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LETTERS

HIV and AIDS

The article "Keystone's blunt message: 'It's the virus, stupid' " by Jon Cohen (News, 16 Apr., p. 292) describes the state of the art of AIDS research, but also the state of the minds of AIDS researchers (*1*). Cohen writes that to AIDS researchers it is either a "conundrum," or "many puzzles," or a "disparity" that "the immune system collapses despite . . . only minute amounts of HIV . . . ." Yet they reject an alternative explanation as an "anti-HIV hypothesis" and dissidents with the slogan "It's the virus, stupid." Is a non–HIV-AIDS hypothesis stupid because it is an anti-HIV hypothesis?

The drug-AIDS hypothesis I have proposed is not a puzzle. It predicts AIDS after individuals inject themselves with psychoactive street drugs (as more than 80,000 American AIDS patients have done) and after they inhale mutagenic and toxic nitrites (as many male homosexual AIDS patients have done) for the 10 years that it is said that HIV requires to cause AIDS (*1*). It also predicts immunodeficiency from the killing of the highly proliferative cells of bone marrow with the DNA chain terminator AZT (*2*), which is currently prescribed to more than 200,000 HIV-positive people with and without AIDS (*1*).

Indeed, the recent summit of HIV trackers that Cohen reviews has provided the best alibi yet for HIV: "Using creative new techniques . . . that are much more sensitive than previous methods, several scientists have found that there is far more HIV in infected people than was previously thought." For example, "quantitative competitive PCR" (polymerase chain reaction) analysis was shown by George Shaw and his colleagues (M. Piatek, Jr., *et al.*, Reports, 19 Mar., p. 1749) "to be as much as 60,000 times more sensitive than culture-based plasma viremia assays at detecting HIV in plasma." But does it help the emperor to wear clothes that can only be seen with "creative new techniques"?

In my view, Shaw and his colleagues virtually prove, with an impressive and exhaustive collection of new data, that HIV is not the cause of AIDS. (i) During the primary infection, before immunity, there are 10 to 10^4 infectious HIVs and 3×10^5 to 2×10^7 HIV RNAs per milliliter of plasma. Thus the new technique sees indeed 10^3 to 10^5 times more RNA than infectious HIV. But there is no AIDS, and the T cell counts are normal. (ii) After immunity, there are no infectious HIVs and about 10^3 to 5×10^5 HIV RNAs per milliliter of plasma. There is also no AIDS, and the T cell counts are normal or almost normal. (iii) Once immunodeficiency is acquired and AIDS appears, there are no infectious HIVs per milliliter in 5 out of 27 cases, fewer than 25 in 6 out of 27 cases, and 10^2 to 10^5 in 16 out of 27 cases. HIV RNAs range from 3.6×10^4 to 9×10^6 per milliliter, despite the complete absence of T cells, the presumed source of HIV, in several HIV RNA-millionaires! The fluctuation of infectious HIV from 0 to 10^5 in otherwise identical AIDS patients indicates to me that HIV is not the cause of AIDS, but instead an optional opportunist of immunodeficiency.

If HIV were the cause of AIDS, T cells would drop and AIDS would appear during the primary infection, when HIV titers are high and there is no antiviral immunity. But if it were an opportunist of an immunodeficiency induced by another cause such as drugs, its titer might be either high or low or zero, exactly as Shaw and his colleagues report. Thus HIV appears to be just another AIDS opportunist like *Pneumocystis carinii*, candida, cytomegalovirus, and so forth. Sound stupid? And are the more than 3000 documented HIV-free AIDS cases (*1*) stupid too?

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Response: Duesberg's views on the pathogenesis of AIDS (*1*), responses to his hypothesis from other investigators (*2*), and comments on the rhetorical approaches Duesberg has employed in presenting his views (*3*) have been sufficiently documented in the literature to preclude the need for recapitulation here. Suffice to say that, in contrast to the interpretation offered by Duesberg, we believe our results, along with the data presented in recent publications by Pantaleo *et al.* (*4*) and Embretson *et al.* (*5*), in combination with an extensive body of clinical, epidemiological, and laboratory data accumulated over the past 12 years [reviewed in (*6*)], are

consistent with a central role for HIV-1 in the pathogenesis of AIDS. While Duesberg is entitled to his opinions, we share neither his views on the pathogenesis of AIDS nor his interpretation of our results.

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There is no question that people infected with HIV will eventually develop AIDS, and one should take every precaution to avoid becoming infected. There is also no doubt that we could cure AIDS if we could eliminate HIV from the body of infected individuals. Unfortunately, this is an unrealistic goal. In order to develop more effective AIDS treatments that might induce remission, we need to pay more attention to the human immune system, and not just the virus. As in the many other mammalian diseases associated with retroviruses, the immune system itself is partly to blame for AIDS. In this sense, the political slogan, "It's the virus, stupid," may be counterproductive.

In a recent clinical trial of an experimental AIDS vaccine (*1*), we found a statistically significant negative correlation between the proliferation of CD8-type lymphocytes and the survival of CD4-type lymphocytes. An increase in CD8 cells and a decrease in CD4 cells are both characteristic of AIDS, and the latter leads to the immune deficiency that characterizes the disease. By "correlation," we do not just mean that CD8 cells increased as CD4 cells decreased. If it were that simple, both phenomena could be independent effects of HIV infection. We also mean that a vaccine used to reduce CD8 cells caused a rebound in CD4 cells. This would not be possible if the virus were the whole story.

Perhaps a more compelling example is the response of an HIV patient who was injected with a test dose of monoclonal antibodies that produced a marked decrease

1993
AAAS Philip Hauge Abelson Prize
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The AAAS Philip Hauge Abelson Prize, established by the AAAS Board of Directors in 1985, is awarded annually either to:

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in the patient's suppressor CD8 cells (*2*). Within 3 days, the patient's CD4 cells had rebounded into the normal range, with the CD4 percentage rising from 15 to 36%. Although the effect of one dose was short-lived, it underscores the important role of the immune system in the destruction of CD4 cells and the fallacy of focusing on the virus alone.

Readers interested in the mechanisms by which HIV-stimulated CD8 cells kill CD4 cells may refer to the work of Zarling *et al.* (*3*). The main point is that restricting attention to HIV may preclude the development of promising therapeutic approaches, such as those outlined above.

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During the past decade, several investigators not mentioned by Cohen have emphasized the role of the lymphoid organs as a reservoir for HIV-1, especially the group of Paul Rácz and Klara Tenner-Rácz in Hamburg, Germany. These investigators put the presence of HIV-1 particles and proteins in the germinal centers into the broader perspective of the physiological function of these anatomical sites (*1*). They emphasized the follicular dendritic cells (FDCs), which form an intricate network of dendrites in close contact with B cells, and which are the pivotal antigen-presenting cells in the generation and maintenance of B cell memory because they retain immune complexes. Embretson *et al.* (*2*) extended this work, using advanced polymerase chain reaction techniques, and several other European and American groups, using similar histopathological approaches, made early crucial contributions [cited in (*1*)].

The finding that CD8-positive cells infiltrate germinal centers during the development of AIDS, including detailed quantitation of CD8 cells in the germinal centers (*3*), has been described extensively in these earlier studies. However, clear hypotheses about the role and function of these cells were scarce. Therefore, my colleagues and I postulated that they are involved in cytotoxic activity directed against the FDC network (*4*). This network progressively degenerates and eventually disappears over the course of HIV-1 infection and the development of AIDS, which leads to the loss of lymphoid architecture and to

dramatically altered immune responsiveness (*1*). It is possible that the immune complexes which are retained on the membrane of FDCs by Fc- and C3b-receptors during the physiological process of B memory cell formation serve as a target for CD8-positive cytotoxic T cells (*4*). The abundance of HIV-1 particles and of immune complexes containing HIV-1 antigens in the germinal center may promote access of $CD8^+$ cells to this anatomical site, where these cells are not found in control lymph nodes. Some HIV-1 antigens mimic self-proteins and may provoke autoimmune-like reactions. In addition, the $CD8^+$ cells in the lymphoid follicle may belong to the population of $CD8^+$ cells (*4*) that secrete a soluble factor which inhibits HIV-1 replication (*5*).

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Sorry, Doctor

I was appalled to learn of the new layers of bureaucracy established at the National Institutes of Health (NIH) for controversial proposals (News & Comment, 26 Mar., p. 1820). The establishment of the protocol implementation review committees (PIRCs) and a second-tier "panel to review the research further" has significant, adverse consequences for many clinical and basic researchers. Doesn't the premier research institution in the world know that research, by definition, is controversial?

Just think of the potential "good" such a bureaucracy could serve. Fetal tissue research? Nope, can't fund it. Too controversial. Research about children's knowledge about sex and birth control? Nope, can't fund it. Has offensive language in the questionnaire and it's too controversial. Racial violence research? Nope, can't fund it. Might upset certain minority groups. Animal research? Nope, can't fund it. The animal rights lobby is too strong. Besides, it's too controversial. Cochlear implants for deaf infants and children? Nope, can't fund it. A few deaf advocacy groups think that