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LETTERS

"The Duesberg Phenomenon": What Does It Mean?

Science is to be commended on a balanced and objective examination by Jon Cohen of "The Duesberg phenomenon" (Special News Report, 9 Dec., p. 1642). We in the field of AIDS research can only hope that Peter Duesberg and his supporters will be equally fair as they reassess their hypothesis that acquired immunodeficiency syndrome (AIDS) is caused by agent(s) other than the human immunodeficiency virus (HIV).

The essence of science is objectivity and open debate. Duesberg's critics and supporters alike would not deny him his opportunity to examine the body of evidence supporting alternative causation for AIDS; one would hope science has progressed from the era of Galileo when contrary opinions were held as heresy. But this reexamination needs to go both ways.

Cohen's excellent point-by-point analysis of the data cited to advance the counter-HIV hypothesis should provide Duesberg and his supporters food for rethinking their arguments. That they do so with equal frankness is imperative, for their own credibility, as well as for the example they set. As Duesberg travels and speaks to audiences, especially to young scientists-in-training and the AIDS community, he needs to be fully aware of the heavy responsibility that accompanies a high profile and teach the real lesson of science—trust the facts to speak for themselves.

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Although different viewpoints about Peter Duesberg's hypothesis that HIV is not the cause of AIDS should be presented, we question the usefulness of devoting eight pages of a *Science* Special News Report to "The Duesberg phenomenon." As AIDS researchers, we were disappointed that important information from nonhuman primate models of AIDS that fulfills Koch's postulates and demonstrates the usefulness of antiretroviral treatment was omitted. There is no animal model of any human infection that reproduces exactly all aspects of a human disease. Accordingly, no animal model of HIV infection reproduces exactly all aspects of human AIDS. However, a

closely related primate lentivirus causes infection and immunodeficiency in macaques (simian immunodeficiency virus, SIVmac) that is remarkably similar to HIV infection and AIDS in humans. Well-documented observations from the SIVmac-rhesus macaque model of AIDS have addressed Koch's postulates (1). In addition, the beneficial effects of AZT treatment on SIV infection are clearly shown in our experiments: Newborn rhesus macaques infected with SIVmac developed rapid, fatal immunodeficiency (five of six animals died within 3 months); in contrast, SIV-infected neonatal macaques treated with AZT had reduced levels of SIV and very slow disease progression (seven of nine animals were healthy after 15 months), while uninfected control neonatal macaques that received prolonged AZT treatment all remained healthy (2). We think that data from animal models of AIDS is not only relevant, but critical to the success of research on human AIDS and should be reviewed with as much emphasis as was given to "The Duesberg phenomenon."

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As one of those interviewed for Cohen's article about Duesberg, I would like to clarify what I said to him. In response to a question concerning my support for Duesberg's theory that HIV does not cause AIDS, I clearly stated my position that evidence for the HIV-AIDS hypothesis remains at the level of correlation and that Duesberg is correct in asserting that there is no direct proof for the hypothesis. Nothing in Cohen's article shows any data that moves that hypothesis from correlation to proof. Inability of HIV research to move beyond correlation to causality is the major issue so easily glossed over and is the essential reason why the Duesberg phenomenon has refused to go away. Instead of facing this issue squarely and looking for alternative explanations, we are continually exposed to a mountain of HIV molecular biological data that, while technically excellent, re-

mains circumstantial with regard to cause. How many times does this simple concern need to be stated before journals like *Science* begin to ask for a more rigorous approach?

In response to my comments, Cohen mentioned three cases of workers infected with HIV who then developed AIDS. I responded that surely after 10 years and billions of dollars of intensive research there should be more evidence than three cases where HIV-positive status was correlated with immunodeficiency and AIDS (still no direct proof that HIV kills immune cells in humans). We have seen "clear" cases like this before that were regarded as convincing by some scientists that HIV caused AIDS, but concerning which later investigation revealed a more complicated situation, with possibly other pathogenic factors at work. So anecdotal sampling such as that offered by Cohen proves nothing.

But even accepting the three cases, which remain unpublished in a peer-reviewed journal, can we not agree that, for any other research paradigm with so much time and money spent for so meager a result, we would by now have mounted a research attack with a much broadened base of inquiry—in this case, a base that went beyond a virus-only hypothesis, and one that took seriously many of Duesberg's crit-

icisms, and others as well, that immunodeficiency has many causes? In light of so much that Duesberg offers as reasonable objection, does it not seem equally reasonable that our research base be broadened to include well-controlled studies that directly test the killing powers of drugs, and other negative addictions, on immune cells?

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Cohen's articles about Peter Duesberg and AIDS leave the impression that drugs and HIV are the only two contenders for the cause of AIDS. The difficulty of transmitting HIV sexually is well known, an average of 1000 heterosexual and 100 to 500 homosexual contacts being required (1). It is simple logic to infer that the average patient who contracted HIV infection this way has been infected with other viral and bacterial agents, as many of them are much more contagious than HIV (2, p. 31). A similar case can be made for the other major AIDS connection, intravenous drug use. The usual argument against the involvement of herpes, hepatitis, and cytomegalo-

virus, as well as the bacteria of syphilis and gonorrhea, is that they do not show a sharp enough difference of incidence in people with and without AIDS to account for the disease, and they have always been around anyway. This argument does not take into account differences in degree and frequency of infection with this plethora of agents, particularly with the increase in unprotected sex and drug use of the last two decades. The sum of all these exposures, plus the nutritional and drug problems of high-risk groups and excessive use of antibiotics, present a formidable stress to the immune system. It is well established that excessive stress of the types mentioned eventually overcomes the responsive capacity of the immune system. None of this rules out a contribution of HIV to this phalanx of assaults, but it seems naïve in the extreme to single it out as the sole or even primary cause until full consideration is given to all the possibilities in their various combinations. HIV may be the straw that breaks the camel's back, but the camel, in the major risk groups, is already carrying a staggering load. This position of a multifactorial origin of AIDS is similar to that of the immunologist Robert Root-Bernstein (2, p. 339) and the epidemiologist Gordon Stewart (3) and one that deserves a lot more attention than



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it has gotten. Admittedly such an approach is more complex than focusing on HIV alone, but that very feature recommends it for a problem as complex as AIDS. It behooves us to remember that Kaposi's sarcoma, once the flagship of AIDS diseases in homosexuals, has slipped away from its mooring to HIV (Y. Chang *et al.*, Reports, 16 Dec., p. 1865). Maybe Duesberg wasn't so stupid after all (J. Cohen, News, 16 Apr. 1993, p. 292).

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2. R. S. Root-Bernstein, *Rethinking AIDS* (Free Press, New York, 1993).
3. G. T. Stewart, *Lancet* **i**, 1325 (1989).

I may not be supportive of Peter Duesberg's arguments and dogmatism in rejecting HIV as the cause of AIDS, but Jon Cohen, in citing my criticism, did not make it clear that I continue to believe that the issue of AIDS causation still remains open.

AIDS is clearly a transmissible disease, but as long as there is an explanation for the association of HIV seropositivity with AIDS that either does not require that it play an etiologic role, or that it does so only in conjunction with other factors (1), we should at least keep an open mind about causality.

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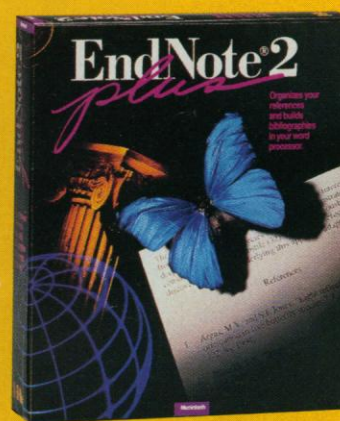
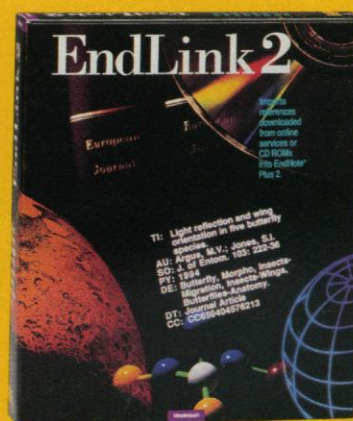
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Thank you for identifying me as a Duesberg critic. I worry, however, that many investigators will misinterpret my position. The question is not "HIV or not HIV?" It is whether HIV is both *necessary* and *sufficient* to cause AIDS. While the studies cited by Cohen address the question of necessity, none addresses the issue of sufficiency. At least four other well-established infectious disease models exist besides unifactorial causation: synergistic, multifactorial or multi-step progression, opportunistic, and autoimmune (1, 2). None of these has been adequately tested. The issue of Koch's postulates is critical. Diseases that are not

unifactorial must satisfy criteria other than Koch's. For example, in 1930, Shope demonstrated that swine flu in pigs is synergistic, requiring both a virus and a bacterium, and could not be induced by either one alone in any dose (3). Autoimmune diseases must also satisfy different causative criteria (2, 4). Thus, HIV may be 100% correlated with AIDS; it may be necessary for disease induction; but it still might not be sufficient. We cannot know until we do the appropriate tests. The fact that HIV is remaining within high-risk groups characterized by immunosuppressive risks (for example, disease, drugs, malnutrition, and blood products) argues in favor of performing such tests.

In this context, the three "risk-free" AIDS cases among laboratory workers that are supposed to prove HIV causation become problematic. What Anthony Fauci, Robert Gallo, William Blattner, and others appear to mean by "risk-free" is that no source of HIV other than occupational exposure has been identified. I accept the source of the HIV infection, but mean something different by "risk-free": I mean, free of non-HIV immunosuppressive risks. Proof is needed that the patients were, in accordance with Koch's postulates, also (i) immunologically healthy at the time of HIV exposure [meaning free of immunomodulatory

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factors, for example, active hepatitis, cytomegalovirus, Epstein-Barr virus; nonintravenous drug use; autoimmune conditions; malnutrition; infections requiring antibiotic use; and so forth (1, 2)] and (ii) free of co-infection with suspected AIDS cofactors such as mycoplasmas, viruses, or human leukemia cells that are universally present with HIV in laboratory situations (2, 4).

Indeed, Cohen's articles do not mention idiopathic CD4-T cell lymphopenia (ICL)—cases that match the clinical description of AIDS but lack all sign of HIV infection. If three cases of "risk-free" HIV infection "prove" causation, then the more than 100 ICL cases "disprove" it. Logically, of course, neither conclusion follows. What we must focus on are the more than 500,000 AIDS cases in North America and Europe in which HIV is accompanied by exposure to cofactors (and the universality of such cofactors in sub-Saharan Africa and Asia). There lies the clue to understanding AIDS, and through intervention with these cofactors, an alternative mode of preventing and treating AIDS.

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Corrections and Clarifications

In the report "Activation and regeneration of rhodopsin in the insect visual cycle" by A. Kiselev and S. Subramaniam (25 Nov., p. 1369), the second and third sentences of the last paragraph on page 1371 were incorrectly printed. They should have read, "When rhodopsin was re-excited immediately after it was regenerated, most of the metarhodopsin formed was thermally stable (that is, M^b was formed predominantly; Fig. 4A). However, when rhodopsin was re-examined after waiting for various lengths of time (in the dark), an exponential increase was observed in the amount of thermally unstable metarhodopsin produced, implying heterogeneity in the rhodopsin population."

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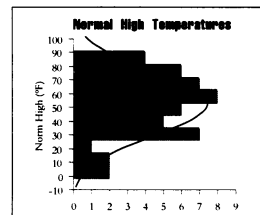
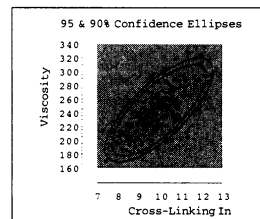
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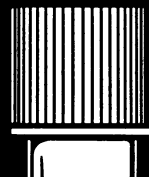


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