A Rebel Without a Cause of AIDS

Biologist Peter Duesberg has gained a lot of public attention and stirred up the wrath of many former colleagues with his claims that HIV is not the culprit behind AIDS

PETER Duesberg does not believe that AIDS is caused by any microbe known to man, especially not the human immunodeficiency virus called HIV. Says Duesberg: "That virus is a pussycat." So sure is Duesberg that AIDS is not caused by HIV that the professor of molecular biology from the University of California at Berkeley is telling reporters that he would gladly be injected with the virus—as long as the concoction is not prepared at the bench of Robert Gallo, the researcher from the National Cancer Institute who is the co-discoverer of HIV.

Basically, Duesberg does not think that HIV is virulent enough to cause AIDS, a conclusion he bases on widely recognized gaps in knowledge about how the virus operates in the body. His unsettling offer to inject himself with HIV and his pointed jabs at fellow scientists have aroused a great deal of anger and exasperation among AIDS researchers, who insist that an overwhelming body of evidence points toward HIV as the culprit behind AIDS. At the same time, Duesberg's remarks have won for the professor a large amount of media attention, particularly in the gay press where he is something of a hero and where government types such as Gallo are often portrayed as villains or fools.

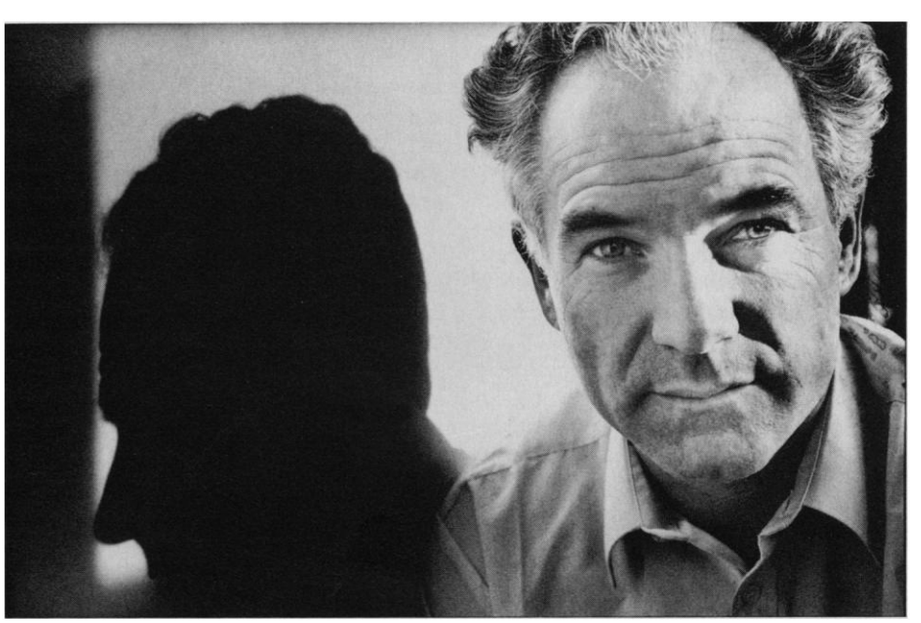
For his part, Duesberg is well suited to the role of iconoclast, and indeed, he has played the part of the gadfly before. Immensely quotable, with a sharp sense of humor and a slight Germanic accent, the 51-year-old professor does not hesitate to tweak the noses of figures in the biomedical research community whose egos often loom larger than life. Yet Duesberg is not an iconoclast without credentials. He is a legitimate investigator. A member of the National Academy of Sciences, Duesberg did pioneering work in the field of viruses and cancer-causing genes in the 1970s. Moreover, Duesberg is an insider, a colleague and sometime friend of the same researchers he now attacks.

None of this, however, has gotten Duesberg a formal response to the article he wrote for the peer-reviewed journal *Cancer Research* in March 1987, in which Duesberg first stated his objections to the HIV orthodoxy. "Why won't they respond to me?" Duesberg constantly asks reporters, who then ask AIDS researchers the same question.

"I cannot respond without shrieking," says Gallo when confronted with one of Duesberg's statements. "It is absolute and total nonsense," says Anthony Fauci, coordinator of AIDS research at the National Institutes of Health (NIH). "Irresponsible and pernicious," says David Baltimore, director of the Whitehead Institute in Cambridge, Massachusetts, and a chairman of the Institute of Medicine–National Academy of Sciences committee that produced the bench mark report *Confronting AIDS*.

Yet Duesberg keeps pressing. "Like a little dog that won't let go," says Gallo. And so a debate of sorts has been lurching along, staged in the most unlikely forums. In January, for example, *Spin*, a rock music magazine produced by the son of *Penthouse* publisher Bob Guccione, ran a question-and-answer interview with Duesberg in which he detailed his objections to HIV and accused "the AIDS establishment" of collusion and intellectual bankruptcy, suggesting that because two leading AIDS investigators have a financial interest in a company that produces diagnostic kits to test for antibodies to HIV, they were incapable of questioning their own AIDS research. (In the world of biomedical research, where ties to industry are pervasive but mentioning the fact is not, these are fighting words.) The following month, *Spin* published a bizarre interview with Gallo, in which the scientist spent half of the piece ranting and raving about the stupidity of Duesberg's statements, while punctuating his remarks with the occasional expletive. (The interview was tape-recorded without Gallo's knowledge.)

In the midst of all this, Jim Warner, a policy adviser in the White House, suddenly became interested in retrovirology. Warner wanted the White House to co-host a meeting organized by Harvey Bialy, an editor at the journal *Bio/Technology*, at which Duesberg would take on someone from NIH. Scheduled for January, the meeting was canceled. Columnists Jack Anderson and Joseph Spear then wrote an article in February in which they chided Gallo for refusing to defend his ideas. The column stated that Duesberg reached his "fresh point of view" after studying HIV in Gallo's laboratory, insinuating that some kind of conspiracy of silence was afoot. Gallo correctly points out that Duesberg has never studied HIV and has never worked in his lab. In fact, Duesberg has not done a single experiment in the AIDS field. As for the proposed White House affair, Gallo claims he only heard



Peter Duesberg *maintains that AIDS is not caused by an infectious agent but by sexual excess and drug abuse.*

rumors. "Quite frankly, unless I was ordered by the President I wouldn't go," says Gallo. "Who do you think there is at the White House who understands this thing?"

"A number of scientists are reluctant to get into a public debate because it pits you against somebody who in many respects is so far off from reality," says Fauci. Many AIDS researchers refuse to comment publicly because they fear it will legitimize Duesberg.

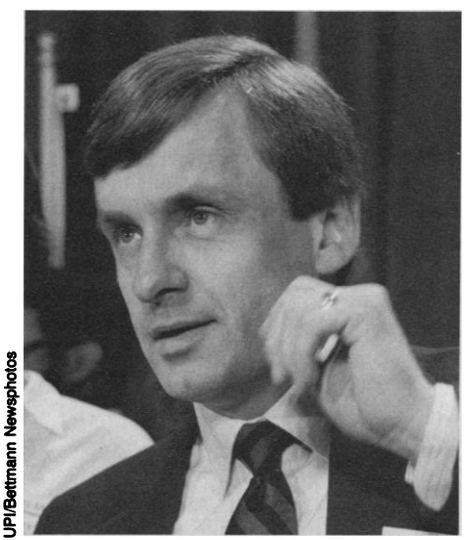
What exactly are Duesberg's objections to HIV? Duesberg bases his critique upon his own experience with animal retroviruses and a reading of the scientific literature on HIV. In a nutshell, Duesberg says that a microbe must satisfy three criteria in order to be considered responsible for disease: it must be "biochemically active," it must "infect or kill more cells than the host can spare," and "the host must be genetically and immunologically permissive." According to Duesberg, HIV misses the mark on all three counts.

Duesberg does not believe that HIV is virulent enough to destroy the body's supply of T lymphocytes, the special class of white blood cells that are the foundation of the immune system. He is particularly suspicious of HIV because the virus infects so few T cells and appears to be latent for so many years. He says that HIV does not operate like any virus he knows. In addition, Duesberg maintains that even the epidemiology of the AIDS epidemic rules out an infectious agent—be it virus, bacterium, or fungus—rather than pointing toward one. Instead of a microbe, Duesberg believes that AIDS is brought about by a way of life that includes sexual excess and drug abuse. In a word, Duesberg believes that one's lifestyle, not a pathogen, causes AIDS.

AIDS researchers respond to Duesberg on several levels. At first, they ignored him. But when pressed by reporters, they would simply dismiss Duesberg's ideas as the work of a man who grossly misrepresents or ignores much of the data. AIDS workers also say that although Duesberg is a brilliant chemist, he is out of his depth when it comes to biology and the complex interplay of the human immune system, which is still very much a black box. Finally, they contend that Duesberg is asking for absolute proof in a field where an enormous amount of circumstantial evidence is often enough to convict a microbe of being responsible for a specific disease. What Duesberg seems to be saying is that "correlations are not causality," says Baltimore. In establishing HIV as the etiological agent in AIDS, correlations are extremely important.

Duesberg is not the only skeptic in the community, as he likes to think. In the early days of the AIDS epidemic, Baltimore says that virologists like himself watched the scientific literature very carefully. When Gallo put forth the notion that AIDS might be caused by HTLV-1, a retrovirus that has been linked to a rare form of cancer, there were few converts. In 1983, when Luc Montagnier of the Pasteur Institute in Paris found a new retrovirus in AIDS patients, there was keen interest, but still great skepticism, since Montagnier had failed to prove that HIV was a causative agent rather than an opportunistic infection. In a rapid series of papers in 1984, Gallo and colleagues reported finding antibodies to HIV in almost 90% of a group of AIDS patients. In 115 healthy heterosexuals, they detected no anti-HIV activity. The studies were conducted double-blind. "This was the kind of evidence that we were looking for. It distinguished between a virus that was a passenger and one that was a cause," says Baltimore.

The new virus discovered by Montagnier and Gallo was a particularly attractive candidate because HIV kills T cells in a laboratory dish—these are the very same cells depleted in persons with AIDS. At the same time, there was rapidly expanding epidemiology indicting HIV, including the very powerful connection between HIV and AIDS cases involving blood transfusions and hemophiliacs.



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James Curran: *The link between HIV and AIDS "hits you in the face."*

As for specific responses to Duesberg's arguments, AIDS researchers offer numerous ones. To begin with, Duesberg is bothered by the absence of viral replication or free virus particles circulating through the blood stream of persons with AIDS or with antibodies to HIV. Duesberg keeps asking, "What is the titer?" He contends that HIV is "inactive," meaning that once the virus gets inside the cells of its host, it fails to produce progeny or viral products, as would a traditional virus such as influenza, which would load up an infected cell with virions and then burst the cell. HIV, on the other hand, "is no more active in those who are dying from it than in those who have no symptoms whatsoever," says Duesberg. "Just like you and me, a virus has to do something to get something done."

Despite what Duesberg says about the virus being a dud, there is evidence of viral activity, though no one is pretending that HIV acts like a traditional virus. For example, the core proteins which serve to encapsulate the genetic material of HIV are composed of molecules called p24 (short for a protein with a molecular size of 24,000 daltons). These molecules can be readily detected in blood sera drawn from AIDS patients as well as healthy asymptomatic carriers of HIV, according to Jerome Groopman, of Harvard Medical School and chief of oncology and hematology at New England Deaconess Hospital. "The infected cells are spitting out core proteins . . . It's a very important indication that you have viral activity," says Groopman, who adds that the more p24 antigen someone possesses, the more likely they are to develop AIDS-related complex (ARC) or full blown AIDS.

Duesberg goes on to question how a retrovirus that "actively infects" at most 1 in 10,000 susceptible T cells could cause AIDS. Says Duesberg: "A virus, or any pathogen, must infect or kill more cells than your body could possibly afford to lose during the course of the disease." So scarce is HIV, says Duesberg, that the virus can only be isolated from about 15% of persons with antibodies to HIV.

Gallo says Duesberg is wrong about the 15% and only partly right about the 1 in 10,000 T cells being infected. "If we're talking about rapid replication of the virus at any one given instant, yes, this is true. It's happening in less than 1 in 10,000 T cells. However, the virus genome is present in many, many more cells. You say so what? Let me tell you what happens in a population of T cells when they become infected with HIV."

Gallo then ticks off a number of mechanisms that have been put forth to explain how HIV could possibly cause the severe depletion of T cells that is the hallmark of AIDS. According to Gallo, T cells infected with HIV dramatically shut down their production of interleukin-2, a growth factor that is instrumental in stimulating T cells to divide and proliferate. T cells infected with HIV may also produce viral protein molecules called gp120 (a glycoprotein of 120,000 daltons) which serve as the enve-

lope for the virus. These envelope molecules may erupt from the infected cell's membrane and bind to special receptor sites on other cells, causing the formation of giant constellations of cells called syncytia. In this way, one infected cell could disable as many as 100 uninfected cells.

There is also some indication that an autoimmune response might be at work, whereby the body's immune system targets for destruction some of its own cells that have been subtly altered by the virus. For example, soluble gp120 might be secreted by infected cells and become attached to uninfected cells, thereby setting them up as targets for attack by "killer" T lymphocytes. The virus may also be infecting populations of precursor cells which give birth to T cells, says Gallo. Or viral products may be directly toxic.

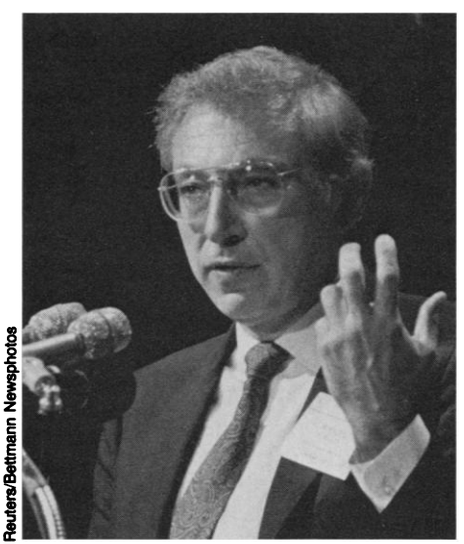
In addition, Gallo and others point out that T cells are not the only targets of HIV: monocytes and macrophages are also infected. Macrophages, which appear to sequester the virus, may prove extremely important in disease progression. Researchers also report that HIV may be passed from cell to cell. Free virus particles may not even be necessary. Again, no one is certain. No one knows exactly how HIV causes the gradual depletion of T cells seen in AIDS. It is a mystery of the most intense interest. But the questions that Duesberg raises about HIV are not novel ones, say AIDS researchers.

"We don't know how the virus is transmitted. Is it free virus particles or do you have to exchange cells? We don't know the initial targets. Are they lymphocytes or macrophages? We don't know where the virus is in the body during the initial stage of infection or during the long period when a person is antibody-positive but still asymptomatic. These are all important issues, but just because we don't know all the answers doesn't mean that we can't extrapolate from pretty good data that keeps pointing toward HIV," says Malcolm Martin, chief of the laboratory of molecular biology at the National Institute of Allergy and Infectious Disease.

AIDS investigators say that it is important to remember that the depletion of T cells is gradual. According to Fauci, when a person is first infected with the virus, there is a big burst of viral replication that precedes the production of antibodies against the invading microbe. During this early, acute stage, a person with HIV often gets symptoms similar to the flu. With the onset of antibodies, the virus appears to be inhibited. But the virus persists. Over time, as anti-HIV immunity wanes, the virus continues to replicate in bursts, perhaps activated by as yet unknown signals, which may be other viral infections or the workings of the immune system itself.

Says Gallo: "Everything Peter says about pathogenesis [how a pathogen causes disease] is irrelevant because no one in history has ever had to explain pathogenesis to explain cause. We don't know the detailed pathogenesis of cholera, or tuberculosis, or when you get hit by a truck. It's wonderful if you can explain every molecular change all the way down the line and make it all make sense. But you don't have to. That said, let me add that we understand about as much of the pathogenesis of this disease as we know for most diseases."

As for Duesberg's statement that the virus can be isolated in only 15% of people with antibodies to HIV, the figure comes from an early paper published by Gallo and colleagues (*Science*, 7 December 1984, p. 1165), in which they examined fresh tissue from 65 patients with AIDS or ARC. They found integrated genetic material from HIV in only 9 of the 65 tissue samples. Gallo states that the point of the paper was not to try to isolate virus from all 65 patients, but to see in which tissue samples they could find cells infected with HIV.



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Robert Gallo *cannot respond to Duesberg's statements "without shrieking."*

Duesberg, however, uses these findings to state that HIV is not present in all stages of the illness, meaning that the virus violates the first postulate of Robert Koch, the eminent German bacteriologist who in the 1880s discovered the bacilli that cause tuberculosis and cholera. Koch's first postulate stipulates that for an organism to be considered the cause of a disease it must be present in all stages of disease.

Today, Gallo maintains that a good laboratory can isolate the virus from between 80 and 100% of all persons with antibodies to HIV, including patients with AIDS or ARC. "We're damn close to 100%," says Gallo. With the introduction of gene amplification techniques now being developed, most AIDS researchers say that the difficulty of isolating virus from persons with HIV will be overcome. To this, Duesberg responds: "It doesn't matter if the techniques become more and more sophisticated. There still isn't enough virus to be clinically relevant."

Duesberg keeps pushing. Not only is HIV too inactive to cause AIDS, he maintains that HIV acts like "no known virus" because of its long latency and the fact that it persists despite the production of antibodies.

For most people, learning that their blood contains antibodies to the "AIDS virus" is a traumatic and frightening event. But Duesberg says that such persons should be "congratulated." "Hurrah, your body has won!" says Duesberg. "A cardinal rule in virus infection is that viruses cause disease . . . before immunity and not after immunity. The host, in other words, has to be permissive to the virus to let it happen. If you are not permissive, that is to say, if you have antibodies, the virus doesn't have a good chance to cause disease."

Martin retorts: "This is ignorance." Martin says there are many kinds of antibodies and that the mere presence of antibodies does not equal protection against HIV or any other pathogen. "We know in the lab that some antibodies will bind to the virus particles, some antibodies will immunoprecipitate, some antibodies will neutralize particles, others won't," says Martin.

As for HIV's long latency, Duesberg contends that all known viruses cause disease soon after infection. Says Duesberg: "Shortly after exposure to a virus, you develop symptoms or you don't. If you're lucky, you don't. If you're unlucky, you do. . . . That is to say that viruses work quickly or not at all. Again, the AIDS virus seems to be the exception to the rule."

Yet there are other viruses besides HIV that have long periods between infection and disease, says Bernard Fields, chairman of the Department of Microbiology and Molecular Genetics at Harvard Medical School and editor of the textbook *Virology*. The herpes family, for example, "is notorious for its long latency, despite the presence of antiviral antibodies," says Fields. Herpes simplex virus, for one, continues to causes cold sores and blisters years after infection. The varicella-zoster virus that is responsible for chickenpox also takes up residence in the sensory ganglia and years later produces shingles. The measles virus is responsible not only for the acute disease with its red

splotches and high fevers, but sets the stage for a rare disease called subacute sclerosing panencephalitis, which results from a slow but progressive infection of brain cells by defective measles virus. This occurs years after the acute bout of measles.

To this list of common human pathogens, Gallo adds a number of viruses that cause tumors or disease in cats, mice, horses, and gibbon apes after long periods of time. In cats, for example, infection with feline leukemia virus gradually suppresses the immune system, opening the door to opportunistic infections by fungi, bacteria, and protozoa. Another group of retroviruses called the lentiviruses, often referred to as "slow viruses," cause disease after a long incubation period. For example, the visna and maedi viruses cause a progressive neurologic disorder and chronic pneumonia in sheep after an extremely long latent period. Duesberg says that the visna virus is to sheep what HIV is to man: "A passenger."

Of all Duesberg's objections, however, the one that raises the most hackles is his contention that the epidemiology of AIDS rules out a viral agent. Duesberg told the President's AIDS commission in New York City on 20 February: "Unlike all other viruses known to me—in fact, all other microbes known to me—this virus is said to discriminate between boys and girls, and the marvel is between heterosexuals and homosexuals."

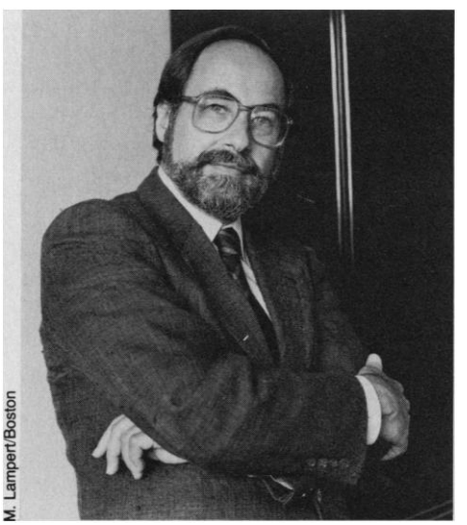
Duesberg says that because 92% of the AIDS cases involve males, this is an indication that HIV is not the cause of AIDS. "If the cause were infectious, it wouldn't be limited to men," says Duesberg.

James Curran, director of the AIDS program at the Centers for Disease Control (CDC) in Atlanta, says Duesberg is wrong. "Other sexually transmitted organisms often appear to have an affinity for one group or another," says Curran. Homosexuals, for example, have higher rates of hepatitis and sexually transmitted diseases than do members of the general population. Because they share dirty needles, drug addicts have high rates of hepatitis infection, too. So do surgeons, for that matter.

Curran says that one reason why the number of AIDS cases in the United States involving men is so high is the fact that intravenous drug abusers, Haitian immigrants, and hemophiliacs are mostly male, while the gender of homosexual males is obvious. These are the populations where the virus first got its footing in the United States and therefore these are the groups who are now—years into the epidemic—dying of AIDS, says Curran.

There is no doubt that women can be infected with HIV and develop AIDS. The wives and girl friends of male drug addicts and male hemophiliacs with AIDS are proof that transmission of virus to women is occurring. These same women may also transfer the infection to their newborn children, who go on to get AIDS. In Central Africa and the Caribbean, the number of men and women who have AIDS is roughly equal, says Curran.

For further epidemiological evidence, Curran points to the cases of AIDS that are associated with blood transfusions. In a paper in the *Journal of the American Medical Association* in August 1985, Harold Jaffe of CDC and colleagues reported on 19 patients with AIDS who had no other known risk factors other than having a blood transfusion in the 5 years preceding the onset of symptoms. The 19 patients received transfusions in ten states. Eight of the 19 were female. Their ages ranged from 46 months to 77 years. All had antibodies to HIV and all had AIDS. Furthermore, all 19 also had at least one blood donor who was in a high-risk group who also had antibodies to HIV. By 1985, of the group of high-risk donors, four had gone on to develop AIDS and eight had swollen lymph nodes, a symptom associated with pre-AIDS conditions. "The evidence just hits you in the face," says Curran.



M. Lampert/Boston

David Baltimore: *HIV is not just a passenger but the cause of AIDS.*

"Is Duesberg trying to tell me that the transfusion cases are caused by life-style?" asks Fauci. "How about the 60-year-old wife of a hemophiliac who gets infected? She's out cruising, too?"

Says Fauci: "I would not underestimate the incredible power of the epidemiological evidence. The public will understand that when someone gets a transfusion and gets the virus, they get sick. They'll understand the mother who has the virus and gives it to her baby and the baby gets sick. While in the same hospital, the mother without the virus has a baby and there's no way her baby gets AIDS. The public will understand that. If you argue that, he's dead. But he likes to talk about expression and pathogenesis and latency and this and that, and then everybody gets confused and says, 'I don't know what those guys are talking about. They're all confused! So maybe this little guy is right.' "

Upon this mountain of confusion, Duesberg heaps questions about the motives of those researching AIDS. In his conversations with *Science*, Duesberg suggests that "the AIDS establishment" is hiding something, that careers and bank accounts are on the line. "How can they be objective?" he asks.

Duesberg often mentions the fact that many of today's AIDS researchers are veterans of Nixon's War on Cancer. Says Duesberg: "What cause for AIDS could retrovirologists come up with but a new retrovirus?" He adds that without AIDS, retrovirologists "would only be a footnote in history." Says Duesberg: "We all have been craving for clinical relevance for the past 20 years."

Conspiracy theories play well in some quarters and are certainly encouraging people to think that the government is prepared to sit idle while homosexuals and drug addicts die. There is also a powerful desire to believe that HIV does not cause AIDS, since prospects for antiviral drugs and vaccines have been slow in coming. As for conspiracies, Fauci counters: "You are not talking about a clique of scientists. You are talking about a range of researchers from Nobel laureates down through the postdoctoral fellows working at the bench. There is not a major conspiracy at that level."

Duesberg has played the role of the rebel before. After years of working on oncogenes, Duesberg began shooting holes in some of the overblown claims that were made linking genes to cancer. Then, after studying how retroviruses might cause disease in animals, he began to challenge the role of retroviruses in human cancer and now AIDS. Duesberg attributes his iconoclasm to a free and inquisitive mind and a distrust of conventional wisdom, while his opponents accuse Duesberg of craving attention and recognition, and of failing to back up any of his ideas with research.

Says Gallo: "It's not a joke anymore. . . . The long-term ramifications of this is to create hate and distrust of the scientific process." Others see Duesberg's influence as more benign. "There's nothing wrong with gadflies. I think that they're healthy," says Groopman. For his part, Duesberg says he plans to keep buzzing about. ■

WILLIAM BOOTH