. (1981) *N. Engl. J. Med.* 305, 1425-1431.
2. Centers for Disease Control (1981) *Morbid. Mortal. Wkly. Rep.* 30, 305-308.
3. Institute of Medicine (1986) *Confronting AIDS* (N .A.S., Washington, D.C.).
4. Centers for Disease Control (1988) *AIDS Weekly Surveillance Report* (August 8).
5. Centers for Disease Control (1987) *J. Am. Med. Assoc.* 258, 1143-1154.
6. Fauci, A. (1988) *Science* 239, 617-622.

7. Institute of Medicine (1988) *Confronting AIDS-Update 1988* (N.A.S., Washington, D.C.).
8. Selik, R., Starcher, E.T. & Curran, J. (1987) *AIDS* 1, 175-182.
9. Colebunders, R., Mann, J., Francis, H., Bila, K., Izaley, L., Kakonde, N., Kabasele, K., Ifoto, L., Nzilambi, N., Quinn, T., van der Groen, G., Curran, J., Vercauteren, B. & Piot, P. (1987) *Lancet* i, 492-494.
10. Pallangyo, K.J., Mbaga, I. M., Mugusi, F., Mbena, E., Mhalu, F.S., Bredberg, U. & Biberfeld, G. (1987) *Lancet* ii, 972.
11. Holub, W.R. (1988) *Am. Clin. Prod. Rev.* 7 (5), 28-37.
12. Gallo, R.C. & Montagnier, L. (1988) *Sci. Am.* 259 (4), 41-48.
13. Gallo, R.C. & Montagnier, L. (1987) *Nature* (London) 362, 435-436.
14. Blattner, W., Gallo, R.C. & Temin, H. (1988) *Science* 241, 514-517.
15. Barré-Sinoussi, F., Chermann, J.C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vezinet-Brun, F., Rouzioux, C., Rosenbaum, W. & Montagnier, L. (1983) *Science* 220, 868-870.
16. Connor, S. (1987) *New Sci.* 113 (1547), 49-58.
17. Weiss, R., Teich, N., Varmus, H. & Coffin, J. (1985) *RNA Tumor Viruses* (Cold Spring Harbor Lab., Cold Spring Harbor, NY), 2nd Ed.
18. Coffin, J., Haase, A, Levy, J.A., Montagnier, L., Oroszlan, S., Teich, N., Temin, H., Toyoshima, K., Varmus, H., Vogt, P. & Weiss, R. (1986) *Science* 232, 697.
19. Friedland, G.H. & Klein, R.S. (1987) *N. Engl. J. Med.* 317, 1125-1135.
20. Rees, M. (1987) *Nature* (London) 326, 343-345.
21. Eyster, M.E., Gail, M.H., Ballard, J.O., Al-Mondhiry, H. & Goedert, J.J. (1987) *Ann. Int. Med.* 107, 1-6.
22. Curran, J.W., Jaffe, H.W., Hardy, A.M., Morgan, W.M., Selik, R.M. & Dondero, T.J. (1988) *Science* 239, 610-616.
23. Duesberg, P.H. (1987) *Cancer Res.* 47, 1199-1220.
24. Rettig, R.A. (1977) *Cancer Crusade: The Story of the National Cancer Act of 1971* (Princeton Univ. Press, Princeton, N J).
25. Sattentau, Q.J. & Weiss, R.A. (1988) *Cell* 52, 631-633.
26. Gartner, S., Markovits, P., Markovitz, D., Kaplan, M., Gallo, R. & Popovic, M. (1986) *Science* 233, 215-219.
27. Popovic, M. & Gartner, S. (1987) *Lancet* ii, 916.
28. Ho, D.D., Pomerantz, R.J. & Kaplan, J.C. (1987) *N. Engl. J. Med.* 317, 278-286.
29. Khan, N.C., Chatlynne, L.G. & Hunter, E. (1988) *Am. Clin. Proc. Rev.* 7 (5), 12-19.
30. Baum, R.M. (1988) *Chem. Eng. News* 66 (13), 29-33.
31. Levy, J. (1988) *Nature* (London) 333, 519-522.
32. Booth, W. (1988) *Science* 239, 1485-1488.
33. Moss, A.R., Bacchetti, P., Osmond, D., Krampf, W., Chaisson, R.E., Stites, D., Wilber, J., Aliain, J.-P. & Carlson, J. (1988) *Br. Med. J.* 296, 745-750.
34. Goedert, J.J., Biggar, R.J., Weiss, S.H., Eyster, M.E., Melbye, M., Wilson, S., Ginzburg, H.M., Grossman, R.J., DiFiola, R.A., Sanchez, W.C., Giron, J.A., Ebbsen, P., Gallo, R.C. & Blattner, W.A. (1986) *Science* 231,992-995.
35. Anderson, R.M. & May, R.M. (1988) *Nature* (London) 333, 514-519.
36. Medley, G.F., Anderson, R.M., Cox, D.R. & Billard, L.(1988) *Nature* (London) 333, 505.
37. Liu, K.-J., Darrow, W.W. & Rutherford, G.W. (1988) *Science* 240, 1333-1335.
38. Osmond, D.H. & Moss, A.R. (1989) The prevalence of HIVinfection in the United States: a reappraisal of the Public Health Service estimate, in *AIDS Clinical Review,* 1-17, 1989
39. Patlak, M. (1988) *Discover* 9 (10), 26-27.
40. Gonda, M., Wong-Staal, F., Gallo, R., Clements, J., Narayan, O. & Gilden, R. (1986) *Science* 227, 173-177.
41. Kolata, G. (1988) *N.Y. Times* 137, June 10.

42. Hager, M. & Monmaney, T. (1988) *Newsweek* 111 (24), 66-67.
43. Centers for Disease Control (1988) *Understanding AIDS,* HHS Publ. No (CDC) HHS-88-8404 (GPO, Washington, D.C.).
44. Barnes, D.M. (1988) *Science* 239, 348-349.
45. Anonymous (1988) *Morbid. Mortal. Wkly. Rep.* 37 (15), 229-239.
46. Curran, J.W., Morgan, M.W., Hardy, A.M., Jaffe, H.W., Darrow, W.W. & Dowdle, W.R. (1985) *Science* 229, 1352-1357.
47. Booth, W. (1988) *Science* 239, 253.
48. Duesberg, P. (1987) *Bio/Technology* 5, 1244.
49. Duesberg, P. (1988) *Science* 241,514-517.
50. Duesberg, P. (1988) *New Sci.* 118 (1610), 34-35.
51. Liversidge, A. (1988) *Spin* 3 (11), 56-57, 67, 72.
52. Farber, C. (1988) *Spin* 4 (2), 71-72.
53. Leishman, K. (1988) *Wall St. J.*118 (39), Feb. 26.
54. AIDS Monitor (1988) *New Sci.* 118 (1603), 34.
55. Ward, R. (1988) *Nature* (London) 332, 574.
56. Lauritsen, J. (1988) *N.Y. Native* 264, 14-19.
57. Miller, J. (1988) *Discover* 9 (6), 62-68.

58. Werth, B. (1988) *N. Engl. Monthly* 5 (6), 38-47.
59. Weber, J. (1988) *New Sci.* 118 (1611), 32-33.
60. Hall, S. (1988) *Hippocrates* 2 (5), 76-82.
61. Schwartz, K.F. (1988) *Ærtztliche Praxis* 45, 1562-1563.
62. Rubin, H. (1988) *Science* 240, 1389-1390.
63. Rubin, H. (1988) *Nature* (London) 334, 201.
64. Rappoport, J. (1988) *AIDS INC.* (Human Energy Press, San Bruno, CA).
65. Matsumura, K. (1988) *Heterosexual AIDS: Myth or Fact?* (Alin Found. Press, Berkeley, CA).
66. Stewart, G.T. (1968) *Lancet* i, 1077-1081.
67. Evans, A. (1976) *Yale J. Biol. Med.* 49, 175-195.
68. Huebner, R.J. (1957) *Ann. N.Y. Acad. Sci.* 67, 430-438.
69. Albert, J., Gaines, H., Sonnerborg, A., Nystrom, G., Pehrson, P.O., Chiodi, F., von Sydow, M., Moberg, L., Lidman, K., Christensson, B., Asjö, B. & Fenyo, E.M. (1987) *J. Med. Virol.* 23, 67-73.
70. Falk, L.A., Paul, D., Landay, A. & Kessler, H. (1987) *N. Engl. J. Med.* 316, 1547-1548.
71. Harper, M.E., Marselle, L.M., Gallo, R.C. & Wong-Staal, F. (1986) *Proc. Natl. Acad. Sci. USA* 83, 772-776.
72. Ranki, A., Valle, S.-L., Krohn, M., Antonen, J., Allain, J.-P., Leuther, M., Franchini, G. & Krohn, K. (1987) *Lancet* ii, 589-593.
73. Richman, D., McCutchan, J. & Spector, S. (1987) *J. Infect. Dis.* 156, 823-827.
74. Biberfeld, P., Chayt, K.J., Marselle, L.M., Biberfeld, G., Gallo, R.C. & Harper, M.E. (1986) *Am. J. Pathol.* 123, 436-442.
75. Shaw, G.M., Hahn, B.H., Arya, S.K., Groopman, J.E., Gallo, R.C. & Wong-Staal, F. (1984) *Science* 226, 1165-1167.
76. Kahn, N.C. & Hunter, E. (1988) *Am. Clin. Prod. Rev.* 7 (5), 20-25.
77. Farzadegan, H., Polis, M.A., Wolinsky, S.M., Rinaldo, C.R., Sninsky, J. J., Kwok, S., Griffith, R.L., Kaslow, R.A., Phair, J.P., Polk, B.F. & Saah, A.J. (1988) *Ann. Int. Med.* 108, 785-790.
78. Groopman, J.E., Hartzband, P. I., Shulman, L., Salahuddin, S.Z., Sarngadharan, M.G., McLane, M.F., Essex, M. & Gallo, R. (1985) *Blood* 66, 742-744.
79. Hearst, N. & Hulley, S. (1988) *J. Am. Med. Assoc.* 259, 2428-2432.
80. Peterman, T.A., Stoneburner, R.L., Allen, J.R., Jaffe, H.W. & Curran, J.W. (1988) *J. Am. Med. Assoc.* 259, 55-58.
81. Gallo, D., Kimpton, J. & Dailey, P. (1987) *J. Clin. Microbiol.* 25, 1291-1294.
82. von Briesen, H., Becker, W.B., Henco, K., Helm, E.B., Gelderblom, H.R., Brede, H.D. & Rübsamen-Waigmann, H. (1987) *J. Med. Virol.* 23, 51-66.
83. Paul, D.A., Falk, L.A., Kessier, H.A., Chase, R.M., Blaauw, B., Chudwin, D.S. & Landay, A.L. (1987) *J. Med. Virol.* 22, 357-362.
84. Rubenis, M., Despotes, J.C., Mack, D., Knigge, M. & Emeson, E.E. (1988) *Ann. Int. Med.* 108, 175-180.
85. Weiss, S.H., Goedert, J.J., Gartner, S., Popovic, M., Waters, D., Markham, P., di Marzo Veronese, F., Gail, M.H., Barkley, W.E., Shaw, G.M., Gallo, R.C. & Blattner, W.A. (1988) *Science* 239, 68-71.
86. Mims, C. & White, D.O. (1984) *Viral Pathogenesis and Immunology* (Blackwell, Oxford, U.K.).
87. Fenner, F., McAuslan, B.R., Mims, C.A., Sambrook, J. & White, D.O. (1974) *Animal Viruses* (Academic, New York).
88. Evans, A.S., ed. (1982) *Viral Infection of Humans: Epidemiology and Control* (Plenum, New York/London).
89. Stewart, G.J., Tyler, J.P.P., Cunningham, A.L., Barr, J.A., Driscoll, G.L., Gold, J. & Lamont, B.J. (1985) *Lancet* ii, 581-584.
90. Baum, R.M. (1987) *Chem. Eng. News* 65 (47), 14-26.
91. Abramson, P.R. & Rothschild, B. (1988) *J. Sex Res.* 25 (1) 106-122.
92. Abramson, P.R. (1988) *J. Sex Res.* 25 (3), 323-346.
93. Barnes, D. (1987) *Science* 236, 1423-1425.
94. Sullivan, J.L., Brewster, F.E., Brettler, D.B., Forsberg, AD, Cheeseman, S.H., Byron, K.S., Baker, S.M., Willitts, D.L., Lew, R.A. & Levine, P.H. (1986) *J. Pediatr.* 108, 504-510.
95. Ward, J.W., Holmberg, S.D., Allen, J.R., Cohn, D.L., Critchley, S.E., Kleinman, S.H., Lenes, B.A., Ravenholt, O., Davis, J.R., Quinn, M.G. & Jaffe, H.W. (1988) *N. Engl. J. Med.* 318, 473-478.
96. Jaffe, H.W., Sarngadharan, M.G., DeVico, A.L., Bruch, L., Getchell, J.P., Kalyanaraman, V.S., Haverkos, H.W., Stoneburner, R.L., Gallo, R.C. & Curran, J.W. (1985) *J. Am. Med. Assoc.* 254, 770-773.
97. Tinker, J. (1988) *Issues Sci. Technol.* IV (1), 43-48.
98. Editorial (1987) *Lancet* ii, 192-194.
99. Fleming, A.F. (1988) *AIDS-Forschung* 3, 116-138.
100. Koenig, R.E., Pittaluga, J., Bogart, M., Castro, M., Nunez, F., Vilorio, I., Devilfar, L., Calzada, M. & Levy, J.A. (1987) *J. Am. Med. Assoc.* 257, 631-634.
101. Chayt, K.J., Harper, M.E., Marselle, L.M., Lewin, E.B., Rose, R.M., Oleske, J.M., Epstein, L.G., Wong-Staal, F. & Gallo, R.C. (1986) *J. Am. Med. Assoc.* 256, 2356-2371.
102. Stoler, M.H., Eskin, T.A., Been, S., Angerer, R.C. & Angerer, L.M. (1986) *J. Am. Med. Assoc.* 256, 2360-2364.
103. Sprent, J. (1977) in *B and T Cells in Immune Recognition,* eds. Loor, F. & Roelants, G.E. (Wiley, New York), pp. 59-82.

104. Goudsmit, J., Lange, J.M.A., Paul, D.A. & Dawson, G.A. (1987) *J. Infect. Dis.* 155, 558-560.
105. Forster, S.M., Osborne, L.M., Cheingsong-Popov, R., Kenny, C., Burnell, R., Jeffries, D.J., Pinching, A.J., Harris, J.R.W. & Weber, J.N. (1987) *AIDS* 1, 235-240.
106. Pederson, C., Nielsen, C.M., Vestergaard, B.F., Gerstoft, J., Krogsgaard, K. & Nielsen, J.O. (1987) *Br. Med. J.* 295, 567-569.
107. Wittek, A.E., Phelan, M.A., Well, M.A., Vujcic, L.K., Epstein, J.S., Lane, H.C. & Quinnan, G.V. (1987) *Ann. Int. Med.* 107, 286-292.
108. de Wolf, F., Goudsmit, J., Paul, D., Lange, J.M.A., Hooijkaas, C., Schellekens, P., Coutinho, R.A. & van der Noordaa, J. (1987) *Br. Med. J.* 295, 569-572.
109. Bialy, H. (1988) *Bio/Technology* 6, 121.
110. Vogt, P.K. (1965) *Adv. Virus Res.* 11,293-385.
111. Baum, R.M. (1987) *Chem. Eng. News* 65 (47), 27-34.
112. Barnes, D.M. (1988) *Science* 240, 719-721.
113. Seligmann, M., Pinching, A.J., Rosen, F.S., Fahey, J.L., Khaitov, R.M., Klatzmann, D., Koenig, S., Luo, N., Ngu, J., Riethmüller, G. & Spira, T. (1987) *Ann. Int. Med.* 107, 234-242.
114. Weiss, R.A., Clapham, P.R., Cheingsong-Popov, R., Dalgleish, A.G., Came, C.A., Weller, I.V.D. & Tedder, R.S. (1985) *Nature* (London) 316, 69-72.
115. Robinson, E., Montefiori, D.C.& Mitchell, W.M. (1988) *Lancet* i, 790-794.
116. Weiss, R.A., Clapham, P.R., Weber, J.N., Dalgleish, A.G., Lasky, L.A. & Berman, P.W. (1986) *Nature* (London) 324, 572575.
117. Ho, D.D., Sarngadharan, M.G., Hirsch, M.S., Schooley, R.T., Rota, T.R., Kennedy, R.C., Chanh, T.C. & Sato, V.L. (1987) *J. Virol.* 61, 2024-2028.
118. Robey, G., Arthur, L.O., Matthews, T.J., Langlois, A., Copeland, T.D., Lerche, N.W., Oroszlan, S., Bolognesi, D.P., Gilden, R.V. & Fischinger, P.J. (1986) *Proc. Natl. Acad. Sci. USA* 83, 7023-7027.
119. Rusche, J.R., Lynn, D.L., Robert-Guroff, M., Langlois, A.J., Lyerly, H.K., Carson, H., Krohn, K., Ranki, A., Gallo, R.C., Bolognesi, D.P., Putney, S.D. & Matthews, T. J. (1987) *Proc. Natl. Acad. Sci. USA* 84, 6924-6928.
120. Douglas, R.G., Jr., & Couch, R.B. (1970) *J. Immunol.* 104, 289295.
121. Koprowski, H. (1977) in *Slow Virus Infections of the Central Nervous System,* eds. ter Meulen, V. & Katz, M. (Springer, New York), pp. 152-158.
122. Koprowski, H., DeFreitas, E.C., Harper, M.E., Sandberg-Wollheim, M., Sheremata, W.A., Robert-Guroff, M., Saxinger, C.W., Feinberg, M.B., Wong-Staal, F. & Gallo, R.C. (1985) *Nature* (London) 318, 154-160.
123. Hahn, B.H., Shaw, G.M., Taylor, M.D., Redfield, R.R., Markham, P.D., Salahuddin, S.Z., Wong-Staal, F., Gallo, R.C., Parks, E.S. & Parks, W.P. (1986) *Science* 232, 1548-1553.
124. Cheng-Mayer, C., Sero, D., Tateno, M. & Levy, J.A. (1988) *Science* 240, 80-82.
125. Preston, B.D., Poiesz, B.J. & Loeb, L.A. (1988) *Science* 242, 1168-1171.
126. Takeuchi, Y., Nagumo, T. & Hoshino, H. (1988) *J. Virol.* 62, 3900-3902.
127. Coffin, J.M., Tsichlis, P.N., Barker, C.S., Voynow, S. & Robinson, H.L. (1980) *Ann. N.Y. Acad. Sci.* 54, 410-425.
128. Temin, H.M. (1988) *Cancer Res.* 48, 1697-1701.
129. Haase, A.T. (1986) *Nature* (London) 322, 130-136.
130. Kessler, H.A., Blaauw, B., Spear, J., Paul, D.A., Falk, L.A. & Landay, A. (1987) *J. Am. Med. Assoc.* 258, 1196-1199.
131. Lairmore, M.D., Rosadio, R.H. & DeMartini, J.C. (1986) *Am. J. Pathol.* 125, 173-181.
132. Perryman, L.E., O'Rourke, K.J. & McGuire, T.E. (1988) *J. Virol.* 62, 3073-3076.
133. Narayan, O. & Cork, L.C. (1985) *Rev. Infect. Dis.* 7, 89-98.
134. Crawford, T.B. & Adams, D.S.(1981) *J. Am. Vet. Med.* 178, 713-719.
135. Lackner, A.A., Rodriguez, M.H., Bush, C.E., Munn, R.J., Kwang, H.-S., Moore, P.F., Osborn, K.G., Marx, P.A., Gardner, M.B. & Lowenstine, L.J. (1988) *J. Virol.* 62, 2134-2142.
136. DeBoer, G.F. & Houwers, J. (1979) in *Aspects of Slow and Persistent Virus Infections,* ed. Tyrrell, D.A.J. (ECSC, Brussels-Luxembourg), pp. 198-220.
137. DeBoer, G.F., Terpstra, C. & Houwers, D.J. (1978) *Bull. Off. Int. Epizoot.* 89, 487-506.
138. Cutlip, R., Lehmkuhl, H.D., Brodgen, K.A. & Sacks, J.M. (1986) *Vet. Microbiol.* 12, 283-288.

139. Rubin, H. & Temin, H. (1958) *Virology* 7, 75-91.
140. Tooze, J., ed. (1973) *The Molecular Biology of Tumor Viruses* (Cold Spring Harbor Lab., Cold Spring Harbor, NY).
141. Ho, D.D., Rota, T.R. & Hirsch, M.S. (1986) J. Clin. Invest. 77, 712-715.
142. Nicholson, J.K.A., Gross, G.D., Callaway, C.S. & McDougal, J.S. (1986) *J. Immunol.* 137, 323-329.
143. Salahuddin, S.Z., Rose, R.M., Groopman, J.E., Markham, P.D. & Gallo, R.C. (1986) *Blood* 68, 281-284.
144. Hoxie, J.A., Haggarty, B.S., Rachowski, J.L., Pilsbury, N. & Levy, J.A. (1985) *Science* 229, 1400-1402.
145. Walker, C.M., Moody, D.J., Stites, D.P. & Levy, J.A. (1986) *Science* 234, 1563-1566.
146. Anand, R., Siegal, F., Reed, C., Cheung, T., Forlenza, S. & Moore, J. (1987) *Lancet* ii, 234-238.
147. Dahl, K., Martin, K. & Miller, G. (1987) *J. Virol.* 61, 1602-1608.
148. Clavel, F. (1987) *AIDS* 1, 135-140.

149. Duesberg, P.H., Vogt, K., Beemon, K. & Lai, M. (1974) *Cold Spring Harbor Symp. Quant. Biol.* 39, 847-857.
150. Wang, L.-H., Galehouse, D., Mellon, P., Duesberg, P., Mason, W.S. & Vogt, P.K. (1976) *Proc. Natl. Acad. Sci. USA* 73, 3952-3956.
151. Martin, M.A., Bryan, T., Rasheed, S. & Khan, A.S. (1981) *Proc. Natl. Acad. Sci. USA* 78, 4892-4896.
152. Weiss, R.A. (1988) *Nature* (London) 333, 497-498.
153. Andrewes, C.H. (1965) *J. Gen. Microbiol.* 49, 140-~56.
154. Gould, R.E. (1988) *Cosmopolitan* 204 (1), 146-147, 204.
155. Brecher, E.M. (1988) *Columbia Journalism Rev.* 26 (6), 46-50.
156. Centers for Disease Control (1985) *Morbid. Mortal. Wkly. Rep.* 34, 245-248.
157. Craighead, J., Moore, A., Grossman, H., Ershler, W., Frattini, U., Saxinger, C., Hess, U. & Ngowi, F. (1988) *Arch. Pathol. Lab. Med.* 112, 259-265.
158. Kestens, L., Melbye, M., Biggar, R.J., Stevens, W.J., Piot, P., DeMuynck, A., Taelman, H., DeFeyter, M., Paluku, L. & Gigase, P.L. (1985) *Int. J. Cancer* 36, 49-54.
159. Sonnabend, J. (1989) in *The Acquired Immune Deficiency Syndrome and Infections of Homosexual Men,* eds. Ma, P. & Armstrong, D. (Butterworth, Stonehan, MA), 2nd Ed., 460-490.
160. Darrow, W.W., Echenberg, D.F., Jaffe, H.W., O'Malley, P.M., Byers, R.H., Getcheil, J.P. & Curran, J.W. (1987) *Am. J. Publ. Health* 77, 479-483.
161. Tedder, R.S., Cheingsong-Popov, R., Weiss, R., McClelland, D.B.L., Philip, I. & Prescott, R.J. (1985) *Lancet* ii, 233-236.
162. Evans, A. (1978) *Am. J. Epidemiol.* 108, 249-258.
163. Pagano, J.S., Huang, C.H. & Levine, P. (1973) *N. Engl. J. Med.* 289, 1395-1399.
164. Gallo, R.C. (1986) *Sci. Am.* 255 (6), 88-98.
165. Gajdusek, D.C. (1977) *Science* 197, 943-960.
166. Martin, G.S. & Duesberg, P.H. (1972) Virology 47, 494-497.
167. Pifer, L.L. (1984) *Eur. J. Clin. Microbiol.* 3, 169-173.
168. Evans, A.S. & Feldman, H.A., eds. (1982) *Bacterial Infections of Humans: Epidemiology and Control* (Plenum, New York/London).
169. Watson, J.D., Hopkins, N.H., Roberts, J.W., Steitz, J.A. & Weiner, A.M. (1987) *Molecular Biology of the Gene* (Benjamin/Cummings, Menlo Park, CA), 4th Ed.
170. Stricker, R.B., McHugh, T.M., Moody, D.J., Morrow, W.J.W., Stites, D.P., Schuman, M.A. & Levy, J.A. (1987) *Nature* (London) 327, 710-713.
171. Yarchoan, R., Weinhold, K.J., Lyefly, H.K., Gelmann, E., Blum, R.M., Shearer, G.M., Mitsuya, H., Collins, J.M., Mayers, C.E., Klecker, R.W., Markham, P.D., Durack, D.T., Lehman, S.N., Barry, D.W., Fischl, M.A., Gallo, R.C., Bolognesi, D.P. & Broder, S. (1986) *Lancet* i, 575-580.
172. Dagani, R. (1987) *Chem. Eng. News* 65 (47), 35-40.
173. Richman, D.D., Fischl, M.A., Grieco, M.H., Gottlieb, M.S., Volberding, P.A., Laskin, O.L., Leedom, J.M., Groopman, J.E., Mildvan, D., Hirsch, M.S., Jackson, G.G., Durack, D.T., Nusinoff-Lehrman, S. & the AZT Collaborative Working Group (1987) *N. Engl. J. Med.* 317, 192-197.
174. Gingell, B.D. (1988) *Issues Sci. Technol.* IV (2), 17-18.
175. Brown, R.K. (1987) *Am. Clin. Pro. Rev.* 6 (11), 44-47.
176. Pitot, H. (1979) *Fundamentals of Oncology* (Dekker, New York).
177. Duesberg, P.H. (1987) *Proc. Natl. Acad. Sci. USA* 84, 2117-2124.
178. Bovi, P.D., Donti, E., Knowles, D.M., II, Friedman-Kien, A., Luciw, P.A., Dina, D., Dalla-Favera, R. & Basilico, C. (1986) *Cancer Res.* 46, 6333-6338.
179. Salahuddin, S.K., Nakamura, S., Biberfeld, P., Kaplan, M.H., Markham, P.D., Larsson, L. & Gallo, R.C. (1988) *Science* 242, 430-433.
180. Duesberg, P.H. (1988) *Science* 242, 997998.
181. Seligmann, M., Chess, L., Fahey, J.L., Fauci, A.S., Lachmann, P.J., L'Age-Stehr, J., Ngu, J., Pinching, A.J., Rosen, F.S., Spira, T.J. & Wybran, J. (1984) *N. Engl. J. Med.* 311, 1286-1292.
182. Konotey-Ahulu, F.I.D. (1987) *Lancet* ii, 206-208.
183. Andrieu, J.E., Eme, D., Venet, A., Audroin, C., Tourani, J.M., Stern, M., Israel-Biet, D., Beldjord, K., Driss, F. & Even, P. (1988) *Clin. Exp. Immunol.* 73, 1-5.
184. N'Galy, B., Ryder, R., Bila, K., Mwandagalirwa, K., Colebunders, R.L., Francis, H., Mann, J. & Quinn, T. (1988) *N. Engl. J. Med.* 319, 1123-1127.
185. Raymond, C.A. (1988) *J. Am. Med. Assoc.* 259, 329, 332.
186. Marcus, R. & CDC Needlestick Surveillance Group (1988) *N. Engl. J. Med.* 319, 118-123.
187. Shaw, G.M., Harper, M.E., Hahn, B.H., Epstein, L.G., Gajdusek, D.C., Price, R.W., Navia, B.A., Petito, C.K., O'Hara, C.J., Cho, E.-S., Oleske, J.M., Wong-Staal, F. & Gallo, R.C. (1985) *Science* 227, 177-182.
188. Haseltine, W.A. & Wong-Staal, F. (1988) *Sci. Am.* 259 (4), 52-62.
189. Kolata, G. (1987) *Science* 235, 1462-1463.
190. Haverkos, H.W. (1988) in *Health Hazards of Nitrite Inhalants,* eds. Haverkos, H.W. & Dougherty, J.A., National Institute on Drug Abuse Monograph 83, pp. 96-105.
191. Lange, W.R., Haertzen, C.A., Hickey, J.E., Snyder, F.R., Dax, E.M. & Jaffe, J.H. (1988) *Am. J. Drug Alcohol Abuse* 14 (1), 29-40.

192. Stoneburner, R.L., Des Jarlais, D.C., Benezra, D., Gorelkin, L., Sotheran, J.L., Friedman, S.R., Schultz, S., Marmor, M., Mildvan, D. & Maslansky, R. (1988) *Science* 242, 916-919.
193. Sonnabend, J. (1989) *AIDS Forum,* ed. Callen, M. 1, 9-15.
194. Fischl, M.A. & the AZT Collaborative Working Group (1987) *N. Engl. J. Med.* 317, 185-191.
195. Dournon, E. & the Claude Bernard Hospital AZT Study Group (1988) *Lancet* ii, 1297-1302.
196. Feinstein, A.R. (1988) *Science* 242, 1257-1263.