REVIEWING THE DATA–IV

Could Drugs, Rather Than a Virus, Be the Cause of AIDS?

In March 1988, the headline of a news article in *Science* called Peter Duesberg a "rebel without a cause of AIDS." But Duesberg says he's a rebel with several causes of AIDS—it's just that none of them happen to be the consensus favorite, HIV. Among the causes he favors (at least for homosexuals and users of injectable drugs, the groups hardest hit by AIDS in the United States and Europe) are drugs. Specifically, he thinks the disease is due to the use of illicit drugs such as heroin, cocaine, and amphetamines, as well as to the first drug approved for treating AIDS, AZT.

"AIDS is new because the drug epidemic is new," argues Duesberg. "We're in the middle of giving 200,000 people AZT for a hypothesis that's at best unproven. ... We're telling 250 million Americans to use clean needles to inject cocaine and heroin. ... What we should do is point out it's not just against the law to use drugs, it may be against your health."

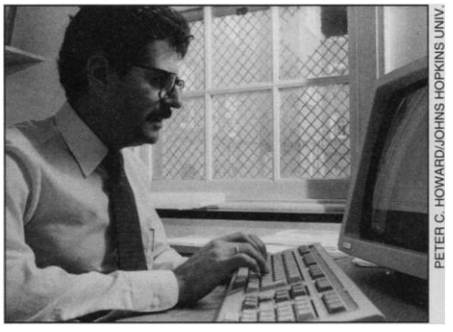
To make his case that drug use causes AIDS, Duesberg points out that drug use (in particular, use of nitrite inhalants known as "poppers") has been high among some subgroups in the homosexual population. AIDS researchers agree. But beyond that, his contention that illicit drugs cause AIDS has provoked heated disagreement. Showing how heated the conflict between Duesberg and the majority of AIDS researchers has become, last year Duesberg charged that the authors of a study in *Nature* showing that only HIV-positive drug users developed AIDS had fabricated data; the charge was found to be groundless by an independent panel at the University of California, Berkeley.

Duesberg builds what he calls his "drug-AIDS" hypothesis using a variety of studies he says show that "a critical lifetime dosage of drugs appears necessary in HIV-positives and sufficient in HIV-negatives to induce AIDS-indicator and other diseases." To make the case that drugs are sufficient to cause AIDS in HIV-negatives, Duesberg highlights data he argues show AIDS-like immune abnormalities and diseases in long-term drug users.

For example, Duesberg cites a study of drug users, both HIV-negative and HIV-positive, in which a Dutch group examined the ability of the drug users' T lymphocytes to kick into action when stimulated. T lymphocytes are an important set of immune-system cells that circulate in the blood; CD4 cells, the group whose progressive decline is the hallmark of AIDS, are a subset of T lymphocytes. The Dutch group found that, among both HIV-positive and HIV-negative drugs users, T cell reactivity decreased as the frequency of injection increased; Duesberg cites this among his evidence that drug use can cause AIDS.

But critics of Duesberg's work say the study actually undermines his case. First, they say, he does not mention that among the drug users in the study who were HIV-negative, the chief indicator of the immune deficiency seen in AIDS—CD4 count—was well within the normal range. The 49 HIV-negative users who injected themselves more than 50 times a month had a mean of 990 CD4s (the normal range is from 600 to 1200); the 55 users who injected from one to 49 times a month had 910 CD4s. The HIV-positive drug users, on the other hand, had a mean CD4 count of 450, less than half the CD4 count among the HIV-negative group (although typically not low enough to cause clinical symptoms). This study, say Duesberg's critics, shows that the decline of CD4 cells—the hallmark of AIDS—is associated with HIV status and not with drug use.

Duesberg counters that this study does not report lifetime dosages of drugs—only current frequency of injections. "Thus the frequent injectors may include more newcomers than the less frequent injectors," he says. In other words, the frequent injectors who were HIV-negative may actually have lower lifetime dosages, and so their drug-caused immune deficiency has not shown up yet.



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Screen test. Alvaro Muñoz and Duesberg disagree about Munoz's findings.

To test Duesberg's hypothesis, one of the co-authors of the Dutch study, Roel Coutinho of Amsterdam's Municipal Health Service, has compared HIV-positive and HIV-negative drug users while controlling for the length of time the two groups injected drugs. Coutinho compared 86 HIV-negative and 70 HIV-positive drug users who had been injecting for a mean of 7.6 and 9.1 years, respectively. When the duration of drug use was controlled, there was a clear difference between the two groups in CD4 status. Among those not infected with HIV, the base line CD4 count was 914, within the normal range. Among those infected with HIV, however, the base line was only 395, well outside the normal range. Between 1989 and 1994, CD4s remained stable in the HIV-negative group but declined steadily among those infected with the virus. And death from AIDS was associated with HIV status but not with drug use alone. Among HIV-positives, there were 25 deaths, 10 attributable to AIDS; among HIV-negatives there were eight deaths, none due to AIDS-defining diseases.

Other checks of the theory that drug use can cause AIDS raise just as many questions. For example, there is evidence that heroin can cause immune abnormalities—but not the type seen in AIDS. According to Rockefeller University's Mary Jeanne Kreek, who studies immune responses in heroin addicts, heroin users do not experience a decline in CD4 counts unless they are infected with HIV. Indeed, in 1989 Kreek reported in the *Journal of Pharmacology and Experimental Therapeutics* that 11 long-term heroin users had a mean of 1500 CD4s—a significant elevation from the norm and the opposite of what is seen in AIDS. "Heroin is a blessedly untoxic drug," concludes Kreek.

If Duesberg's effort to show that AIDS can be caused by drug use alone elicits sharp criticism, his critics say that his attempt to find AIDS-defining illnesses among those not infected with HIV is also problematic. One piece of research Duesberg cites to show that HIV-negative drug users have AIDS-defining illnesses is a 1992 study from Johns Hopkins University. In his 1992 paper in *Pharmacology and Therapeutics* Duesberg says that in the Hopkins study, the fraction of the 160 HIV-negative people with AIDS-defining diseases was roughly equal to the fraction of the 590 HIV-positives with AIDS-related conditions.

Duesberg refers to a table in the paper listing "clinical symptoms," which are defined in a footnote as oral thrush (a mouth infection caused by the fungus *Candida albicans*), fatigue, chronic diarrhea, weight loss, and shortness of breath. But Hopkins epidemiologist Alvaro Muñoz, the study's first author, says "None of these clinical symptoms were AIDS."

Muñoz says his statement is based on the definition of AIDS developed by the Centers for Disease Control and Prevention (CDC). That definition is specific about the type of weight loss that is considered AIDS-defining. A weight loss of greater than 10% combined with at least two loose stools per day for 30 days constitutes the AIDS-defining "HIV wasting syndrome." The patients in the Hop-

kins study did not meet this definition. When *Science* asked Duesberg about Muñoz's claim, Duesberg said: "These are HIV-free drug users. How do you think they lost weight, even if it's 9.8% or 10%? How do you think they got diarrhea?"

Nor did Duesberg accept CDC's definition of another AIDS-defining illness: esophageal candidiasis. This illness is caused by the same agent as oral thrush, but it occurs in the esophageal passage, a distinction Duesberg characterizes as arbitrary: "I know, 10 centimeters down the throat is candidiasis, and 11 centimeters is AIDS."

But clinicians who specialize in treating AIDS patients say the distinction is not arbitrary. *Science* asked Joseph Sonnabend, a New York clinician specializing in treating AIDS patients, whether the distinction is clinically well founded. Sonnabend, an early Duesberg sympathizer who now says he thinks Duesberg has not been open enough to evidence that HIV is involved in causing AIDS, says: "Oral thrush occurs in people who are relatively immunologically intact. Esophageal candidiasis is more or less confined to people who are much worse off, immunologically speaking." When the definitions established by CDC are used, the Hopkins study reveals that none of the HIV-negative patients had AIDS-defining illnesses, while 47 of 590 HIV positives did.

In addition to heroin and cocaine, Duesberg argues that AZT, the very drug designed to treat AIDS, can, in fact, cause it. And even his severest critics concede that AZT is no wonder drug. Although it is one of the few drugs approved for fighting AIDS, AZT can be severely toxic, and there is compelling evidence that the drug probably doesn't help infected people live longer unless they already have full-blown AIDS. Yet those reservations pale next to the position of Duesberg, who contends AZT is "AIDS by prescription."

Duesberg attacks AZT on several different levels. His most sweeping attack is on the rationale for using AZT in AIDS therapy. AZT interrupts synthesis of viral DNA, and in so doing prevents HIV from replicating, which AIDS researchers say is necessary for the virus to cause disease. But Duesberg notes that AZT is not specifically targeted against the DNA of the virus but against DNA synthesis. "Since DNA is the central molecule of life, AZT treatment is not compatible with life," he wrote in response to questions from *Science*.

AMSTERDAM DRUG STUDY

Characteristic	HIV positive	HIV negative
Total	70	86
Female	18	24
Mean age	31.9	31.4
Mean years regularly injecting drugs	9.1	7.6
Recent injecting		
Not injected	18	23
< daily	20	18
≥ daily	32	45
Total deaths	25	8
AIDS	10	0
Overdose	4	3
Suicide	1	3
Pneumonia/sepsis	3	1
Other	7	1

SOURCE: R. COUTINHO, M. LANGENDAM, H. VAN HAASTRECHT, AMSTERDAM MUNICIPAL HEALTH SERVICE

While mainstream AIDS researchers say Duesberg is correct in noting that AZT is toxic because it interrupts DNA synthesis generally, that contention, they say, is a far cry from claiming that the drug causes AIDS. And researchers who have conducted large-scale studies of the drug's effects say that it does not cause the fatal illness.

The most comprehensive data on AZT come from the "Concorde"—the largest, longest running study of the drug. This 3-year, British-French study included 1749 HIV-positive people who initially showed no AIDS symptoms. Because of its large numbers, Concorde has more statistical power than the seven other major AZT trials to date combined. The main conclusion of the Concorde's investigators was that patients treated with AZT soon after entering the study (the "Imm" group) fare no better than those who defer use or do not take the drug (the "Def" group). The study did show, however, that the Imm group had fewer AIDS-related diseases during the first year of the study than the Def group did.

CONCORDE RESULTS

	"Imm" group (n = 877)	"Def" group (n = 872)	Log rank p***
Total deaths	96	76	0.13
HIV-related deaths*	81	69	0.34
AIDS or death**	176	171	0.94
ARC§, AIDS, or death**	267	284	0.18
Advanced ARC, AIDS, or death	191	186	0.91

§ARC is AIDS-related complex, a pre-AIDS condition.
* Includes six deaths (4 Imm, 2 Def) possibly HIV-related or drug-related and excludes 22 (15 Imm, 7 Def) unlikely to be HIV-related or drug-related.
** As first event.
***A measure of statistical significance.
SOURCE: CONCORDE COORDINATING COMMITTEE/*LANCET*

That wasn't a very hopeful finding: AZT clearly isn't a very effective anti-AIDS drug. But gloomy as those conclusions are, the Concorde's principal investigators disagree sharply with Duesberg's hypothesis that AZT, rather than HIV, causes AIDS. The Concorde data in "no way argue in favor of the hypothesis that AIDS is caused by AZT," Concorde's French principal investigator, Maxime Seligmann of Paris' Hopital Saint-Louis, wrote *Science* in response to a query.

Duesberg, however, does not accept this conclusion. In his written response to questions from *Science*, Duesberg wrote: "The Concorde data exactly prove my point: The mortality of the AZT-treated HIV-positives was 25% higher than that of the placebo group."

But the method he uses to arrive at that figure is sharply disputed by experts in clinical trials. Duesberg notes that there were 96 total deaths in the Imm group and only 76 in the Def group. He therefore concludes that the mortality rate among those given AZT immediately is 25% higher than among those who take it later. One problem with this analysis, say experts familiar with the Concorde data, is that it includes 22 deaths from events such as traffic accidents and suicides. Subtracting deaths that were not related to AZT or AIDS yields 81 Imm deaths and 69 Def deaths.

In addition, say the critics, there is a deeper flaw in Duesberg's analysis: He does not take account of the total number of people in the Imm and Def groups. His reasoning for ignoring the denominator is, as he told *Science* in an interview, that "it was the same in the two groups." But National Institute of Allergy and Infectious Diseases Director Anthony Fauci says this type of analysis means "ignoring an important part of a calculation." Specifically, there were 96 total deaths out of 877 in the Imm group, implying that 10.9% of the people who were immediately treated with AZT died. In the deferred treatment group, there were 76 deaths among 872 people, or 8.7%.

The appropriate conclusion, say the authors of the Concorde study, is that the difference in mortality between Imm and Def groups is not 25% but 10.9% minus 8.7%—or 2.2%. Subtracting the deaths from causes unrelated to AZT or AIDS, the difference drops to 1.3%. As the Concorde paper notes, neither difference (2.2% or 1.3%) is statistically significant.

"If the Concorde study showed anything, it showed that AZT's benefit is of limited duration," says Fauci, referring to the fact that the Imm group had fewer AIDS-related illnesses during the study's first year. Duesberg replies that "according to my analysis of this paper, this paper shows that AZT is harmful ... 25% more people die in the AZT group than in the placebo group. That matters to me. Because even a single life seems to matter to me. Maybe not to you. You like to normalize that. To me it does. Period."

–Jon Cohen