

REVIEWING THE DATA—I

Duesberg and Critics Agree: Hemophilia Is the Best Test

Peter Duesberg and his critics in the community of AIDS researchers disagree violently about the cause of AIDS. But they agree on one thing: Hemophiliacs provide a good test of the hypothesis that HIV causes AIDS. Hemophiliacs offer a unique window on the effects of HIV infection because there are solid data comparing those who have tested positive for antibodies to HIV—and are presumably infected—with those who have tested negative. In addition, the health status of hemophiliacs has been tracked for more than a century, providing an important base line. And unlike homosexual groups, hemophiliac cohorts are not riddled with what Duesberg thinks are confounding variables, such as illicit drug use.

Where AIDS researchers argue that HIV causes AIDS in hemophiliacs, Duesberg points to another cause: contaminants of factor VIII, a clotting factor derived from donated blood that is used to treat hemophilia. Factor VIII is frequently contaminated with foreign proteins from blood donors, and Duesberg suggests that these contaminants cause the immunodeficiency seen in AIDS. In his view, HIV is a harmless passenger that serves as an index of the number of blood transfusions. "Since HIV is a rare contaminant of factor VIII, it is a marker of the number of immunosuppressive transfusions re-

ceived," argues Duesberg. He contends that hemophiliacs infected with HIV are simply the ones who have received the most factor VIII—with the accompanying contaminants.

AIDS researchers interviewed by *Science* contend that this view is contradicted by two large studies of hemophiliacs. Those studies, say AIDS researchers, show that being HIV positive is the key variable associated with the disease and death that accompany AIDS—not contaminants of factor VIII. In addition, some researchers contacted by *Science* say Duesberg has drawn incorrect conclusions from their work.

In making his argument that hemophiliacs suffer from AIDS independent of HIV, Duesberg cites 16 studies showing that HIV-negative hemophiliacs have abnormal ratios of two types of critical immune-system cells: CD4 and CD8. The normal ratio of CD4s to CD8s is about 2, but the studies Duesberg cites indicate that hemophiliacs who are not HIV-positive have ratios closer to 1. He concludes that even in the absence of HIV, hemophiliacs suffer immune deficiencies—and hence that some factor other than HIV is responsible for AIDS among them.

But researchers familiar with these data say the abnormal ratio Duesberg cites is not indicative of AIDS—and may not even indicate immune deficiency. The chief impact of AIDS on the immune system is a progressive decline in the number of CD4 cells. A change in the CD4/CD8 ratio doesn't in itself say anything about the number of CD4 cells, AIDS researchers say, as it could be due to an elevation of CD8 cells alone. "Anything that would give your CD8s an elevation could give you a ratio of 1," says immunologist Michael Ascher, an AIDS researcher with the California Department of Health Services. People with a ratio of 1 "could have more CD4s—and that may be immuno wonderful," adds Ascher.

When asked about this point in relation to a specific paper he cites, Duesberg responded: "Look, why don't you call [the paper's author] and ask the fool, 'Why did you idiots describe your paper as immunodeficiency in patients with hemophilia?'"

Pediatrician Donald Kaufman of Michigan State University, who co-authored the study in question, says Duesberg's interpretation of their data is "erroneous." In Kaufman's 1989 study, CD4 counts of HIV-negative hemophiliacs showed no significant difference from normal controls. The number of CD8 cells, however, was higher in hemophiliacs—regardless of whether they received factor VIII treatment. The treated patients did show some immune deficiencies that Kaufman thinks may be related to factor VIII, but he emphasizes that these were nothing like what is seen in AIDS, and indeed, none of these nine patients has developed AIDS.

Other AIDS researchers cite additional data from the two large epidemiologic studies that they argue show factor VIII has little to do with causing AIDS. One of these studies,

the Multicenter Hemophilia Cohort Study (MHCS) sponsored by the National Cancer Institute (NCI), follows 2000 hemophiliacs at 16 centers in the United States and Western Europe. In 1989, the *New England Journal of Medicine* published a study from the MHCS comparing 242 HIV-infected hemophiliacs who received high, medium, or low doses of factor VIII. If exposure to contaminants in factor VIII were the cause of the immune suppression seen in AIDS, it would be expected that those who received higher doses of the factor would be more likely to develop AIDS, says NCI's James Goedert, the principal investigator of MHCS. But the study, says Goedert, found no association between dose levels and the likelihood of coming down with AIDS.

Duesberg, however, thinks studies such as

DEATHS IN HEMOPHILIA COHORT SINCE 1985*

Factor VIII Dose	HIV+	HIV-
High	10/29	0/0
Moderate	103/264	0/17
Low	40/103	1/49

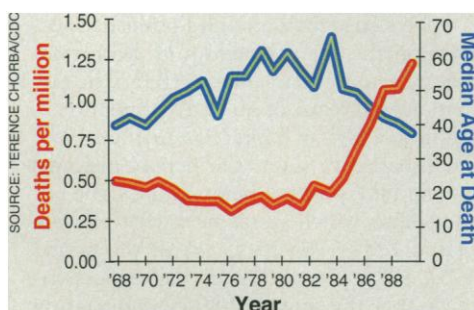
*Groups are based on cumulative dosages of factor VIII from 1978 to 1984.

JAMES GOEDERT/NCI

MHCS aren't sufficient for establishing AIDS causality. He says more research is needed—specifically, a study that doesn't combine hemophiliacs into groups such as "high, medium, and low dosage" and that instead includes records of exactly how much factor VIII each patient has received during his or her lifetime. "We would need a study comparing 100 hemophiliacs—and it's very doable; it's probably in the computer—having received 2 million lifetime units [of factor VIII] to 100 guys having received exactly the same number of units, HIV positive and negative. And then compare [the diseases in each group]. Not this type of stuff."

In spite of Duesberg's contention that such a study is "very doable," researchers working with hemophilia databases say it is impossible, because hemophiliacs do not keep track of each factor VIII treatment. "There's no place that would even begin to have cumulative lifetime dosages," says the University of Southern California's James Mosley, who heads the other large study of hemophiliacs, the Transfusion Safety Study Group (TSSG), which has tracked 1200 hemophiliacs at six U.S. sites. "It's sort of like trying to count grains of sand on the beach."

Although Mosley and others say precise lifetime dosages of factor VIII for large study groups are impossible to obtain, they say it is possible to do less ambitious studies that look at cumulative dosages of factor VIII for specific periods, such as when hemophiliacs are being monitored in a study. NCI's Goedert did such an analysis using his MHCS data-



Crossing pattern. Death rates for hemophiliacs rose sharply in the 1980s. AIDS researchers disagree with Duesberg on the cause.

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The Transfusion Studies

Although science has produced no AIDS cure or vaccine, AIDS researchers like to point to one dramatic victory: the blood test that prevents people from being infected during transfusions. According to the Centers for Disease Control and Prevention (CDC), as of mid-1994, 6888 AIDS cases had been linked to blood transfusions. But those people were almost all infected before screening began, and the blood test has essentially eliminated the risk of AIDS from transfusions—only 29 cases stem from blood that was screened for HIV. This dramatic decrease has been invoked by AIDS researchers as evidence that HIV causes AIDS.

Peter Duesberg says these data are meaningless. He argues that AIDS is not caused by HIV in transfused blood but by the disease that required transfusion in the first place. And, he says, the drop in AIDS cases after HIV was removed from the blood supply has a "trivial explanation." Because the standard definition of AIDS requires the presence of HIV, when the virus was removed from the blood supply, people were no longer categorized as having AIDS—although their diseases had not changed. "Without HIV antibodies," contends Duesberg, "the diseases are called by their old names."

Proof that AIDS has vanished along with HIV, Duesberg says, would be a decrease in AIDS-defining diseases among transfusion recipients and a corresponding decrease in transfusion-associated mortality. In an interview with *Science* he criticized CDC scientists—whom he described as "officers of the U.S. Army who are paid to find HIV is the cause of AIDS"—for not providing that data. Harold Jaffe, head of the CDC's Division of HIV/AIDS, said "I don't believe there's national mortality data for all who have been transfused." Jaffe added that he doesn't think such figures would be "particularly useful" in relation to AIDS causality "because the overall mortality in people who are transfused is high, and AIDS has contributed relatively little."

Duesberg also argues that mainstream AIDS researchers attribute death among transfusion recipients to HIV "without considering HIV-free controls." But in 1990 the Transfusion Safety Study Group (TSSG) published just such a report. The TSSG compared HIV-negative and HIV-positive recipients who had been given transfusions for similar diseases. Approximately 3 years after transfusion, the mean CD4 count in 64 HIV-negative recipients was 850 (the normal adult range is 600 to 1200). In contrast, 111 HIV positives had an average of 375 CD4s. By May 1993, there were 37 AIDS cases in the HIV-infected group, says TSSG Director James Mosley of the University of Southern California. In contrast, there has not been a single AIDS-defining illness in the HIV-negative transfusion recipients, says Mosley.

Duesberg says these data neatly fit his theories. HIV, he says, is a rare contaminant of blood transfusions and therefore indicates the volume of transfusions received. "HIV-positive transfusion recipients have received more blood because they had more severe underlying diseases than HIV negatives," he wrote in response to questions from *Science*. "The more severe the underlying disease, the more likely are subsequent AIDS diseases."

—J.C.

base. Goedert analyzed which was better correlated with a hemophiliac's risk of death: cumulative dosage of factor VIII or having tested positive for HIV. (He did not use AIDS as an endpoint because since the mid-1980s, when the medical community accepted HIV as the cause of AIDS, clinicians have primarily diagnosed AIDS in people who test positive for HIV.)

To make the comparison, Goedert divided hemophiliacs of similar age into HIV-positive and HIV-negative groups. He then divided the two groups into those who had received high, moderate, or low cumulative dosages of factor VIII. Dosages were totaled from 1978 to 1984; the study analyzed the hemophiliacs' survival from 1985 on.

The 29 people in the highest dose category were all infected with HIV and therefore could not be used in the comparison. In

the moderate-dose group, there were 264 HIV positives. Of that total, 103 have died. In comparison, among 17 HIV negatives there were no deaths. In the low-dose group, there were 103 HIV positives, of whom 40 have died; among 49 HIV negatives there has been only one death. Dosage of factor VIII, says Goedert, "had absolutely nothing whatsoever" to do with a person's risk of dying. Being HIV positive, however, increased a person's risk of dying almost 20-fold.

Goedert's counterpart, TSSG Director Mosley, offers additional data that he says link HIV to disease and death, specifically illnesses associated with AIDS. Data from the TSSG reported in the *New England Journal of Medicine* in 1993 show that none of the 419 HIV negatives from that large study had AIDS-defining diseases. In contrast, Mosley says, by May 1993, the most recent analysis,

165, or 31%, of the 519 HIV-positive hemophiliacs had developed AIDS. In the HIV-positive group there were 176 deaths, and of those, 135 were from AIDS.

For many "HIV dissenters," Duesberg's most compelling argument against HIV as the cause of AIDS in hemophiliacs is his observation that the median age of hemophiliacs has increased in spite of high HIV infection rates. As Duesberg notes, studies have reported that the median age of hemophiliacs in the United States has risen from 11 years in 1972 to more than 25 years by the early 1980s. "Thus," he says, "one could make a logical argument that HIV, instead of decreasing the lifespan of hemophiliacs, has in fact increased it."

Researchers who study health patterns among hemophiliacs agree that life-span in this group has increased over the last two decades. But if were not for HIV, they say, the increase would have been far higher. What is more, they argue that life-span among hemophiliacs has actually been sharply decreasing recently.

That conclusion is supported by a study from the Centers for Disease Control and Prevention (CDC), published this year in the *American Journal of Hematology*, evaluating two decades of death certificates from hemophiliacs. CDC's Terence Chorba and his co-workers concluded that, because of the introduction in the 1960s of clotting treatments that prevent death from hemorrhage, death rates dropped from 0.5 to 0.4 per million from 1968 to 1978. But from 1979 to 1989, the period when most U.S. hemophiliacs became infected with HIV, the death rate among hemophiliacs increased dramatically—to 1.3 per million.

The same study provides other perspectives on the sharp increases in death rates among hemophiliacs due to AIDS. The median age at death of all U.S. hemophiliacs fell from a high of 63 in 1983 to 38 in 1989. That change was due to the increase in deaths among HIV-positive hemophiliacs, the authors note, which soared from 19.9% in the period 1983–1985 to 55.1% in the period 1987–1989. Chorba and his colleagues conclude that the spread of HIV "significantly disrupted the progress in mortality statistics for this population."

Duesberg replies that this study "confirms very much everything I have said." He argues that the life-span dropped between 1987 and 1989 because of "the large-scale administration of AZT to American hemophiliacs." He calls the drop "an iatrogenic artifact."

For researchers such as TSSG's Mosley, however, the hemophilia data leave no question that HIV causes AIDS. Indeed, says Mosley, in the face of the data on hemophiliacs he has a hard time understanding why Duesberg continues to stick to his arguments.

—Jon Cohen