

Rethinking

AIDS

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Cofactors, HIV-Free AIDS, and the Shape of the U.S. Epidemic: More Conundrums for the HIV/AIDS Hypothesis

The hallmarks of a good hypothesis are its ability to cogently explain current observations, and accurately predict future ones. Attempts to salvage poor hypotheses, which do neither, are characterized by increasing and imprecise reliance on secondary assumptions and revisionist interpretations in light of new data.

The failure of the first version of the HIV/AIDS hypothesis, which held that HIV was a directly cytotoxic virus that specifically infected and killed T4 cells, has spawned a variety of new, unproven explanations of how HIV causes AIDS (see *The New Scientist*, 18 July, 1992), some of which are incompatible with each other (and with the possibility of vaccinating against AIDS). This inability to offer even a basic mechanism is dismissed as being irrelevant to the issue of causation by absurd statements such as, "We haven't the foggiest notion how *Mycobacteria* cause leprosy or TB" (attributed to Anthony Fauci in the same *New Scientist* article), or by asserting the formulaic, "Where there is HIV there is AIDS, and where there is no HIV, there is no

AIDS." Similarly, it is widely believed that both HIV infection and AIDS are growing epidemics in the United States and other countries.

As discussed below, the "cofactor" hypothesis, recent acknowledgment of HIV-free AIDS cases, and the actual shape of the U.S. AIDS epidemic (which are all incompatible with general perceptions of HIV's role in AIDS) at the very least demand a clear restatement of the HIV/AIDS hypothesis that defines, both scientifically and with respect to public health policies, precisely what is meant by "cause."

—The Editors

Cofactors: HIV Without AIDS

The growing acceptance of the idea that infection with HIV is not a sufficient prognosticator of future disease represents the first crack in the monolithic version of the HIV/AIDS hypothesis. The most extreme form of this idea was attributed, by *Nature's* editor John Maddox, to Luc Montagnier, the discoverer of "HIV," when he wrote, "Montagnier said clearly what he meant. HIV is a necessary but not, without the cofactor, a sufficient cause of AIDS" (*Nature* 1992, 357:189). But any form of cofactor hypothesis, whether weak or strong, must explain how the cofactors act jointly to destroy T cells that neither alone can kill. In addition, proponents of cofactors must be consistent and acknowledge the implications of their new hypothesis, the most obvious being that HIV antibodies alone are neither a death warrant nor justification for administering toxic drugs, like AZT.

—Harvey Bialy

H.B. is the Research Editor of *Bio/Technology*.

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AIDS Without HIV

HIV-free cases of AIDS are not new. They have been reported in the medical literature since 1986. Cases since 1986 have been verified to be uninfected over extended periods (6 months to several years) using ELISA, Western blot and PCR. Patients have developed low CD4 counts, Kaposi's sarcoma, disseminated candidiasis, disseminated tuberculosis, thrombocytopenia, and other opportunistic infections (Root-Bernstein, 1990, *Pers. Biol. Med.*, 33:480). Cases matching the CDC surveillance definition of AIDS can also be found in the medical literature as far back as 1872, well before HIV is assumed to have emerged (Hummer et al., 1987, *Rev. of Inf. Dis.*, 9:1102).

The number of HIV-free cases is significant. As of 1989, the CDC reported that 5% of all U.S. AIDS patients who had been tested for HIV to that time were HIV-negative. No figures have been reported by the CDC since 1989.

The existence of HIV-free AIDS proves that HIV is not a necessary cause of acquired immunodeficiency. This does not preclude HIV from playing some role in most AIDS cases,

but it may also mean that HIV is not the primary immunosuppressive agent in AIDS.

If non-HIV immunosuppressive agents can cause AIDS in HIV-free people, they can also cause AIDS in HIV-infected people. Essentially all AIDS patients have several immunosuppressive risks concurrently. The public acknowledgment of HIV-free AIDS makes it untenable not to reconsider the idea that these agents are themselves sufficient to cause AIDS. It is unlikely that a new, previously unknown virus related to HIV is the cause of HIV-free AIDS. Given the amount of work done on HIV over the past years, the possibility that a new lymphotropic virus related to AIDS has been overlooked by almost every laboratory in the world is remote. It is much more likely that HIV-free AIDS cases are due to known causes of immunosuppression that have not previously been considered significant by mainstream researchers.

—Robert Root-Bernstein

R.R.-B. is an Associate Professor of Physiology at Michigan State University.

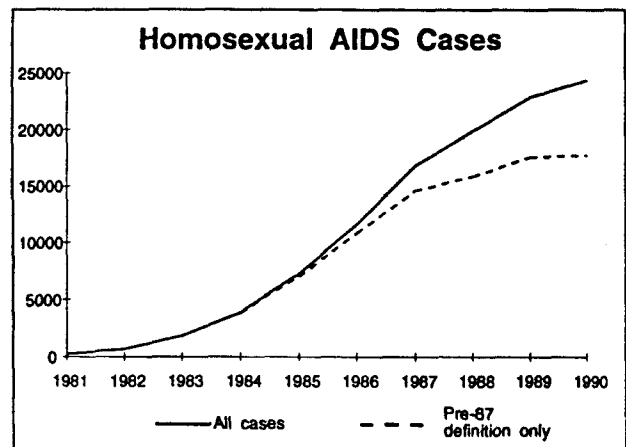
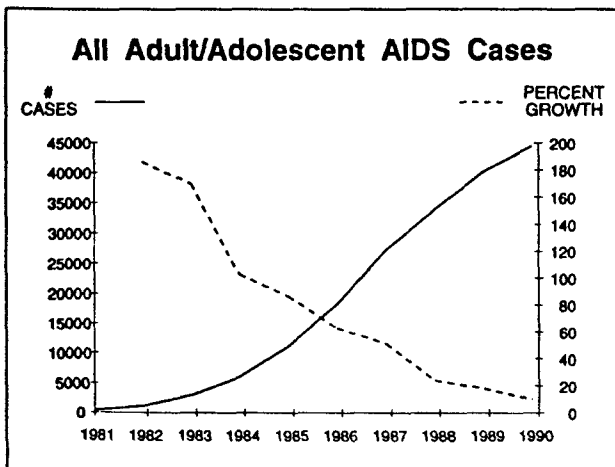
AIDS in the U.S.: A Growing Epidemic?

The following analysis is based on AIDS cases reported to the Center for Disease Control (CDC) through December 31, 1991. In order to obtain a clear picture of the growth of the epidemic, cases must be viewed by diagnostic year. This is accomplished by analyzing the lag between the date an AIDS case is diagnosed and the date it is reported to CDC. A series of "lag completion" factors can be generated from an analysis of prior lag patterns. For example, by the end of 1991, virtually all cases diagnosed prior to 1987 have been reported. On the other hand, based on prior years' actual runout, we can expect approximately 20% of cases diagnosed in the 4th quarter of 1990 are still unreported.

In the exhibits that follow, actual cases reported by diagnostic year have been increased by "lag completion factors"

to reflect expected ultimate reporting. So much of 1991 diagnoses remain unreported that 1990 is the last year used.

The most elementary evaluation of the growth of the epidemic entails solving for the annual growth rate. The growth rate is the number of cases diagnosed in the current year divided by the number of cases diagnosed in the prior



year. Converting these numbers to percentages (as shown in the graph), one can readily see that the growth rate of the epidemic has decreased every year since 1982 and is approaching zero. The inevitable conclusion is that the epidemic is cresting, and the number of cases diagnosed will begin to decline. This can already be seen in certain patient risk groups.

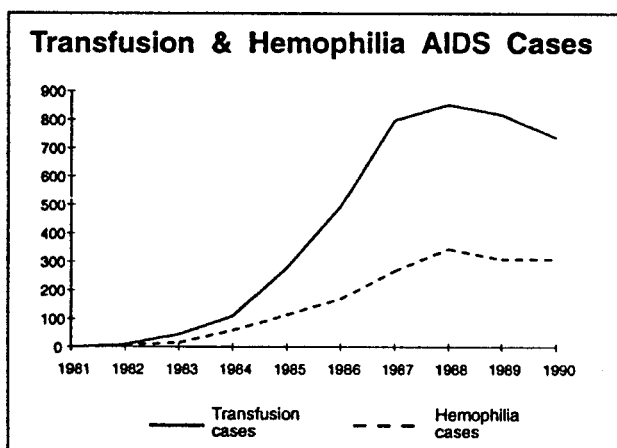
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A Growing Epidemic?

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The homosexual AIDS cohort, which accounted for 55% of all cases diagnosed in 1990, is shown in the accompanying graph. When all cases are counted, the cohort is seen as approaching a crest. However, when only those homosexual AIDS cases meeting the more limited 1985 definition are counted (which provides consistency throughout all diagnosed years), the crest is clearly seen in 1990. The expanded definition has added 38% more cases in 1990 and delayed the epidemic's crest.

Graph 3 shows that the hemophiliac cohort and the blood transfusion cohort both crested in 1988. This is a most curious result. "Evidence from several studies indicates that



exposure to HIV began in 1978 for the U.S. hemophiliac population and that 70-85% of this population had been infected with the virus by the end of 1984, most becoming infected in 1981-82" (McGrady, et al., 1987, *American Journal of Epidemiology*, 126:25). The U.S. hemophiliac population was estimated to be 14,467 as of 1980 (National Heart, Lung and Blood Institute, DHEW pub no. NIH 77-1274). This equates to about 11,000 HIV+ hemophiliacs, infected for 10 years, only 1,713 (15.6%) of whom developed AIDS. The median incubation period implied by these statistics begins to approach 25 to 30 years. This is tantamount to saying that for a significant percentage of hemophiliacs, HIV infection does not lead to AIDS, because the incubation period exceeds the life expectancy.

It is estimated that 12,000 transfusion recipients were infected with HIV in the early 1980s before regular screening of the blood supply was implemented (Ward et al., 1989, *NEJM*, 321:947). Through 1990, about 35% had been diagnosed with AIDS. This would imply a 10 year median incubation period. Perhaps the more interesting observation with respect to transfusion AIDS is that HIV seropositivity does not appear to confer increased mortality. A 1989 study by Ward and colleagues at the CDC, designed to ascertain whether HIV increases risk of death after transfusion, reported that "of 233 recipients [HIV+ transfusion cases] whose medical records were lo-

cated, 95 (41%) had died within one year of transfusion By comparison, 73 (50%) of 146 recipients of components from a random selection of donors not known to be infected with HIV died in the year after transfusion" (Ward, et al., *ibid.*). Thus transfusion cases with HIV actually had a better mortality than transfusion cases without HIV (41% vs. 50%).

The intravenous drug user cohort evidences the same pattern as the homosexual cohort, but is less mature and thus further from its crest. And the heterosexual cohort is the least mature of all. The growth rate in this cohort has decreased every year, but the growth rate in 1990 is still a substantial 39%.

Along these lines, it is of interest to note that heterosexual AIDS remains virtually nonexistent among teenagers. There have been only 5 cases ever reported of teenage male heterosexuals contracting AIDS through sexual activity (1 case in 1990 and no cases diagnosed in 1991), and only 89 female cases (26 cases in 1990 and 13 diagnoses so far in 1991).

It is difficult to reconcile estimates of HIV infectivity with the above analysis of AIDS cases. One reason is that the CDC changes its estimate of HIV prevalence retroactively. E.g., in *MMWR* Vol. 38/No. 5-4 (May 12, 1989), CDC said, "Thus, while variable, the observed HIV antibody prevalence data are compatible with CDC's 1.0 million-1.5 million working estimate, particularly with the lower end of the range." Then, in *MMWR* Vol. 39/No. RR-16 (November 30, 1990), "CDC now estimates that approximately 750,000 persons in the United States were infected with HIV at the beginning of 1986." They also estimated HIV infections as of July 1989 at "approximately 1,000,000."

These CDC estimates are based largely on back-calculation methods. Back-calculation assumes that the incubation curve is known and that the epidemic's curve is known (from reporting of actual AIDS cases). Thus, one can solve for the implied HIV infection curve that produces the incubation period assumed and the number of cases actually materializing. It is apparent that if one changes the incubation assumption, HIV prevalence changes.

The CDC also uses extrapolation from empirical data as a method to arrive at HIV prevalence. Such empirical data include military studies, Red Cross blood donor studies and studies of homosexual male cohorts. Interestingly, a pilot survey of Dallas County, Texas in 1989, designed to measure HIV prevalence in the general population, did not corroborate the back-calculation models used by CDC. In fact, even after adjusting upward to reflect non-response bias, the survey estimated HIV infections at a number 50% to 70% lower than three back-calculation models. Similarly, data from the six pilot sentinel hospitals, which are located in cities that in the aggregate have an HIV prevalence in applicants for military service of approximately the national average, show a median prevalence of .24%. This would translate to 600,000 HIV infections in the U.S. general population of 250,000,000.

—Robert Maver

R.M. is an actuary with 17 years experience in the life and health insurance industry.

Falsification and Progress

Progress in the science of biology, like progress in biology itself, depends almost entirely on falsification. Evolution has "falsified" billions of point mutations to produce the readers of this newsletter. Falsification is the critical element for progress. It provides room for alternative ideas.

David Horrobin, the editor of *Medical Hypotheses*, writing in *The Scientist* (November 1990), notes: "Biomedical science may be more complex than physics and chemistry

The Group for the Scientific Reappraisal of the HIV/AIDS Hypothesis came into existence as a result of our efforts to get the following four sentence letter published in a number of prominent scientific journals. All have refused to do so.

"It is widely believed by the general public that a retrovirus called HIV causes the group of diseases called AIDS. Many biomedical scientists now question this hypothesis. We propose that a thorough reappraisal of the existing evidence for and against this hypothesis be conducted by a suitable independent group. We further propose that critical epidemiological studies be devised and undertaken."

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and therefore a more difficult field in which to theorize. But if we do not try we shall certainly not succeed." "We, more than any other scientists, labor under the misapprehension that our observations are theory-free. Because we are so little conscious of theory we fail to develop coherent underlying concepts against which our observations are clearly tested." "We have no tradition of analytical criticism of existing theoretical concepts." In addition, "... most established scientists do not actually want to make rapid progress. A state of atheoretical confusion is agreeable to them because in that state almost nothing can ever be shown to be wrong ... As a result, general beliefs persist within the biomedical community long after the evidence is available to destroy them."

One of these general beliefs holds that all viruses are pathogenic, because some of them are. According to Gallo and Montagnier a new virus must cause a new disease, their "new disease—new agent" postulate (*Scientific American*, 1988, 259:41). This seems plausible because in this century some of the worst human epidemics, the small pox, yellow fever, flu and most recently polio, have all been diagnosed as viral diseases and most have been eliminated or controlled with vaccines developed by scientists whose names are still household words, like Andrewes, Burnet, Enders, and Sabin. But in fact, most viral infections, even by potentially pathogenic viruses, are latent or restricted to small numbers of cells and hence asymptomatic. Above all, the modern virus hunters pursue their latent viruses oblivious to the lessons of lysogeny. Lysogenic lambda phage provided the first examples of how even the most deadly viruses can be harmless genetic passengers, as long as their cytotoxic genes are inactive.

Despite enormous efforts to date, the belief that the latent virus HIV is the cause of AIDS has not been proven and has not yielded clinically useful results, a traditional indication for a poorly grounded hypothesis. Instead it has generated unprecedented volumes of scientific dinosaurs and a pandemic of public hysteria. According to Horrobin "...discovery in science almost always begins with an observation that can be seen to be anomalous against the background of a *clearly defined* theoretical construct." It is hoped that AIDS will be the ultimate loser in the present battle for the best hypothesis.

—Peter Duesberg

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"I think we should put the same weight now on the cofactors [as we have on HIV]."

—Luc Montagnier at the 8th International AIDS conference, Amsterdam, July 1992