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Five myths about AIDS that have misdirected research and treatment

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Abstract

A number of widely repeated and factually incorrect myths have pervaded the AIDS research literature, misdirecting research and treatment. Five of the most outstanding are: 1) that all risk groups develop AIDS at the same rate following HIV infection; 2) that there are no true seroreversions following HIV infection; 3) that antibody is protective against HIV infection; 4) that the only way to treat AIDS effectively is through retroviral therapies; and 5) that since HIV is so highly correlated with AIDS incidence, it must be the sole necessary and sufficient cause of AIDS. A huge body of research, reviewed in this paper, demonstrates the falsity of these myths. 1) The average number of years between HIV infection and AIDS is greater than 20 years for mild hemophiliacs, 14 years for young severe hemophiliacs, 10 years for old severe hemophiliacs, 10 years for homosexual men, 6 years for transfusion patients of all ages, 2 years for transplant patients, and 6 months for perinatally infected infants. These differences can only be explained in terms of risk-group associated cofactors. 2) Seroreversions are common. Between 10 and 20 percent of HIV-seronegative people in high risk groups have T-cell immunity to HIV, and may have had one or more verified positive HIV antibody tests in the past. 3) Antibody, far from being protective against HIV, appears to be highly diagnostic of loss of immune regulation of HIV, and some evidence of antibody-enhancement of infection exists. 4) Non-retroviral treatments of HIV infection, including safer sex practices, elimination of drug use, high nutrient diets, and limited reexposure to HIV and its cofactors have proven to be effective means of preventing or delaying onset of AIDS. 5) Many immunosuppressive factors, including drug use, multiple concurrent infections, and exposure to alloantigens, are as highly correlated with AIDS risk groups as HIV. These data are more consistent with AIDS being a multifactorial or synergistic disease than a monofactorial one.

Introduction

Many commentators on AIDS have neatly divided the AIDS world into those who believe that HIV is the sole necessary and sufficient cause of AIDS, and those who believe that it plays no role in AIDS at all. In fact, many investigators believe that HIV definitely plays some role in AIDS, but that its role is as yet undefined. Whether it is necessary but not sufficient to cause AIDS, one of the many factors acting synergistically, or a player in the induction of lymphotoxic autoimmune processes is still an open question (Buimovici-Klein *et al.*, 1988; Donohoe & Falek, 1988; Duesberg, 1987, 1989, 1990, 1992; Fernandez-Cruz *et al.*, 1988; Haverkos, 1988; Hoff & Peterson, 1989; Hoff *et al.*, 1991; Kion & Hoffmann, 1991; Littlefield, 1992; Lo *et al.*, 1991; Lusso, Lori & Gallo, 1990; Macon *et al.*, 1993; Mathé, 1992; McClean & Nowak, 1992; Montagnier *et al.*, 1990; Papadopulos-Eleopulos, 1988; Pifer *et al.*, 1987; Root-Bernstein, 1990a, 1990b, 1990c, 1992a, 1992b, 1993, 1994; Root-Bernstein & Hobbs, 1993; Root-Bernstein & DeWitt, 1994; Rubin, 1988, Shearer & Levy, 1984; Sonnabend & Saadoun, 1984; Sonnabend, Witkin & Portillo, 1984; Sonnabend, 1989, Stott, 1991; Wang *et al.*, 1992; Ziegler & Stites, 1986).

The crucial point for any theory of AIDS is to account for not only the presence of HIV and antibodies to it in the vast majority of AIDS patients, but also why some people develop all of the symptoms

of AIDS in the absence of HIV, why others remain healthy for decades after HIV infection and may even serorevert, and why the time between HIV infection and full-blown (CDC stage 4) disease varies tremendously between patients. I will argue that neither the theory that HIV is necessary and sufficient, nor the theory that it is irrelevant to understanding AIDS, is satisfactory for explaining AIDS because both theories are based upon misleading, but widely held myths about the disease and about how biomedical research should best demonstrate the cause(s) of AIDS.

Five myths, in particular, are often repeated in the medical literature, and are demonstrably incorrect: 1) that all risk groups develop AIDS at the same rate following HIV infection; 2) that there are no true seroreversions following HIV infection; 3) that antibody is protective against HIV infection; 4) that the only way to treat AIDS effectively is through retroviral therapies; and 5) that since HIV is so highly correlated with AIDS incidence, it must be the sole necessary and sufficient cause of AIDS. We will not be able to understand and effectively treat AIDS until these myths are exploded and the facts of AIDS installed in their place.

Myth 1: HIV progresses to AIDS at the same rate in all risk groups

The most powerful and often-cited argument against the need for cofactors and for the sufficiency of HIV is that people in all risk groups progress to AIDS at the same rate following HIV infection. Roy Anderson, for example, states, 'The median incubation period of AIDS (time from infection to the development of AIDS) appears to be approximately 10 years in sexually active adults in developed countries irrespective of risk group' (Anderson, 1993). He, James Curran and many others have argued from such evidence that cofactors associated with particular risk groups cannot have any effect of AIDS progression. Similarly, Robin Weiss states that the development of AIDS is a purely 'stochastic process' and agrees with Anderson 'that population groups with different lifestyles have similar rates of progression to AIDS' (Weiss, 1993, his Fig. 2; see my Fig. 1). The one admitted exception are hemophiliacs under the age of 25 who progress more slowly to AIDS than other groups. Weiss claims, however, that after a lag period, they have 'a similar rate of progression to AIDS' as all other risk groups (Weiss, 1993). A review of the relevant literature casts doubt on these crucial claims, however, and thereby on the implication that cofactors are irrelevant to AIDS progression.

Weiss, Anderson, and Curran have evidently failed to examine all of the available studies, or have not paid attention to sophisticated mathematical models of epidemics. For one thing, most hemophilia studies differentiate between hemophiliacs age 25–44 and those over the age of 44, because the rate of AIDS development in the over 44 group is two or four times faster than that of the 25–44 age group. Weiss can make hemophiliacs have the same rate of AIDS progression as homosexual men only by lumping the 25–44 and over 44 age group together. (Weiss, 1993). Furthermore, reference to a large body of studies not cited by Weiss or Anderson reveals a rate of progression to AIDS among hemophiliacs less than 25 years of age that is significantly different from that found in Figure 2 of Weiss's article, and with a slope different than that for homosexual and hemophiliac men in general (Fig. 1) (Darby *et al.*, 1990; Schinaia *et al.*, 1991; Sorice *et al.*, 1989; Giesecke *et al.*, 1988; Eyster *et al.*, 1987).

The discrepancy in the two sets of data is due to reliance by most experts (including Weiss, Anderson, and Curran) on studies performed at hemophilia treatment centers (HTCs) in the United States and Britain. HTCs see only a fraction of all hemophiliacs, generally the most severe cases, but do not see symptom-free hemophiliacs (Stehr-Green *et al.*, 1989; Eyster *et al.*, 1987). The majority of the patients studied in the references cited by Weiss (1993), for example, are severe type A hemophiliacs (see Lorenzo *et al.*, 1993 for another example in which 64% of the cohort had severe disease and had exactly the rate of development predicted by Weiss). Less than a third of hemophiliacs have severe disease, however, and the incidence of AIDS in mild hemophiliacs is 1/7 that of severe hemophiliacs (Goedert *et al.*, 1989; Hardy *et al.*, 1985). Thus, incubation periods based on severe hemophiliacs overestimates rate of progression to AIDS, and are not representative of all hemophiliacs (Giesecke *et al.*, 1988). Severity of hemophilia is independently predictive of development of AIDS, possibly due to increased frequency of use of clotting concentrates, transfusions, viral contaminants, and steroidal, colloidal gold, and opiate drugs associated with joint injury treatment (Rosendaal, Smit & Briet, 1991; Root-Bernstein, 1993). In consequence, several studies have shown that reliance on data from HTCs results in large overestimates of rates of AIDS and of total numbers of AIDS cases among hemophiliacs (Stehr-Green *et al.*, 1989; Eyster *et al.*, 1987). Overall, only about 15

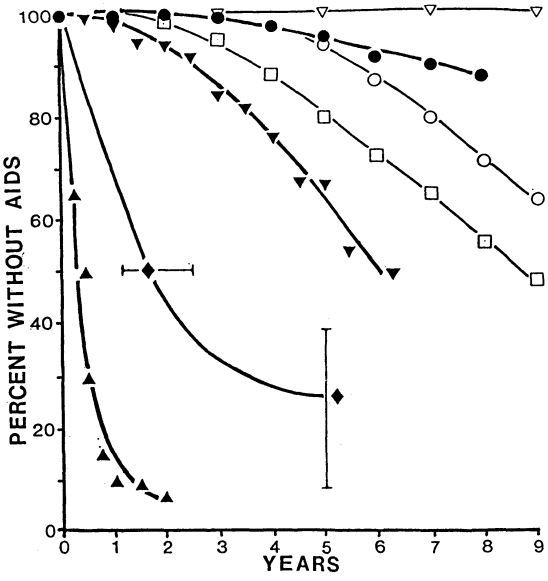

Fig. 1. Proportion of individuals surviving without AIDS plotted with data combined from various European and North American studies detailed in the text: HIV- homosexual men and hemophiliacs ▽ (Weiss, 1993); HIV+ homosexual men and hemophiliacs over the age of 25 □ (Weiss, 1993); HIV+ hemophiliacs under the age of 25 ○ (Weiss, 1993); HIV+ hemophiliacs under the age of 25 • (this study); HIV+ blood transfusion patients ▼ (this study); HIV+ transplant patients ♦ (this study); HIV+ pediatric patients ▲ (this study). Note that no study of HIV+ transplant patients larger than 25 has been performed so that statistical variation in reported AIDS-free survival times vary much more widely than in studies of other risk groups. In order to indicate the variation, bars have been added to the transplant patient points indicating the *range* of reported data, and the points themselves are drawn from a single large study of 22 patients by Lang *et al.* (1991). Note the tailing off of AIDS risk with increasing length of AIDS-free time in infants and transplant patients. I predict that a similar tailing off will cause all other risk groups to have rates of AIDS that become sigmoidal.

percent of HIV infected hemophiliacs have developed AIDS in the United States and the United Kingdom at present (CDC, 1993), although one would expect over 40 percent according to the rates of development projected by Anderson and Weiss (Weiss, 1993; Stehr-Green *et al.*, 1989).

Further data also contradict the current dogma concerning rate of disease development. Weiss and many other investigators attribute the lower rate of development of AIDS in young hemophiliacs to age. Perhaps, he conjectures 'younger persons have greater CD4 lymphocyte reserves and precursors for renewal' (Weiss, 1993; see also Goedert *et al.*, 1989). Studies of people infected with HIV through transfusions prove this conjecture wrong. Transfusion patients younger than 5 years of age develop AIDS significantly *faster* than older children, while children over the age of 2 but under 13 years of age develop AIDS at almost exactly the same rate as people between the ages of 13 and 39 and between 40 and 60 (Lui *et al.*, 1986; Medley *et al.*, 1987; Wang & See, 1992; Krasinski, Borkowsky & Holzman, 1989; Kopec-Schrader *et al.*, 1993). Only people over the age of 59 have a rate of AIDS onset that is shorter than that of younger patients, and the difference is not statistically significant (Kopec-Schrader *et al.*, 1993). Weiss's conjecture also fails to address why hemophiliacs over the age of 44 should have greatly increased rates of progression to AIDS compared with 25–44 year olds when such a phenomenon is not apparent in transfusion patients, nor can it explain why hemophilic men age 20 to 44 years who have additional risk factors such as drug abuse, homosexual activity, or both, have significantly decreased rates of survival (Holman *et al.*, 1992). Moreover, no one has ever reported that age affects the rate of progress to AIDS among HIV infected homosexual men, although a substantial number of these men contract the disease either prior to the age of 25 or after their 44th year. I presume that no age effect has been reported among gay men because no such effect exists although I can find no studies specifically addressing this question.

Those who claim that AIDS develops at the same rate in all risk groups also ignore data showing that transfusion patients of all ages develop AIDS at a significantly greater rate (50 percent have AIDS an average of 5.5 to 7.0 years after infection) (Lui *et al.*, 1986; Medley *et al.*, 1987; Ward *et al.*, 1989; Downs *et al.*, 1991; Msellati *et al.*, 1990; Kopec-Schrader *et al.*, 1993) than do homosexual men or hemophiliacs (an average of ca. 10 years or more). Moreover, the slope of the progression for transfusion patients differs from that seen for homosexual men or hemophiliacs (Figure 1), indicating that the increased rate is not due simply to fewer T-cells at the time of infection, but rather to ongoing synergistic effects with other factors. These factors include the disease process that required surgery in the first place, infection with, or reactivation of, latent immunosuppressive infections including cytomegalovirus, Epstein-Barr virus, and hepatitis viruses, the immunosuppressive effects of anaesthetics, opiate analgesics, chronic and high dose antibiotics, and (following some types of surgery) malnutrition, not to mention chronic health problems that often follow major surgery (reviewed in Root-Bernstein, 1990a, c, 1991, 1992, 1993).

The proof that immunologic status and ongoing exogenous immune suppression are determinants of progression to AIDS comes from studies of organ transplant patients who are infected with HIV (and often other viruses and bacteria) at the time of their operation (Fig. 1). Fifty percent of these patients develop AIDS within 1.2 to 2.8 years, depending on the types of transplant and the type of immunosuppressive treatment they receive (Cooper *et al.*, 1993; Schwarz *et al.*, 1993; Ribot & Eslami, 1992; Lange *et al.*, 1991; Tzakis *et al.*, 1990; Atkinson *et al.*, 1987).

It is clear from all of the published studies that the type of immunosuppressive regimen used to control transplant rejection has a very significant effect on the rate at which AIDS develops and on survival, but different investigators have found contradictory results concerning the influence of cyclosporine. Lang *et al.* (1991) found that four year *survival* of HIV+ transplant patients treated with the triple drug therapy (azathioprine + steroids + cyclosporine) was 19% compared with 57% in HIV+ patients without cyclosporine. Schwarz *et al.* (1993), however, have reviewed published cases and claim that the cumulative incidence of *AIDS* (not survival!) after 5 years was 31% in patients treated with cyclosporine versus 90% in those receiving immunosuppressive treatments other than cyclosporine. These data may be compatible if one considers the possibility that patients treated with cyclosporine do not generally live long enough to develop AIDS, or that their risk of other forms of death are increased so that AIDS is a less probable diagnosis. Indeed, one problem evaluating all data concerning transplant patients is the very high rate of mortality among these patients regardless of their HIV status. For example, mean *survival* time for HIV+ dialysis patients, most of whom were intravenous drug abusers in this particular study, was found to be a mere 1.5 years — too short for most of them to develop AIDS (Lang *et al.*, 1991). On the other hand, kidney transplant patients who must return to dialysis because of transplant failure have much better odds of survival than those whose transplanted kidney remains functional (Lang *et al.*, 1991), suggesting that treatments such as plasmapheresis, which have been reported to help some AIDS patients, may indeed be effective. In any event, Lang *et al.* (1991) summarize their study with words that aptly convey the conclusions of all of the cited transplant studies by saying that 'survival is much lower than in nontransplanted patients contaminated through blood transfusion ... This shorter survival is due to both a reduced AIDS-free time period and an accelerated course between the diagnosis of AIDS and death.' Clearly, then, chronic treatment with known immunosuppressive agents demonstrably and quite dramatically speeds up the rate of onset of AIDS.

The conclusion that chronic immunosuppressive treatments increase the rate of AIDS development is confirmed by studies of patients who are treated for combined Hodgkin's disease-HIV infection, and have an average AIDS-free time of only 3 years as a result of cancer chemotherapy (Roithmann *et al.*, 1993). Blood transfusions are also known to be acutely immunosuppressive, and are often given to AIDS patients to correct anti-retroviral-induced anaemia. Some evidence suggests that this practice increases the rate at which AIDS progresses (Vamvakas & Kaplan, 1993). One might expect that other immunosuppressive treatments, such as systemic corticosteroids for autoimmune conditions, will also be found to be contraindicated for people at risk for AIDS. On the other hand, non-immunosuppressive medical treatments have little effect on AIDS progression, as has been demonstrated by a study of HIV-infected individuals who require cardiopulmonary bypass surgery (Aris, Pomar & Saura, 1993).

Finally, although everyone knows that perinatally infected infants have the fastest rate of progression of any risk group (Weiss, 1993), the huge magnitude of the rate of increase (median of 6 months) (Fig. 1) is often ignored (Blanche *et al.*, 1990; Minkoff *et al.*, 1987; Mayers *et al.*, 1991; Kraskinski, Borkowsky & Holzmann, 1989). This huge increase in rate of AIDS progression has never been explained adequately except in terms of predisposing immunological debilitation caused by maternal cofactors experienced by the fetus or newborn. These factors include drug addiction, multiple concurrent viral and bacterial infections, exposure to blood products and anaesthetics, malnutrition and anemia. A very large proportion of children who develop AIDS are also significantly premature, underweight for their age, jaundiced, and malnourished — all factors associated with immune suppression even in HIV-seronegative infants (*ibid.*; Rubenstein *et al.*, 1983; reviewed in Root-Bernstein, 1990a, c, 1992, 1993).

I conclude that arguments as to the sufficiency of HIV as the cause of AIDS are not supported by epidemiological evidence. Different risk groups progress to AIDS at substantially different rates, as do different individuals within risk groups. The so-called age factor in hemophiliacs is unique to this group,

and must therefore be related to the very significant changes in the treatment of hemophilia over the past few decades (e.g., the switch from heavily virus contaminated plasma, to less contaminated factor concentrate, to ultrapurified and recombinant DNA derived clotting factor), which has saved young hemophiliacs from many cumulative immunosuppressive cofactors that affect older hemophiliacs (Rosendall, Smit & Briet, 1991; Root-Bernstein, 1990a, 1993). Cofactors known to cause immune suppression and to significantly increase the rates of AIDS development, which are also known to be much more common in older than younger hemophiliacs, include infections (sometimes chronic) with herpes viruses, hepatitis virus types B and C, and cytomegalovirus (Sullivan *et al.*, 1986; Goedert *et al.*, 1989; Webster *et al.*, 1989; Higgins & Goodall, 1991; Sabin *et al.*, 1993) and exposure to alloantigens in impure factor concentrates themselves (Hilgartner *et al.*, 1993; Schulman, 1991; Goedert *et al.*, 1989; Sullivan *et al.*, 1986). All of these cofactors are also present in other AIDS risk groups at unusually high rates compared to the general population (Root-Bernstein, 1993). Attenuation or elimination of these cofactor exposures through changes in hemophilia treatment since the 1960s resulted in a rise in the average life expectancy of hemophiliacs from 33 years in 1960 to nearly 57 years in 1980 (Aronson, 1988; Rosendaal, Smit & Briet, 1991). (Life expectancy has unfortunately plunged again to 40 years during the period 1987-1989 due primarily to AIDS, but also to increases in non-AIDS-associated pathologies as well [Lorenzo, *et al.*, 1993; Mares, Sartori & Girolami, 1992; Ritter, 1994]).

One crucial study that would help to clarify the rate-of-progression issue has not yet been done, and that is to examine the rate of AIDS onset in *spouses* of HIV-positive hemophiliacs and blood transfusion patients as a function both of HIV infection and cofactor acquisition (e.g., exposure to hepatitis viruses, cytomegalovirus, etc.). Presumably, spouses who acquire HIV heterosexually and have no drug or medical problems of their own will have the longest AIDS-free time of any group yet studied. Only two studies have been carried out that are relevant to this issue (Peterman *et al.*, 1988; Andes, Rangan & Wulff, 1989), but neither calculates rate of onset of AIDS, nor gives the elapsed time from HIV exposure. Notably, however, of four women who contracted HIV from their hemophiliac husbands prior to 1985, none had developed AIDS by 1989 and only one had developed AIDS-related complex in one study (Andes, Rangan & Wulff, 1989), while in the other study, one of 12 spouses had died of AIDS, three had developed lymphadenopathy, and eight had remained asymptomatic by 1988 (Peterman *et al.*, 1988). If one AIDS case out of 16 infections over four to eight years is an approximately accurate interpretation of these results, then the rate of AIDS onset among this group is, indeed, very low.

One interesting observation that has not been made before is that the rate of onset of AIDS in infants and transplant patients appears to level off after a few years, suggesting that those HIV-infected people who remain AIDS-free for extended periods of time have an ever-decreasing probability of developing AIDS. The data are not yet conclusive on this point, but if it is true, then one may predict that the probability of developing AIDS in all HIV+ risk groups will come to resemble sigmoidal curves. Long-term HIV+ survivors in all risk groups will, in other words, become less and less likely to develop AIDS. One indication that such a trend has already begun comes from a study of HIV+ gay men in Los Angeles which found that among those infected in 1979, 28% developed AIDS within six years, whereas among those infected in 1983, 25% developed AIDS within six years (Taylor, Kuo & Detels, 1991). The authors of the study suggest three possible explanations: mutation of HIV toward less pathogenic strains; better health care for pre-AIDS HIV-infected individuals; or control of cofactors through safer sex, clean needle, and education programs. The phenomenon of ever-slowing progression to AIDS has been observed in homosexual and bisexual men in Amsterdam as well, where the hazard rate has been decreasing consistently (Hendriks *et al.*, 1993).

It is important to stress that cofactor models of AIDS are completely consistent with current data concerning AIDS. In fact, several mathematical models of AIDS epidemiology demonstrate that the observed rates of development in each risk group can be explained only by models involving two or more synergistic agents. Weyer and Eggers (1990), for example, show that even if one assumes the rates of AIDS onset to be the same for each risk group, the 'drastic overrepresentation of the sexually highly active groups and drug abusers in the number of AIDS cases obviously requires that the transmission of AIDS unequivocally depends on the sexual and drug risk ... The observed parallel time series for the spread of AIDS in groups with different risk of infection can be realized by computer simulation, if one assumes that the outbreak of full-blown AIDS *only* occurs if HIV and a certain infectious coagent (cofactor) are present. Such

a situation is not uncommon, see, e.g., the influenza virus-*Staphylococcus aureus* system.' Similarly, McClean and Nowak (1992) have produced a mathematical model of AIDS in which HIV forms diverse quasi-species that have specificities for different T-cell clones and which can be activated synergistically by other T-cell-affecting agents (cofactors). While these authors claim that the criteria necessary to satisfy their models are not satisfied by existing data — i.e., that rates of AIDS progression do not differ with different risk groups or the presence or absence of known coinfections — this paper and previous reviews of the literature (Root-Bernstein, 1990a, b, c, 1993; Root-Bernstein & Hobbs, 1993) have shown conclusively that these criteria *are* met, and that the cofactor model is therefore accurate and tenable.

Myth 2: Once infected with HIV, always infected with HIV

A second myth that has misdirected research and treatment for nearly a decade is the oft-stated belief that once a person is infected with HIV he or she will remain infected until death. No one, to put the myth in a different way, beats an HIV infection.

The basis of the belief that HIV infections are irreversible apparently comes largely from the experience of major cohort studies in the United States and Europe, and from a detailed study of the issue by the United States Armed Forces. The first large scale study to report any examples of HIV seropositive individuals who subsequently seroreverted to HIV negative status was by Farzadegan and his colleagues of The Multicenter AIDS Cohort Study (USA) (Farzadegan *et al.*, 1988). They found that four of 4,954 men participating in the study seroreverted over a 2.5 year period. All four men had been demonstrated to have an HIV infection by ELISA, Western blot, and polymerase chain reaction (PCR). All four then lost all signs of HIV antibody. Two of the four men also became PCR negative. Similar results were reported from other cohort studies, but never published (Barnes, 1988). The authors of the study and other investigators, rather than concluding that HIV had been defeated, argued instead that these four cases may have represented a new phenomenon they called an 'incomplete' infection and attention was focused not on the good news that these men may not get AIDS, but rather that two of them remained antibody negative but PCR positive and so might inadvertently infect someone through blood or semen (Zuck, 1988).

At least one European group questioned whether the Americans had really seen any true seroreversions, arguing that they had no similar examples in their cohort. The only apparent cases of seroreversion they had encountered were all due to mixing up of blood samples or tests (Gürtler, Eberle & Deinhardt, 1989). A subsequent study by the U.S. Army seemed to confirm the absence of true seroreversion. Army personnel reviewed 5,446,161 HIV tests that it had performed on 2,580,974 people from 1985 through 1992. Of 4,911 people with at least one positive HIV test, only 6 potential cases of seroreversion were found, all of which were attributed to sample mix-ups. 'Testing errors' were given as the cause of 26 further individuals whose HIV infections were not confirmed by a follow-up test. The authors of the study therefore concluded that there is an 'absence of true seroreversion of HIV-1 antibody in seroreactive individuals.' (Roy, Damato & Burke, 1993)

In fact, several dozen well-documented cases of seroreversion, often accompanied by return to PCR-negative status, have been published. For example, in 1985 the case of a woman who had contracted HIV from her hemophiliac husband (who subsequently died) was reported. She had tested HIV positive repeatedly in January 1984 with a T-cell count of 561 (more than one standard deviation below normal variation [Laurence, 1993]). She was seronegative when retested in April and October of 1984 and April of 1985, and her T-cell counts were back up to 698 (a 25% increase, which is within average intrapatient variation [Hughes *et al.*, 1994]) by October 1984 and remained at that level through 1985. She was completely healthy when last reported (September 1986) (Burger & Weiser, 1986), and no report of illness or her death has appeared since.

Fribourg-Blanc reported two cases of seroreversion in which infection was demonstrated by isolation of proviral DNA in addition to ELISA and Western blot methods. One instance involved a heterosexual male who reported having a single, high risk 'adventure', and the other instance involved a biological technician without identifiable risks who sustained a needlestick injury while working with HIV-infected material (Fribourg-Blanc, 1988). Perrin *et al.* (1988) also described two men who had repeated contact with HIV-seropositive individuals, seroconverted, and developed HIV-infections confirmed by PCR. They subsequently lost all trace of antibody, retained normal T-cell function, and remained healthy. In addition, most

studies of the accuracy and reliability of Western blot, immunoprecipitation, and polymerase chain reaction (PCR) testing report several cases of seroreversion and loss of detectable virus among groups of tested individuals of varying sizes (e.g., four of twelve cases in Jaffe *et al.*, 1985; four in a hundred in Horsburgh *et al.*, 1990; and one of the 29 in Knüver-Hopf *et al.*, 1993).

Several very recent reports confirm the existence of unexpectedly large numbers of seroreverters. Scott Tanenbaum and Cindy Leissinger, researchers at Tulane University found five severe hemophiliacs (representing 10% of their cohort) with HIV-seropositive blood samples at one or more time points, all of whom subsequently seroreverted (Tanenbaum *et al.*, 1993; Anonymous, 1994). These researchers point out that between 10% and 15% of severe hemophiliacs who were probably exposed to HIV-contaminated factor one or more times have remained seronegative. Indeed a substantial proportion of people exposed to HIV-contaminated blood factor lots and blood transfusions have also been found to be seronegative on later testing. Henrard *et al.* (1993), for example, studied 103 high risk seronegative individuals, including 85 hemophiliacs, of whom 52 were known to have been exposed to HIV-contaminated factor concentrates. Seventy-six plasma samples (72%) were consistently negative for HIV-1 DNA by PCR; 24 (22%) were positive only once, but were not so upon multiple retesting; and 4 (3%) were positive twice, and then negative thereafter. When cellular DNAs were extracted from the blood specimens of PRC-positive plasma samples, none were found to be positive for HIV-1 DNA, suggesting that the plasma-based PCR test has a very high rate of false positive results when performed on HIV-seronegative samples. On the other hand, 10 of 10 PCR tests of cellular DNA from HIV-seropositive individuals yielded PCR-positive results. Henrard and his collegues concluded that HIV-seronegative individuals who are known to have been exposed to HIV have truly eliminated the retrovirus, and do not remain latently infected.

It is probable that the results reported by Henrard *et al.* (1993), and Tanenbaum *et al.* (1993) are very common. Ward and his collegues at the AIDS Program of the Centers for Disease Control studied 765 people who received HIV-tainted blood transfusions. Only about 60% were found to be seropositive within an average of 5 years after exposure (Ward *et al.*, 1989). Similarly, Ludlum *et al.* (1985) found that of 34 hemophiliacs transfused an average of over a dozen times each with a single batch of HIV-contaminated clotting factor VIII concentrate, only 18 became HIV-seropositive, and the risk was not associated with number of transfusions since most of the men seroconverted after receiving only three treatments while others remained seronegative after more than a dozen.

Similarly, Clerici *et al.* (1992) have documented dozens of instances of seronegativity among high risk individuals, including gay partners of HIV-infected men who have engaged in repeated acts of unprotected receptive anal intercourse, health workers exposed to HIV by subcutaneous cuts and needlestick accidents, and drug users who have shared needles with HIV-infected addicts (Brown, 1992). All of these people, although antibody-negative at the time they were tested, nonetheless displayed active T-cell responses to HIV antigens, suggesting that they had, in fact, been infected previously by HIV. Berkeley researchers have also reported seven healthy people — at least five of whom were definitely exposed to HIV — with T-cell mediated immune responses to HIV, but without HIV antibody. Two of the seven had urine samples positive for HIV-antibodies at one time, but seroreverted during the study (Urnovitz *et al.*, 1993).

In addition, many research groups have reported that the existence of significant numbers (hundreds all told) of people who are at least transiently (and sometimes chronically) PCR-positive for HIV, but persistently antibody negative (reviewed in Imagawa & Detels, 1991). These are individuals who have normal immune responses, with normal antibody production. While most of these investigators have interpreted their results as evidence for chronic, latent infection with HIV, Imagawa and Detels have argued that such data are more compatible with the concept of transient or incomplete infection, because subsequent verification of PCR positivity at later time periods is often impossible (*ibid.*). The transient interpretation is given added weight by the fact that all of the cases reported have been healthy individuals.

Documented cases of seroreversion, in sum, appear to represent the tip of a very large iceberg consisting of thousands of people who have been exposed to HIV and successfully fought off the infection without developing antibodies, or who developed antibodies but seroreverted prior to testing. The reasons for the iceberg being overlooked can be understood if we now go back and reanalyze the methods used by large cohort studies that report extremely low or non-existent seroreversion rates. These studies all have major flaws in their design. First, most cases of seroreversion seem to occur in people with limited exposure to HIV and who

have no ongoing cofactor exposure (Fribourg-Blanc, 1988; Root-Bernstein, 1993). People involved in most AIDS cohort studies, on the contrary, are by the design of the studies in high risk groups and very often have continued exposure to both HIV and putative cofactors. Second, the timing of seroreversion appears to be such that many people may have been infected with HIV but seroreverted *prior* to first being tested for the cohort study, and some appear to remain HIV-seronegative during the study despite being exposed to HIV. These people are not identifiable as having been exposed to HIV because of the use of antibody tests for initial screening for infection. Exposure leading to successful T-cell immunity without antibody cannot be documented without the more tedious efforts of T-cell antigen recognition studies, which are very rarely performed. And third, the U.S. Army study is irremediably flawed by the very fact that their data base consists of confirmatory tests, which are normally carried out within a few weeks or months of one another, rather then over the several years that appear to be necessary for loss of HIV antibodies and elimination of HIV from infected cells to occur. Thus, the Armed Forces study is not at all relevant to determining the rate of true seroreversion (Tanenbaum, Leissinger & Garry, 1993).

Fribourg-Blanc concludes that 'these observations [of seroreversion] are certainly not rare, but authentification of such cases requires conditions that are difficult to satisfy'. His work, and that of an ever-increasing number of other investigators tells us that we must stop assuming that if a person is infected with HIV, they will necessarily produce antibody, and that following infection, they will necessarily remain infected forever. For many people, HIV infection is transient, and such people hold the keys to understanding how to combat AIDS.

Myth 3: Antibody to HIV is protective so vaccination is possible

The third myth that I want to discuss is one that is shared alike by those who believe that HIV accounts for all of the immune suppressions in AIDS, and by those (such as Duesberg) who believe that HIV has nothing to do with AIDS. This myth maintains that antibody against HIV is protective, and therefore that the presence of antibody indicates that the retrovirus has adequately been controlled. Duesberg uses this argument in order to contend that since all AIDS patients have high levels of antibody against HIV, therefore HIV cannot be doing any significant damage to the immune system or body (Duesberg, 1989, 1990). Those who believe that HIV is the sole cause of AIDS argue, to the contrary, that if only people can be vaccinated against HIV so that antibodies are present prior to infection, then exposure to HIV will carry no risk of AIDS. Old and new evidence suggests that both of these positions are wrong.

The most important evidence in this regard has already been reported under Myth #2 above, and consists of the fact that HIV-seropositivity is usually associated with low CD4 counts that rectify themselves when seroreversion occurs. Additionally, as we have just seen, a significant proportion of people repeatedly exposed to HIV become PCR positive but remain antibody negative and healthy. Other people repeatedly exposed to HIV remain antibody negative, are PCR-negative, but demonstrate T-cell activation toward HIV antigens, strongly suggesting that they have previously mounted an effective T-cell response to HIV (or some cross-reactive alloantigen [Stott, 1991; Kion & Hoffman, 1991]). In short, HIV is controlled by the T-cell response, and antibody positivity to HIV is negatively correlated with control of HIV infection.

These data strongly suggest that the primary line of defense, and the only effective one against HIV is a T-cell response (Clerici *et al.*, 1992; Clerici & Shearer, 1993; Salk *et al.*, 1993). T-cell regulation is reasonably common for non-cytolytic encapsulated viruses, and antibody enhancement of infection is relatively common for these viruses as well (see below). Antibody is only produced when T-cell immunity fails to control viral replication and a sufficient amount of free virus is present in blood, lymph, or tissues to activate B cells. Clearly, as the cases of seroreversion prove, this antibody is short-lived in the absence of active, ongoing infection, and does not remain to protect against further infection. This phenomenon of rapid loss of antibody is also consistent with a primarily T-cell regulated immune response, rather than a primarily B-cell regulated immune response.

In fact, there exists a class of infectious diseases, most of which consist of noncytopathic encapsulated viruses (of which HIV is one), the pathological effects of which are actually exacerbated by the presence of antibody. One example is lymphocytic choriomeningitis virus (LCMV) infection in mice, which has many similarities to hepatitis B virus and HIV infection in man (Oehen, Hengartner & Zinkernagel, 1991). In LCMV, as in many other viral infections in which the immune response, rather than the virus infection itself,

causes lymphocyte death, survival is dependent on a successful T-cell response rather than upon antibody production. Production of antibody, whether naturally occurring or as a result of vaccination, is highly associated with death of the animal (Oehen, Hengartner & Zinkernagel, 1991). Dengue virus infection in human beings presents a similar picture. The severe hemorrhagic fever associated with the virus is almost always a result of an anamnestic or secondary antibody response. Presence of antibody has been found to be a strong predictor of severe disease following reinfection with a variant strain of the virus (Halstead, 1988; Kliks *et al.*, 1989). Since HIV mutates very quickly, and an extremely large number of HIV strains are known, probability of antibody-mediated enhancement of secondary infection with variant HIV strains in AIDS becomes a very likely event, which may, indeed, explain the long latency found in the syndrome.

LCMV and dengue virus are only two of many examples antibody-enhanced disease. Porterfield (1986) and Burke (1992) have summarized the relevant data for a very wide range of non-cytopathic viruses, including dengue, Japanese encephalitis, yellow fever, tick-borne encephalitis, Sindbis, respiratory synctial virus, rabies, reoviruses, murine cytomegalovirus, corona viruses, and lentiviruses (e.g. the visna virus of sheep). In some cases, vaccines (usually live attenuated strains) against these viruses have been very effective, but in others, such as respiratory synctial virus, measles virus, and visna virus, vaccination with formalin-inactivated whole virus dramatically increased the probability of severe or life-threatening infection among recipients (Burke, 1992). Burke has concluded that antibody-dependent enhancement of infection is a general *in vitro* property of all enveloped viruses, and that this *in vitro* activity is more often than not mirrored by physiological enhancement of infection as well, particularly when humoral immunity is not complete.

Particularly frightening in this respect is significant data that antibody-dependent enhancement of HIV infection occurs *in vitro* and possibly *in vivo* as well (reviewed in Burke, 1992). The problem is exacerbated by the mimicry between HIV proteins and HLA proteins of lymphocytes that results in immunologic cross-reactivity between HIV and lymphocyte cellular receptors (Golding *et al.*, 1988; Vega, Guigo & Smith, 1990; Garry *et al.*, 1991; Bjork, 1991; Kion & Hoffman, 1991; Stott, 1991; Clerici *et al.*, 1992; Dalgliesh *et al.*, 1992; Süsal *et al.*, 1993; Root-Bernstein & Hobbs, 1991, 1993; Root-Bernstein & DeWitt, 1994). Thus, a recent study of the immunological effects of recombinant HIV gp160 resulted in 3 of 5 human volunteers developing anti-idiotypic antibodies that cross reacted with their CD4 protein. The study concluded that such vaccine-induced anti-CD4 antibodies 'potentially may: (1) limit the use of vaccines which elicit them; (2) contribute to the immunodeficiency occuring in HIV-1-infected individuals, and (3) provide evidence of HIV-1 infection during the period when anti-HIV-1 antibodies are not detectable, (Keay *et al.*, 1992; see also Sabin, 1988).

The presence of non-HIV-induced HIV-like immune responses in several animal models of AIDS (Stott, 1991; Kion & Hoffmann, 1991) also raises the uncomfortable possibility that allogeneic exposure may confound all tests for AIDS, including T-cell tests. Salk *et al.* (1993) have argued, on the other hand, that allogeneic exposure might be protective, thus providing an alternative explanation for why people with *apparent* T-cell responses to HIV antigens may have avoided infection (Clerici & Shearer, 1993; Clerici *et al.*, 1992).

It follows that presence of HIV antibody is symptomatic of a failure of T-cell immunity. The issue in understanding AIDS now becomes that of establishing what causes the failure of T-cell mediated immunity. Since this failure does not occur in a large proportion of people exposed to HIV (e.g., the 15% of severe hemophiliacs who have not become HIV seropositive and perhaps susbstantially higher percentages of mild hemophiliacs), it is unlikely that HIV is, itself, the cause of this failure. HIV is more likely an opportunistic or synergistic infection that becomes manifest only in people predisposed to or with ongoing causes of immune suppression, just as cytomegalovirus and Epstein-Barr virus, which are also extremely highly correlated with AIDS, remain latent in immunologically healthy people, but are reactivated to produce significant viremia and immune suppression in people whose immune systems are suppressed (see references below).

Primary T-cell regulation of HIV explains why HIV is such a good marker for AIDS, regardless of whether it is a causative agent, a synergistic one, or an opportunistic one. If we assume 1) that reexposure to HIV is quite frequent among high risk groups; 2) that exposure to variant HIV strains is therefore common; 3) that only those with concomitant and ongoing immune impairment actually become infected; and 4) that of those infected, only those with ongoing immunological stimulation that adversely effects T-cell control of HIV

go on to produce antibody; then HIV-seropositivity becomes a very selective criterion for AIDS risk.

One would expect that whatever processes make an active HIV infection possible will also activate other latent viral disease agents. This is, in fact, the case. Both Epstein-Barr virus and cytomegalovirus reactivation and viremia — *not* the mere presence of antibody — have been reported to be accurate markers of AIDS progression (Biggar *et al.*, 1983; Drew *et al.*, 1985; Fiala *et al.*, 1986; Rinaldo *et al.*, 1986; Rahman *et al.*, 1989; Munoz, *et al.*, 1988; Sumaya *et al.*, 1985), and so have diagnostic signs of autoimmune processes such as the development of lymphocytotoxic antibodies and circulating immune complexes (Clerici *et al.*, 1992; Zarling *et al.*, 1990; Sonnabend, 1989; Daniel *et al.*, 1989; Ozturk *et al*, 1987; Stricker, *et al.*, 1987a, b; McDougal *et al.*, 1985). HIV antibody production and viremia, in other words, are only one of a very large *set* of immunologic events that occur simultaneously in people at high risk for AIDS, and any or all of these events can trigger the very wide range of interferon, interleukin, tumor-necrosis-factor, and other immunological events that are often mistakenly attributed solely to HIV (Sonnabend, Witkin & Portillo, 1984; Sonnabend, 1989; Papadopulos-Eleopulos, 1988; Root-Bernstein, 1993; Fauci, 1993).

The treatment implications are manifest. By the time active antibody production against latent viruses has begun in people at risk for AIDS, T-cell disregulation is already severe. Those people who seroconvert immediately following exposure to HIV can therefore reasonably be conjectured to have been previously or concurrently immunosuppressed by non-HIV agents, and I have summarized extremely extensive evidence to this effect elsewhere (Root-Bernstein, 1990a, c, 1992a, b, 1993). For example, progression to AIDS in hemophiliacs is highly correlated with low T-cell counts (T-helpers < 500) at the time of infection, whereas high T-cell counts (T-helpers > 750) are predictive of very slow progression (Lorenzo *et al.*, 1993; Sabin *et al.*, 1993). The object of AIDS prophylaxis must therefore be to prevent the immune system from decaying to the point that seroconversion becomes possible, or to eliminate ongoing factors that prevent seroreversion. It follows that antibody-stimulating vaccines may actually be detrimental.

Alternative approaches for treating HIV-seropositive people are needed that eliminate ongoing T-cell suppression and rebuild immunity. Some approaches that embody these principles have apparently been successful, as the next section will outline.

Myth 4: The only way to treat AIDS is to treat HIV

The need for understanding how to treat HIV infections and AIDS raises the fourth myth that has plagued AIDS research. For a decade, the paradigm for preventing AIDS has been to treat HIV, since it is believed that HIV was solely and completely responsible for all aspects of the pathogenesis of AIDS. It is now well established that this HIV-centered paradigm has not yielded any appreciable benefits for AIDS patients and no miraculous antiretroviral drugs or effective HIV vaccines are on the medical horizon (Weiss, 1993; Fauci, 1993). If we accept that AIDS is an immunological disease (rather than a virological disease) in which the major disruption occurs in T cells, and if we accept the fact that different risk groups, and different individuals within risk groups, progress to AIDS at different rates due to different cofactor exposures (see above, Myth #1), and that it is possible for some people spontaneously to eliminate HIV (see above, Myth #2), it becomes manifest that there must be effective approaches to treating people at risk for AIDS that do not depend upon targeting HIV. We need to identify and use these non-HIV-centered approaches to AIDS on the widest possible scale, regardless of whether we believe that HIV is needed to cause AIDS or not, if only because we do not have any effective way of controlling HIV directly at present, and have no real hopes of doing so within the next decade.

One approach that has yielded positive clinical trial results, but little fanfare, is immunologic reconstitution utilizing thymomimetic compounds to treat pre-AIDS patients (reviewed in Hadden, 1991). Gottlieb *et al.* (1991) have reported very good results in slowing AIDS progression in a multicenter, double-blind, placebo-controlled trial of the leukocyte-derived immunomodulator, IMREG-1, and the pharmaceutical agent has been approved by the U.S. FDA for full-scale clinical trials. Interest has also been increasing in the use of non-specific potentiators of delayed-type hypersensitivity (DTH) reactions, such as dinitrochlorobenzene (DNCB), that have been found to stimulate T-cell responses, and limited trials suggest some success (Mills, 1986; Stricker, Elswood & Abrams, 1991; Stricker *et al.*, 1993).

A second approach to AIDS is revealed by reviewing of all known cases of true seroreversion (see references in Myth #2 above). Such a review reveals that none of the seroreverters have been treated with antiretroviral drugs. Few, if any, of the cases have been

treated for AIDS-associated infections at all. Other factors seem to be operative.

One factor seems to be limited reexposure to HIV. Fribourg-Blanc (1988) noted that in the cases of spontaneous seroreversion he documented, exposure to HIV was limited to only one or a few instances. Certainly exposure was limited (by the death of the sexual partner) in the case of the hemophiliac wife described by Burger *et al.* (1985). Similarly, Farzadegan *et al.* (1988) report that seroreversion in their four gay men followed substantial lifestyle changes that included switching from multiple concurrent and multiple serial sexual partners to a single, stable sexual relationship, and rigorous implementation of safer sexual practices.

Personal interviews with three seroreverters who have provided me with the records of their HIV-testing have revealed that all underwent significant lifestyle changes. All three totally eliminated drug use, began practicing safe sex measures, and went on high-nutrient diets. These same factors were reported to be common to all of the long-term AIDS survivors profiled by Michael Callen in his book, *Surviving AIDS* (1990) and by anecdotal and self-reporting in *The Continuum Magazine* (England), *Praxis* (U.S.), and other publications by people with HIV.

Unfortunately, no formal studies of longterm survivors of HIV, or of significantly large groups of seroreverters have yet been carried out, so that it is impossible to say for certain what factors — genetic susceptibility, viral variation, viral load and reexposure, immunological status and at time of infection, subsequent exposure to cofactor infections or immune impairments from other sources such as chronic medical treatments, nutritional determinants — or other factors are responsible for the difference between healthy seroreversion and fatal development of AIDS. Some clues do exist, however, in a handful of well-controlled studies.

Substantial data indicating that elimination of one or more of the non-HIV immunosuppressive risks listed above substantially alters the rate of progression to AIDS in the absence of retroviral treatments. Studies of HIV-positive intravenous drug abusers show that the probability of progression to AIDS can be decreased by a factor of three or more by simply eliminating ongoing drug use (Groenbladh & Gunne, 1989; Weber *et al.*, 1990). Additional treatment for malnutrition and rigorous practice of safe sex procedures decreases the rate of HIV progression among IVDUs even further (Moretti, 1992).

Additional evidence for controllable cofactors in AIDS comes from studies of HIV-seronegative hemophiliacs who display pronounced decreases in CD4 counts, decreased capacity to produce interleukin II, and immune suppression (Watson & Ludlum, 1992; Hassett *et al.*, 1993; Madhok *et al.*, 1990; Hay, McEvoy & Duggan-Keen, 1990). This immune suppression has been related to factor VIII therapy (*ibid.*, and Farrugia, 1992), active cytomegalovirus and hepatitis C infections, and lymphocytotoxic autoantibodies. It is believed that affected hemophiliacs are consequently predisposed to HIV infection and an increased rate of development of AIDS (Sabin *et al.*, 1993; Goldsmith *et al.*, 1991; Higgins & Goodall, 1991; Madhok *et al.*, 1991; Schulman, 1991; Webster *et al.*, 1989; Daniel *et al.*, 1989). Replacing medium purity blood clotting factor concentrates with high purity, antibody purified, or recombinant factor that lacks viral and alloantigenic contaminates for the treatment of both HIV-seronegative and HIV-infected hemophiliacs has resulted in stabilization of T-cell counts, and in some patients, increasing T-cell counts over several years (Hilgartner *et al.*, 1993; Mannucci *et al.*, 1992; Gompert *et al.*, 1992; De Biasi *et al.*, 1991; Schulman, 1991). Increased T-cell counts are a very favorable prognosticator of continued health in HIV-infected hemophiliacs (Daniel *et al.*, 1991).

Another broadly effective approach to AIDS prevention is prophylaxis against cofactor infections. Vaccinations that have proven effective in delaying AIDS onset significantly include Mycobacteria (Kallenius, Hoffner & Svenson, 1989). Prophylactic treatment of cofactor infections such as cytomegalovirus and *Pneumocystis pneumonia* are also associated with decreased disease progression and also significantly improve survival among HIV-seropositive individuals (Odell & Green, 1990; Montaner *et al.*, 1991; Palestine *et al.*, 1991; Hoover *et al.*, 1993). Such results suggest that approaches to AIDS prevention that focus on cofactor prevention, elimination or control may be more effective than treatment of HIV itself and demonstrate that HIV alone is not responsible for AIDS. Thus, development of vaccines against cytomegalovirus, Epstein-Barr virus, hepatitis C, and a set of more effective and less toxic antiviral drugs might be more important for preventing AIDS than an HIV vaccine, and more widely applicable in other medical settings (Root-Bernstein, 1992b, 1993).

The evidence that cofactors are necessary to the progression of AIDS has now convinced a number of investigators that no comprehensive treatment of AIDS will be possible without addressing the full range of cofactors that may influence disease progression. For

example, Lafeuillade and Quilichine (1992) argue that the study of cofactors promises greater 'understanding of AIDS and hence its therapeutic approach'. Littlefield (1992), in an even stronger statement, says that it has now become clear that 'one or more supplemental mechanisms must be involved in the pathogenesis of AIDS,' beyond HIV infection *per se*, and that 'identification of the nature of this [these] supplemental process[es] has become essential for successful, nonharmful intervention'.

Since data concerning the role of cofactors as regulators of AIDS are limited, four types of tests need to be carried out to confirm the observation that elimination of ongoing immunosuppressive risks (including reexposure to HIV) is effective in preventing progression to AIDS. First, large-scale, formal studies of people exposed to HIV without seroconversion, people who have seroreverted, and longterm survivors of both HIV infection and AIDS are desperately needed. Such studies can conclusively demonstrate whether HIV is sufficient to cause AIDS.

Second, a large-scale formal study is needed of ongoing immunosuppressive risks among HIV-seropositive people progressing to AIDS. It is assumed, but by no means demonstrated, that the immune suppression manifest in such people is due solely to HIV, but no attempt has been made to investigate ongoing immunosuppressive exposures.

Third, a study of people exposed to the same sorts of immunosuppressive agents in the absence of HIV is mandatory. It is well established that all risk groups have some degree of immune suppression independent of exposure to HIV (reviewed in Root-Bernstein, 1993). No study has ever been carried out that has examined HIV-positive and HIV-negative individuals in the same risk groups, paired by ongoing non-HIV immunosuppressive risks. Do all severe hemophiliacs actively infected with hepatitis B virus, cytomegalovirus, Epstein-Barr virus, and using intermediate purity clotting factor experience the same T-cell depletion regardless of HIV infection, or not? To what degree is their T-cell depletion greater than or less than uninfected hemophiliacs, or those who use ultrapure factor, regardless of HIV status? (That we should even have to ask for such studies a decade after the discovery of HIV is a symptom of how poorly controlled and designed research on AIDS has been).

Fourth, a converse study is also necessary that could potentially prove that HIV is both necessary and sufficient to cause AIDS: I have challenged the medical community for four years now to find me a significant number of people (say 100 or more) with AIDS who have HIV as their sole immunosuppressive risk (as defined by the set of clinically recognized factors known to cause immune suppression that are listed in my book, *Rethinking AIDS* [Root-Bernstein, 1993]), whose T-cell counts and other immunological parameters were normal at the time of HIV infection, and who have nonetheless developed T-cell counts below 500 and an opportunistic infection. So far, no one has responded to this challenge. Surely it is not too much to ask that a hundred such cases be found among the hundreds of thousands of AIDS cases that have been documented, if we are to accept the oft-repeated assertion that HIV alone is sufficient to cause AIDS.

One caveat that must be understood in setting up the above-mentioned studies is that AIDS itself (as opposed to HIV infection) may not be reversible. AIDS may involve slowly progressive processes including vicious cycles in which multiple sets of infections coactivate one another, and autoimmune processes that inexorably cause immune system or other forms of systemic decay. It may not be possible to reverse AIDS by simple remediation of risk factors after a certain point in the disease, as both Sonnabend and I have pointed out.

We will need, in addition to preventative measures against AIDS, new, non-retroviral approaches to disease treatment of multiple, concurrent infections (many of which are not susceptible to individual antibiotics), ways to reverse autoimmune processes, and methods to reconstitute immune function. The frightening fact is that very little of this very necessary research has even begun. The HIV paradigm has blinded most researchers to the undeniable fact that every AIDS patient (as opposed to HIV-infected person) has one or more autoimmune diseases, and we do not know how to treat adequately, let alone cure, any human autoimmune disease; and that every AIDS patient, even if cured of their HIV infection, would still have sustained possibly irreversible immunologic damage. It is entirely possible that we may one day learn how to vaccinate against or eliminate HIV in AIDS patients and still have people dying of AIDS-associated autoimmune conditions and opportunistic infections simply because we have not yet begun to investigate the causes or cures of the relevant *immunologic* processes (Root-Bernstein, 1992a, b, 1993; Root-Bernstein & Hobbs, 1993).

Myth 5: AIDS must have a single etiologic agent

Another myth that has adversely affected AIDS research is the assumption, common to much of modern biomedical research, that every disease has a single etiological agent. As powerful as the one-germ/one-disease/one-cure paradigm has been in the development of modern medicine, it has now been admitted by most HIV experts that the immune system destruction observed in AIDS cannot be accounted for by any known mechanism of direct HIV pathogenicity (Cohen, 1993; Fauci, 1993; Gougeon & Montagnier, 1993; Littlefield, 1992; Lo *et al.*, 1991). Surprisingly, this admission has not, however, caused any major AIDS researchers to question whether HIV is therefore sufficient to cause AIDS. There are, however, other paradigms for disease etiology that are relevant to AIDS besides the one-germ paradigm that are fully consistent with existing data, as Sonnabend and Saadoun pointed out as early as 1984 (Sonnabend & Saadoun, 1984). Unfortunately, these alternatives are less well-known than the one-germ/one-disease dogma and their implications have been generally ignored (Root-Bernstein, 1993).

The least revolutionary alternative to the one-germ paradigm is the two-germ or infectious synergism paradigm (reviewed in Root-Bernstein, 1993). Perhaps the earliest proven case of virus-bacterium synergism was discovered by Shope in 1931, when he showed that neither *Hemophilus influenzae* nor an unidentified virus, each of which could be isolated from 100% of pigs who contracted fatal swine flu, was capable of causing disease in healthy animals. A combination of the virus and bacterium, however, nearly always caused a fatal pneumonia (Shope, 1931). A similar synergism was found by Dudding *et al.* (1972) between adenovirus and several bacteria, including *Hemophilus influenzae*, which caused fatal pneumonias in man. Huang and Hong (1973; and Huang *et al.*, 1973) found that multiple viral infections often resulted in the production of lymphocytotoxic antibodies in human patients, accompanied by significant immune suppression. Hamilton, Overall and Glasgow (1976) found similarly that combinations of murine cytomegalovirus with Pseudomonas, Staphylococcus, or Candida infections were much more likely to be fatal to mice than individual infections, even when the combined doses of infectious agents were thousands of times smaller. Another well-established human example is the combination of influenza virus with *Staphylococcus aureus* to yield a severe and often lethal pneumonia (Klenk & Rott, 1988). It is likely that the terrible influenza epidemic that killed so many people after World War I was in fact the result of two or more epidemics (one influenza, the other(s) unidentified bacteria that overlapped.

Significant evidence exists to suggest that HIV may interact synergistically by mechanisms such as transactivation or immunologic cross-reactivity with other infectious agents associated with AIDS, including herpes simplex viruses, cytomegalovirus, Epstein-Barr virus, HTLV-1, mycoplasmas, and mycobacteria (Littlefield, 1992; Lo *et al.*, 1990, 1991; Lusso *et al.*, 1990, 1991; Montagnier *et al.*, 1990; Root-Bernstein, 1990a, 1992a, 1992b, 1993; Wang *et al.*, 1992). All of these infectious agents are present in people in AIDS risk groups and in people with AIDS at incidences hundreds of times higher than in the general population (Buimovici-Klein *et al.*, 1988; Macon *et al.*, 1993; Root-Bernstein, 1993; Sonnabend, Witkin & Portillo, 1984; Sonnabend, 1989).

A second alternative to the one-germ model is the multifactorial or predisposition model. HIV may be an opportunistic agent that, like *Pneumocystis carinii* or cytomegalovirus, is not deadly except in immunosuppressed individuals. In this case, a broad set of immunosuppressive agents, including many addictive drugs, malnutrition, immunosuppressive infectious agents, and exposure to alloantigens in semen, blood, blood products, or contaminated needles may interact to set the stage for active HIV infection (Sonnabend, Witkin & Portillo, 1984; Sonnabend, 1989; Donohoe & Falek, 1988; Duesberg, 1990; Fernandez-Cruz *et al.*, 1988; Papadopulos-Eleopulos, 1988; Pifer *et al.*, 1987; Root-Bernstein, 1990a, c, 1993).

A third alternative model is an autoimmune model for AIDS. Virtually all people with AIDS have lymphocytotoxic antibodies present. Such antibodies are associated with a number of agents, including cytomegalovirus infection, exposure to blood and blood products, and immunologic exposure to semen, in both HIV and non-HIV infected individuals (Huang & Hong, 1973; Huang *et al.*, 1973; reviewed in Root-Bernstein, 1990b, 1992 a, b, 1993; Root-Bernstein & Hobbs, 1993; Root-Bernstein & DeWitt, 1994; Root-Bernstein & DeWitt, this volume). Significant debate surrounds the issue of whether HIV is necessary or sufficient to induce lymphocytotoxic autoimmune processes in AIDS, but significant data point to alloantigen and infectious agents other than HIV as targets for lymphocytotoxic antibodies in AIDS patients, in addition to HIV (Bjork, 1991; Dalgliesh *et al.*, 1992; Garry *et*

al., 1991; Kion & Hoffman, 1991; Stott, 1991; Ziegler & Stites, 1986; Sonnabend, 1989; Hoff & Peterson, 1989; Hoff *et al.*, 1991; Zarling *et al.*, 1990; Morrow *et al.*, 1991). I, personally, believe that the only way to explain any autoimmune disease, including the type that appears in AIDS, is by means of mutiple-antigen-mediated induction (Root-Bernstein, 1990b, 1991, 1993; Root-Bernstein & Hobbs, 1991; 1993).

It is extremely important to realize the statistical implications of multiple-agent-induced diseases (MAIDs), whether they are cofactorial, synergistic or autoimmune, for the epidemiology of such diseases. Very simply, MAIDs grow at rates that are multiplicative functions of the rate of growth of the individual agents. If, for example, two synergistic disease agents are each present in 1 in 1000 people, and the diseases are randomly distributed, then the probability that they will coinfect an individual is 1 in a million. Increasing the incidence of each agent by a factor of ten (so that each is now present in 1 in 100 people) results in a probability of combined infection of 1 in 10,000. In other words, a 10-fold increase in the incidence of individual disease agents results in a 100-fold-increased probability of acquiring a combined infection. Increasing the incidence of each agent by a factor of 100 (so that 1 in 10 people are infected) results in a probability of combined infection of 1 in 100, a 10,000-fold increased probability of co-infection. Thus, relatively small increases in the incidence of cooperative agents lead to extremely large increases in the incidence of the MAID they cooperatively cause. If the two diseases are co-transmitted, or are transmitted in a non-random way such as occurs in high risk groups for AIDS, then the probability of co-infection is obviously increased even further (Root-Bernstein & Hobbs, 1993). The MAID theory may therefore explain the observation that people in the advanced stages of AIDS seem to be more of an infectious risk to their partners than are people with uncomplicated HIV infections (European Study Group, 1989; Padian, Shibosla & Jewell, 1990): people with full-blown AIDS are, by definition, multiply infected.

The application of the MAID concept to AIDS is illuminating. One of the most important questions concerning the current epidemic of AIDS is whether HIV is an old or new virus. A variety of evidence suggests that both HIV and AIDS have existed in human populations for decades, and probably for centuries, prior to the recognition of the first AIDS cases or the discovery of the virus (reviewed in Root-Bernstein, 1990a, c, 1993). Why, then, did AIDS become epidemic only during the 1980s? One possibility, for which extensive evidence exists, is that the modes of transmission grew exponentially during the previous decade as can be verified by huge increases in all sexually transmitted diseases and drug use (both intravenous and otherwise) (Duesberg, 1992; Root-Bernstein, 1993). But these increased modes of transmission spread not only HIV, but many of its putative cofactors — whether they consist of co-infections, drugs, or exposure to alloantigens or all three — simultaneously. The simultaneous spread of HIV *and* cofactors (consider the co-transmission of hepatitis viruses and HIV in gay men during the late 1970s), in this case *non-randomly* in specific risk populations, would have resulted in increases several orders of magnitude larger in the incidence of any disease manifestations that are multiple-agent dependent. (Recall, on this point, that the incidence of HIV seropositive individuals must represent only a fraction of the people actually exposed to HIV —the fraction that did not successfully combat HIV without developing an antibody response, or who subsequently seroreverted — see Myth #2 above. Persistently HIV seropositive individuals therefore probably represent people who have ongoing cofactor exposure). I have, in fact, demonstrated that the incidence not only of HIV, but of *active* cytomegalovirus and Epstein-Barr virus infection, hepatitis viruses, Mycoplasma infections, addictive drug use, lymphocytotoxic antibodies, and various other immunosuppressive agents is often hundreds of times higher among high risk group populations than among low or non-risk heterosexuals and lesbians (Root-Bernstein, 1993), which would make the incidence of MAIDs tens of thousands of times higher among risk groups then in the general population. Thus, if AIDS is a MAID, both the time course of the epidemic, its exponential growth, and its maintenance within specific high risk populations can be explained by the unusual co-incidences of both HIV and all of its possible cofactors. If, on the other hand, AIDS is caused solely and simply by HIV, then neither the timing of the current epidemic nor its specificity for risk groups is comprehensible.

It should also be noted that a direct consequence of considering etiologies for AIDS that are more complex than a single agent immediately invalidates two standard approaches to determining disease causation: epidemiological correlations and Koch's postulates. If AIDS is more complex than a simple HIV infection, then the high correlation between HIV and AIDS (Koch's first postulate) is not sufficient to demonstrate that HIV is *the* causative agent. The observed corre-

lation strongly suggests that HIV is *one part of* the cause of AIDS, but it should be expected that other immunosuppressive agents and/or behaviours will be as highly correlated with either all AIDS cases, or with individual risk groups. Thus, it is not surprising to find that statistically significant correlations exist between AIDS risk and unprotected receptive anal intercourse in both men and women (Naz *et al.*, 1990; Adams *et al.*, 1988; Morrow *et al.*, 1991; Sonnabend, 1989; reviewed in Root-Bernstein & DeWitt, this volume); to use of inhalant nitrites by gay men (Vandenbroucke & Pardoel, 1989; Haverkos, 1988); to general use of drugs in all risk groups (Duesberg, 1992); and to the incidence of active infection (not presence of antibody) with cytomegalovirus, Epstein-Barr virus, and mycoplasmas in all risk groups (Buimovici-Klein *et al.*, 1988; Munoz *et al.*, 1988; Rahman *et al.*, 1989; Rinaldo *et al.*, 1992; Lo *et al.*, 1992; Wang *et al.*, 1992). But just as HIV is not sufficient to cause AIDS, so, apparently, are these agents not sufficient to cause AIDS. Thus, demonstration that people with exposure to these non-HIV agents do not get AIDS in the absence of HIV does not prove that they are not *part of the cause* of AIDS. What must be tested, both epidemiologically and experimentally, are their *combinations*. Moreover, there is no requirement in a multi-factorial disease that one specific pair of agents be necessary to cause the disease. One agent may have several different cofactors, none of which correlate highly with the disease. Or there may be several combinations of agents that can create the same pathological symptoms (as, for example, in the case of pneumonia), and therefore no single agent or set of agents that correlates one hundred percent with all clinically diagnosed cases of the disease.

What is at issue here are the criteria for evaluating disease causation. Koch's postulates, focusing as they do on a single etiologic agent, do not apply to diseases that are caused by multiple, interacting agents. Thus, the reason why HIV has failed to satisfy Koch's postulates, despite its obvious presence in virtually all AIDS cases, may have nothing to do with the oft-cited species specificity of HIV (an observation belied by the fact that HIV does infect and replicate in chimpanzee and macaque lymphocytes) but rather may result from the fact that Koch's postulates are irrelevant to testing AIDS etiology (Root-Bernstein, 1992b, 1993). HIV may not be able to cause AIDS because it is not *sufficient* to cause AIDS. This is no different than saying that neither influenza virus or Staphylococcus are sufficient to cause pneumonia. But both are *necessary*.

Diseases such as AIDS that are autoimmune in nature, or are the result of synergistic or multifactorial processes require the satisfaction of a set of postulates other than Koch's (Witebsky *et al.*, 1957; Root-Bernstein, 1991). For example, MAIDs may be characterized by satisfying the following criteria: '(1) two or more infections or immunosuppressive agents will be active simultaneously in individuals affected with a particular disease; (2) people with only one of these agents will either have no symptoms of the disease or symptoms of another disease that is associated with the single agent; (3) these multiple agents will be isolatable or identifiable individually; (4) no single one of these agents will be capable of inducing the disease by itself when introduced into healthy human beings or animals (although they cause different disease symptoms); (5) an immune response to each agent will be demonstrable during disease induction and will be significantly altered by the combination of agents as compared with any agent individually; (6) the disease will be transmissible from one animal or human being to another by means of an appropriate combination of the putative causative agents. In the case of autoimmune diseases, the transmissible factors may include tissue or purified proteins, immune serum, lymphocytes, other cells or antibodies' (Root-Bernstein, 1993). As far as I am aware, no one has yet set up an animal model of AIDS that would satisfy these criteria, and therefore model AIDS as a MAID. We cannot, therefore, rule out the possibility that AIDS is caused by some combination of agents, of which HIV is likely to be one.

The fact is that until someone is able to produce an animal model of AIDS using the exact set (or sets) of agents found in human beings (not merely analogous agents such as feline or simian immunodeficiency virus, for example), we will not know whether we are working with correct or incorrect theories of causation. My tendency is to believe that having failed to cause AIDS with HIV alone, we must assume that AIDS is more complicated than a mere retroviral infection. On the other hand, the same reasoning makes me reject Duesberg's suggestion that opiate or other drug abuse is the cause of AIDS: investigators have worked with animal models of addiction for decades without observing AIDS in their animals. Thus, AIDS is more than just HIV or just drugs or just any single agent that we currently understand. We must now build on what we know of HIV, but in such a way as to expand our range of research to look at how it behaves in the much more complicated conditions that actually exist in real AIDS patients with multiple infections,

blood product exposures, drug exposures, malnutrition, and alloantigen exposure. These conditions have never been duplicated in animals or test tubes.

On this final point I must insist upon the accuracy of the following observations. First, there is no documented case of anyone who has developed AIDS who does not have several of the following immunosuppressive agents at work prior to, concomitant with, or following their HIV infection: multiple, concurrent infections with identified immunosuppressive viruses and bacteria (e.g. herpes viruses, hepatitis viruses, and mycoplasmas); immunologic exposure to alloantigens (e.g., semen, blood or lymphocytes); chronic or high dose treatments with antibiotics; anaesthetics; chronic or high dose use of immunosuppressive addictive drugs irrespective of mode of use (e.g., heroin); malnutrition; and autoimmunity directed at T-cell subsets (reviewed in Root-Bernstein, 1990a, c; 1992 a, b; 1993). As a result of these immunosuppressive risks, many hemophiliacs, blood transfusion patients, drug abusers, infants of people in these risk groups, and homosexual men are significantly immuno-suppressed even in the absence of HIV infection (reviewed in Duesberg, 1992; Root-Bernstein, 1990a, 1993). Second, and conversely, there is no evidence that HIV can cause disease in an immunologically healthy person free of these causes of immune suppression: people with limited exposure to HIV and no ongoing risks of the sort just enumerated, do not become infected with HIV or serorevert (see above); and there appear to be no verifiable tertiary cases of AIDS (i.e., non-risk group heterosexual to heterosexual transmission) in Western nations. AIDS is therefore remaining in identified risk groups (National Research Council, 1993; Fumento, 1990) — a fact that cannot be explained except if prior immune suppression or cofactors are necessary for HIV transmission and seroconversion.

New directions in AIDS research

The recognition that AIDS may be more complex than HIV is important because it allows us to re-evaluate existing data in new ways that reveal both new problems and new solutions to the epidemic. For example, any multiple-agent-induced disease (MAID) can be eliminated by controlling any of the multiplicity of necessary agents. Thus, we need not target only HIV in order to control AIDS, if AIDS can be demonstrated to be a MAID. Both HIV and its cofactors (see Myth #4 above) become viable targets for prophylaxis, treatment and cure. Indeed, one of the reasons that current public health policies such as safer sex, elimination of drug use, and clean needle exchanges may be working effectively in many communities (Van Griensven *et al.*, 1989; Judson, 1990; Winkelstein *et al.*, 1988; Weber *et al.*, 1990) is that both HIV and many of its cofactors are *simultaneously* being controlled. According to the MAID theory, the result of simultaneous control should be a reduction in new AIDS cases that is a multiplicative function of HIV and cofactor prevalences. This possibility mandates a much higher interest in non-HIV factors associated with AIDS than has thus far been manifest.

Beyond the obvious point that there are models of disease causation (and therefore prevention and treatment) that have been ignored by the majority of AIDS researchers lies an even more important point: scientific research consists of elaborating all of the possible explanations of a phenomenon and then eliminating, through controlled observation and experiment, all but one of these (Root-Bernstein, 1989). Because this is the way all good science works, philosophers and practitioners of science both agree that one can never prove that the remaining answer is true; one can only prove that all of the other possibilities are not (Popper, 1962; Medawar, 1967). (Anyone who remembers learning Mendelian genetics will recall that the key to solving genetics problems is not determining what type of inheritance explains any particular cross, but remembering all of the different possibilities and searching for the crucial evidence that makes all but one of them untenable). Good scientific research therefore consists primarily of performing experiments that *disprove* theories, rather than gathering data that purport to support a preconceived notion.

In pointing out that too much AIDS research has been directed by myths that have been accepted uncritically by the majority of investigators, and that several well-established models of disease causation have been ignored as well, I am therefore arguing that AIDS research as a whole has not followed standard scientific practice of skeptical elaboration of possibilities followed by disproof. Instead, the community of AIDS researchers has reversed standard practice by leaping to the conclusion that the first obvious answer (HIV) must also be the best and the most correct answer. Until it can be demonstrated that no other possible explanation of AIDS exists besides HIV *alone*, and until specific tests are performed to attempt to *disprove* the HIV theory, there is no methodological justification for

limiting research to HIV *alone*. This is basic scientific method.

Einstein had some advice to scientists. He said that when devising a theory, make it as simple as possible and no simpler. My view of AIDS research, which owes a great deal to the pioneering work of Joseph Sonnabend, is that both those who study HIV and those who refuse to acknowledge its role in AIDS have oversimplified. AIDS is complex. AIDS is multifactorial, and the diverse factors that are correlated with the various risk groups for AIDS all interact synergistically. Until we understand these interactions in their full complexity and set up appropriate experiments to test whether any of them are relevant to AIDS pathogenesis, we will continue to act, as we act today, like the blind men describing the elephant, each attributing all of AIDS to the part of the thing with which we are in closest contact (Root-Bernstein, 1993). Meanwhile, people with AIDS die as a result of our blindness.

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