SKEPTIC

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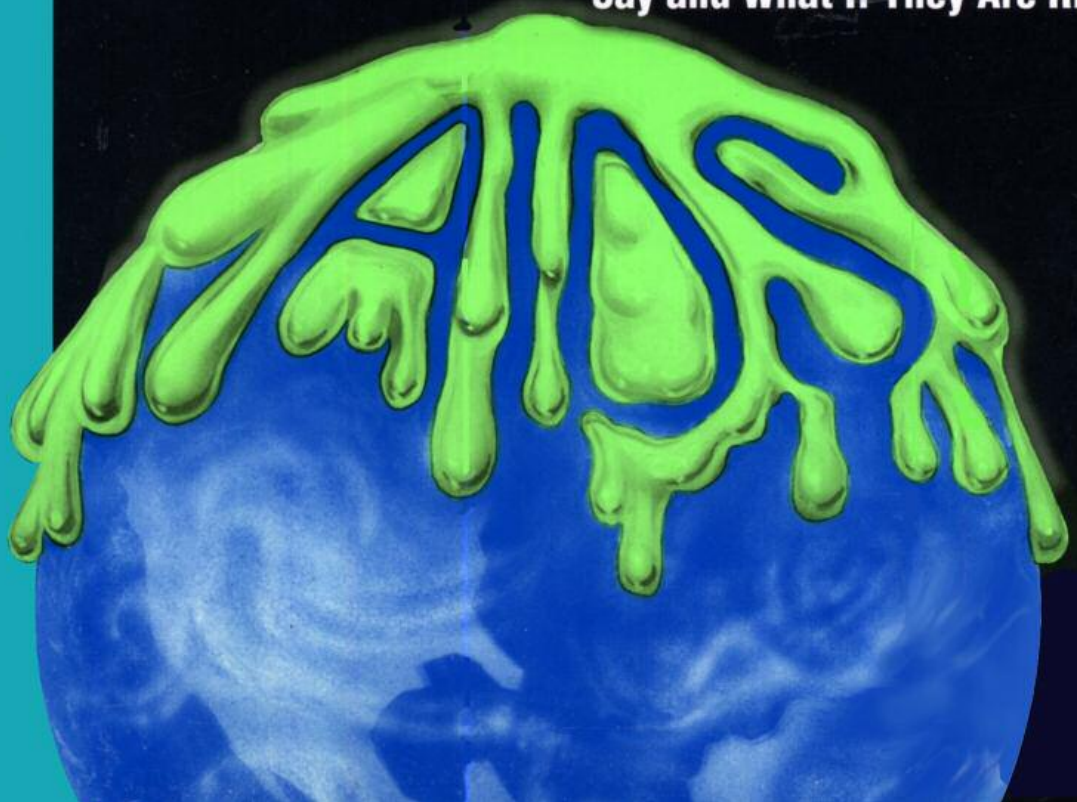
Does HIV Really Cause AIDS?

The AIDS Heretics—What Do They Say and What If They Are Right?



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- Darwin, Wallace, and the Great Priority Dispute
- Why Did God Make Rice Cakes?

BONUS:

A Provocative Interview with Charles Murray, Author of *The Bell Curve*

Note from the editor: *This article is unusual for several reasons: 1.) It is a monograph—longer than an article but shorter than a book; 2.) Skeptic usually features several voices on one subject, but because of the length we decided to allow the AIDS skeptics to respond in the next issue; 3.) Those who do not wish to read the entire article can glean the terms of the debate from certain subtitles and sidebars, especially in Part 1; 4.) Dr. Harris has made an original contribution to the discussion of the AIDS controversy in his analysis of the definition of AIDS, in particular in his use of Venn Diagrams to specify what is unique to AIDS and what is not.* Skeptic *is honored to publish this important contribution to the field and rather than apologize for the length of the article, we remind our readers that the magazine includes its usual array of columns, essays, articles, news items, and forum letters.*

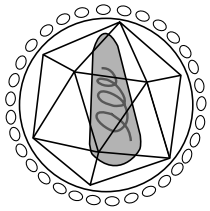
THE AIDS HERESIES

A Case Study in Skepticism Taken Too Far

By Steven B. Harris, M.D.

"Felix qui potuit rerum cognoscere causas."—Virgil
("Fortunate is the man who understands the causes of things.")

"It's the virus, stupid."
—Dr. David D. Ho, AIDS Researcher



ABSTRACT

Nobelist Kary Mullis once asked for a reference paper with the simple statement "HIV causes AIDS." This article reviews the modern argument for the HIV/AIDS hypothesis, covering main lines of evidence from human epidemiology and experimental animal virus research. Special attention is paid to the issue of how AIDS may be defined so that the possibility of AIDS without HIV may still be theoretically discussed. Major emphasis throughout this article is placed on the arguments of modern HIV/AIDS skeptics, Peter Duesberg and Robert Root-Bernstein, who do not believe that HIV has a central role in AIDS. It is concluded that HIV/AIDS skeptics have chosen overly broad definitions of AIDS which are not clinically useful, and which would, if employed, result in many confusing diagnoses of "AIDS" and "HIV-free AIDS" in people with good prognoses. HIV is one of a closely-related family of viruses which causes AIDS-like immunodeficiency diseases in a number of animals species, and HIV/AIDS skeptics have ignored or minimized this research in order to construct needlessly complicated alternative hypotheses for the cause of AIDS. These alternative views are based on correlations between AIDS and toxin exposure shown by epidemiologists to be artificial a decade ago, but which skeptics still refuse to abandon. Examination of the HIV/AIDS controversy thus allows us to draw some general lessons about how skepticism in science works, and the ways in which it can go pathologically awry.

 Acknowledgements: My sincere thanks to Paul Wakfer, Michael Federowicz, Larry Weber, Charles Platt, Sandra Russell, John Richfield, and Dr. Roger Bohman of the UCLA School of Medicine, who each provided many helpful comments on this manuscript during preparation. Special thanks to the editor Michael Shermer and Art Director Pat Linse.

INTRODUCTION: A DIALOGUE IN INDUCTIVE FRUSTRATION

Let us suppose that you have a bright and iconoclastic friend who smokes three packs of cigarettes a day. You remark one day that you would like to see him quit the habit, since he is certainly increasing his chances of lung cancer.

"Prove it," he says.

"Well," you begin, "the Surgeon General and a lot of scientists and doctors say you should quit...."

"Come now!" says your friend, "Since when did you become a fan of The Argument From Authority? I can find you scientists who do NOT believe I necessarily should quit; as well as a lot of intelligent business executives."

"Sure, but all those scientists and executives are paid by tobacco companies or grants from the Tobacco Institute," you protest.

"Well, what do you expect?" says your friend, lighting up and taking a satisfying drag. "Whenever scientists take an anti-establishment position, funding is cut off. The poor scientists then don't have anyone else to support their research but the Tobacco Institute. Do you expect them to drop out of research just because they hold unpopular opinions?"

"Okay, let's look at the data," you say. "What about the fact that 90% of lung cancer occurs in smokers?"

"Yes," says your friend, "and that means that 10% of it occurs in non-smokers, doesn't it? Obviously the 'cigarettes = lung cancer' hypothesis doesn't explain all lung cancer. Even for smokers there must be 'co-factors.' Heck, my grandfather smoked three packs a day right up to the day he was hit by a drunk driver at the age of 92. A lot of people smoke for a whole lifetime and never get cancer."

"Look, I didn't say the correlation was perfect!" you protest. "But it is certainly there. Two-pack-a-day people have 13 times the lung cancer risk of non-smokers."

"Oh, really?" your friend says, "Now, where do you get that number? I suppose somebody did an experiment where they got together a group of nonsmokers and randomized them to start smoking, or else stay smoke-free, and then made sure each and every person did as told for the next 40 years, so as not to bias the results. I must've missed that study."

"You know there is no such study. That experiment would have been impossible, since you can't enforce a random protocol like that. People will start or stop on their own. And besides, any experiment where you try to keep people from quitting would be immoral, since smoking causes cancer."

"So you admit you don't have any study where the two groups of smokers and nonsmokers are exactly equivalent, and only differing by chance or random draw? In every study the smokers and the nonsmokers are self-selected for their behavior and bound to be different not only in smoking behavior, but also because of whatever made them smoke or not smoke to begin with, right?! Not exactly great science, if you ask my layman's opinion."

"But when smokers quit, we know their risk of dying drops," you retort.

"You mean with regard to the smokers who don't quit? So what? The people who quit smoking did so for a reason other than chance or the experimental flip of a coin and again that means they will differ in some way other than their not smoking. Besides, did you know that for the first year after quitting, the risk of death for a new quitter actually goes up with regard to his fellow smokers who keep right on smoking?"

"I knew you'd bring that up. The mortality goes up for the quitter group for a while after they quit only because those people who quit are quite often sick, and that's why they quit."

"If so that makes my point about self-selection, doesn't it? You're saying that in that first year of quitting, the higher death rate of quitters is caused by another factor in our study other than smoking—namely, sickness. Well, so long as we're talking about such third factors, I have a hunch that stress causes cancer, and stressed-out people take up smoking to try to relieve the stress, and that's why there is more cancer in smokers, not because of smoking. Moveover, maybe the act of quitting stresses people out, and that's really why quitters die faster in that first year after quitting. Smoking is just a marker for stress—what you scientists call a "proxy variable."

"All this is ridiculous! You're just using your intellect to make you believe something you want to believe for other reasons. There is experimental evidence! Smoking causes lung cancer in lab animals! Are THEY stressed?"

"Actually, yes—have you seen what they do to them in a modern lab? Ever seen one of those rabbits with a leather muzzle over its nose, and a cigarette stuck in it which it can't take out? But anyway, I don't even believe you can find me a report of an experiment in which smoking causes lung cancer in animals."

Back you go to the scientific literature. And you find nothing. There is no such paper ….

Medical Induction

As this fact-based, fictional dialogue demonstrates, because there are many intellectual steps which are not perfectly secure in any generalization, even the most detailed inductive argument only goes so far toward proof. Not only may the same evidence mean different things to different people, it is more difficult to get people to follow a complicated inductive-reasoning trail when they dislike, or are threatened by, the conclusion at the end.

In the medical sciences, assembling an irrefutable argument for causation is sometimes an impossible task for the same reason it is in astronomy or paleontology: the direct and definitive experiment cannot be done. Scientists cannot travel back in time to watch dinosaurs, nor can they influence the behavior of planets or stars. In medicine, a common difficulty is that the necessary human interventive experiments to perfectly assess "risk factors" for harm may be unethical, and so these risks cannot be studied directly by experiment either.[1] How, then, do we come to *"know"* what things cause lung cancer or AIDS? For that matter, how do we come to know with any confidence that tyrannosaurs ate meat, or what generates

the sun's energy? In other words: how *do* we ever infer causation from looking at events (or records of events) which we cannot influence?

However we do it, it does seem that it can (to some extent) be done. Modern science depends on the fact that "correct" causal relationships can often be guessed entirely from logical and indirect observational tests of competing theories, even where direct experimentation is not possible. This is done using help from knowledge of simpler causal mechanisms which we have gained from similar systems in which experimentation *is* possible. As Einstein observed, one of the most amazing things about the universe is that this kind of inference is possible at all.

Of course, the overall results of this kind of theorizing, like those of any inductive process, are never certain. Still, whenever inferential theories in science finally *do* become directly testable by some new experimental technique, they often prove to be surprisingly sound. Why this should be true remains the deep mystery that it was for Einstein.

It is because of an inferential process, based on many lines of evidence, that we can be reasonably confident of the tobacco causation of much of lung cancer, even in the absence of a definitive experimental study. In the same way, an examination of a large body of related facts allows us reasonable confidence about the causation of other diseases—even a disease far more complicated than lung cancer, and with even more money and passion involved on both sides of the issue.

PART I

THE AIDS SKEPTICS AND THEIR CLAIMS

Should We Be Skeptical?

Recently, several popular lay publications (*Reason, Spin, New York Native*) have run articles calling into question the theory that the viral agent with the conclusion-asserting name, the "human immunodeficiency virus (HIV)," is the cause of the epidemic of human acquired immune deficiency syndrome, known as AIDS.

What do we mean by talking of the "cause" of AIDS? We know that the common cold or the flu—indeed all infectious diseases—are in some sense "caused" not only by the organism. Also important in the causal chain are host factors (such as immune response), and even simple host-overwhelming factors, such as the infectious dose of organism which enters the body (called the "inoculum"). These additional causal factors, which have nothing to do with the microbe itself, can be extremely important. They may in some cases outweigh everything else. Nevertheless, because the smallpox virus (for example) is necessary for smallpox, medical science still regards it as "causal" in the sense that if there is no microbe, there is no illness. Eliminate the smallpox virus from the population and one eliminates the disease (as was in fact done in the 1970s).

Even this kind of "causal" connection between a disease syndrome and infectious agent is what is under attack in recent articles about HIV and AIDS. Some skeptics have claimed not only that HIV is not the *only* external factor necessary for AIDS, but that if HIV were eliminated from the Earth, at least some AIDS would still be with us. Still others have gone further and claimed that HIV infection is totally harmless and does not even *contribute* to the development of AIDS. These people believe that if HIV were to disappear, AIDS would continue exactly as before.

In what follows, we will examine the best evidence behind what most researchers believe is the role of HIV and other factors in AIDS. We will also examine leading skeptical views on the causation of AIDS. Because a great deal of published research is available on this issue, our examination of AIDS will also let us illustrate how science closes in on cause and effect, even when direct experimental "proof" is not available.

We will thus be interested in not only AIDS, but also larger questions about science, and scientific debate. What makes a good scientific theory, and what makes a poor one? Are there reasons for hope in looking at the disease of AIDS in particular, and the workings of the biomedical scientific "establishment" in general? Are we making any progress with AIDS, or just wasting billions each year chasing fantasies?

This essay will argue that we are not wasting all that money, and that when it comes to critics of the HIV/AIDS hypothesis, we have a practical case in which skepticism has been taken too far. Science, we are happy to report, still works, and it is making progress with AIDS. That some critics have failed to recognize this only highlights the fact that science is only partly an empirical enterprise, and that it also has an intuitive and aesthetic side which is subject to arguments over taste. This is not a thing which is taught to students in schools, but it is a concept key to understanding most scientific controversies.

Defining AIDS

Scientific problem-solving begins with definitions, and in choosing a definition for AIDS we run immediately into the HIV/AIDS controversy. Some of the difficulty is that definitions, even in science, are chosen partly on aesthetic grounds, partly on utilitarian ones.

In medical science we rarely know in detail at the molecular or even cellular level what causes most human illness,

and so in our ignorance we are often forced to work with "disease syndromes," which are collections of symptoms and sometimes lab tests which seem to "go together." In order to usefully define a "disease syndrome" we need to pick our defining characteristics so as to include all of the sick people who we are interested in for good clinical reasons, and exclude everyone else.

What are good clinical reasons? In medicine there is not much point in defining a new *"disease"* which, when present, makes no difference in either prognosis or treatment. Nor is there any point in defining a disease so poorly that it fails to capture all the sick people who seem to have pretty much the same thing wrong with them from the prognosis or treatment viewpoint. If (as always happens) we lack information about what impact certain definitional characteristics have upon treatment or prognosis, then we are forced to guess, as best we can, what definition will be most useful. It is at this point, in deciding whether two people have "pretty much" the same thing wrong with them, that aesthetic and intuitive considerations unavoidably enter into medical science.

"In the medical sciences, assembling an irrefutable argument for causation is sometimes an impossible task for the same reason it is in astronomy or paleontology: the direct and definitive experiment cannot be done."

Utility imposes other constraints, too. A disease definition which is to be used during a hunt for the disease's causation, should not assume any cause which is in question. In other words, if we choose a definition for AIDS which requires infection with the HIV virus (the current way it is done in many countries, including the U.S.), then we will have chosen our terms so as to be of little help in the question of whether HIV causes AIDS. Obviously, it would be nothing remarkable if we "discovered" that 100% of people with AIDS were infected with HIV, if we defined AIDS in such a way as to require HIV infection.

In re-opening the question of the cause of AIDS, what we need is a modified AIDS definition which does not involve HIV, so that the question of whether or not all AIDS cases are infected with HIV is an empiric one, not simply a semantic one. When we have a suitable HIV-free candidate definition for AIDS, we can then ask two critical questions about it: 1) Have we captured with our definition all of the people with the new medical problem that we historically came up with the AIDS label, in order to describe and encompass in the first place? 2) If we test our defined group, are 100% of the people encompassed by our AIDS definition found to be infected with HIV, an otherwise rare virus in the population? If the answer to both these questions is yes, then HIV is promoted to a good candidate for a cause of AIDS. If either answer is no, then the HIV/AIDS hypothesis obviously has severe problems right from the start.

Fortunately, however, we can easily construct a workable definition of AIDS which does not include any reference to HIV, but which still describes the new epidemic in which we are interested. Such a definition will not be the standard one, of course, but since the standard modern HIV-containing AIDS definition is unusable for this purpose, both we and the AIDS skeptics are required to construct special AIDS definitions even to continue to talk about the problem of causation.

Redefining AIDS: Acquired Immune *Failure* Syndrome

What is the best way to define AIDS without reference to HIV? Acquired Immune Deficiency Syndrome is the name historically chosen for a new medical syndrome which is essentially 100% fatal, and thus in defining it we are looking for people with an immune deficiency in the range which is life-threatening and will continue to grow relentlessly worse until life is impossible.

One possible way to define immune deficiency would be to define it by what problems it causes—for instance, one could pick people who have gotten so-called "opportunistic infections" or strange infections which are seldom if ever seen in people whose immune systems are fully functional. In the early days of AIDS, before HIV was discovered, the syndrome was indeed defined using such opportunistic diseases (***Fig. la***), and people with these infections are still included in the federal Centers for Disease Control (C.D.C.) clinical surveillance definition of AIDS (but now only if they are also HIV infected). We will not be able to use this C.D.C. definition (***Fig. lc***). Not only does it assume HIV infection, but for historical, political, and technical reasons, it also is constructed in a way which does not assess current immune status in the best way.

Why is this? The basic problem is that only a limited amount of information about a person's immune system function flows from the bare fact that they have an "opportunistic" infection. Certainly there is a good correlation between immune function and what kind of opportunistic infections occur, but the correlation is far from perfect, since opportunistic infection risk is influenced by not only immune status, but also by the quality of what we may term the infectious "assault" to the system. The assault in turn is influenced by a person's physical location, infection contacts, personal habits, and other exposure factors both known and unknown. In the end, assault differences insure that some unlucky, highly infection-exposed people manage to contract opportunistic infections when only mildly immune compromised (though these are rarely fatal). By contrast, the same assault differences insure that other people who are badly immunologically impaired may escape opportunistic infections for an amazingly long time, simply by missing the microbes which will kill them (***Fig. 1a***).

Figure 1

Defining AIDS

The Amount of HIV-Free AIDS Depends on Your Definition of AIDS

These Venn Diagrams Illustrate the Overlapping Classes of Patients for Different Definitions of AIDS. Size and overlap of categories is drawn to be illustrative of concept, and is not necessarily to scale.

No AIDS

AIDS

HIV-Free AIDS as Proposed by AIDS Skeptics

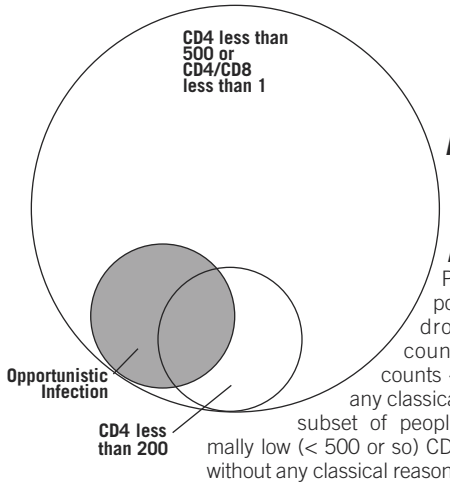


Fig 1a. **Pre-1985 AIDS (Shaded Area)**

People with a potentially lethal drop in CD4+ counts (sustained counts < 200) without any classical reason, are a subset of people with abnormally low (< 500 or so) CD4+ cell counts without any classical reason. The subset of people with opportunistic fungal and viral infections, Kaposi's sarcoma, and certain lymphomas, greatly overlaps the group with the most severe CD4+ loss, but not perfectly. A few people are opportunistically infected with higher CD4+ counts, and a few people manage to drop CD4+ lymphocytes to much lower levels (at least for a time) without infection or other problems. Before 1985, only persons with infections and other problems were given the diagnosis of AIDS, regardless of CD4+ status.

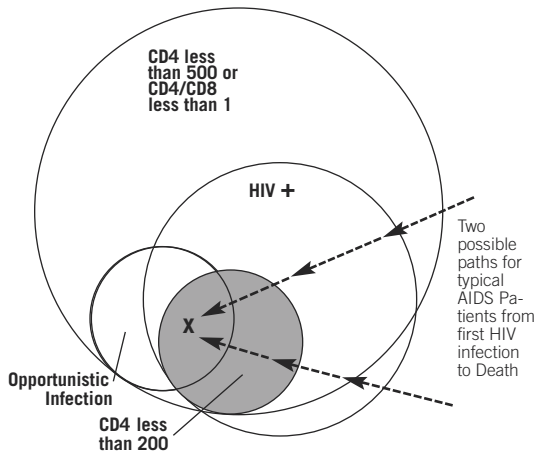


Fig 1b. **Shaded Area Shows AIDS As Defined in This Essay**

When HIV testing became available in 1985, it was found that many people in early stages of HIV had low or even normal CD4+ counts. In people with *sustained* CD4+ counts below 200 without classical reason, however, HIV was always present. This very low count clinically means near immune failure, and its presence without classical reason is used alone (without the HIV test criterion) as the definition of "AIDS" in this review, even if no other clinical problem is present.

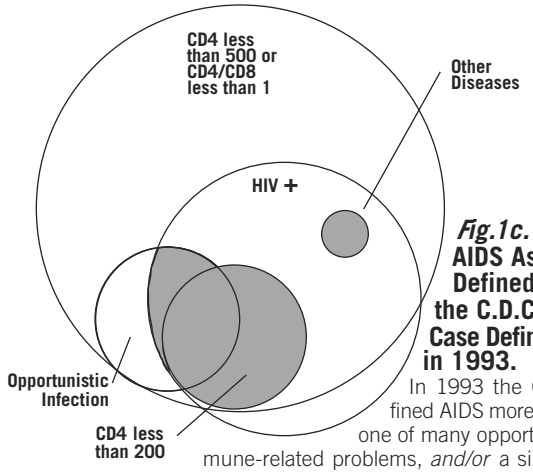


Fig.1c. **AIDS As Defined by the C.D.C. Case Definition in 1993.**

In 1993 the C.D.C. defined AIDS more broadly as one of many opportunistic immune-related problems, *and/or* a single CD4+ count < 200, in HIV+ people. Other less immunosuppressed people with certain immunerelated problems and higher CD4+ counts, so long as HIV-postive, were also included in the category of AIDS, on the basis of their poor prognosis.

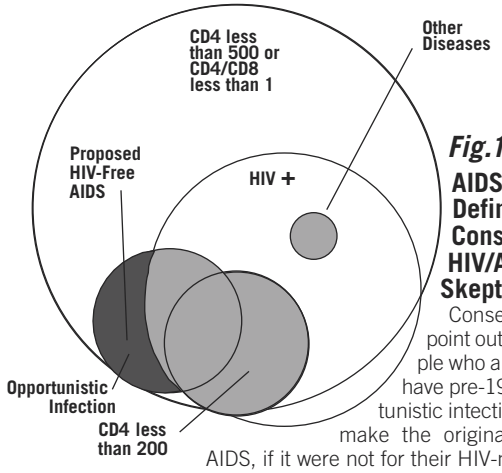


Fig.1d. **AIDS As Defined by Conservative HIV/AIDS Skeptics**

Conservative critics point out that a few people who are HIV-negative have pre-1985 type opportunistic intections, and would make the original definition of AIDS, if it were not for their HIV-negative status. these patients constitute "HIV-negative AIDS" by pre-1985 criteria. Some have ICL and CFIDS by today's definitions/standards. In many ways they are not simply "HIV-negative AIDS," however, since they differ from other AIDS cases by other than HIV criteria (CD4+ counts, CD8+ counts, IgA levels, history of risk behavior, etc). Most importantly, they differ from classic AIDS in prognosis.

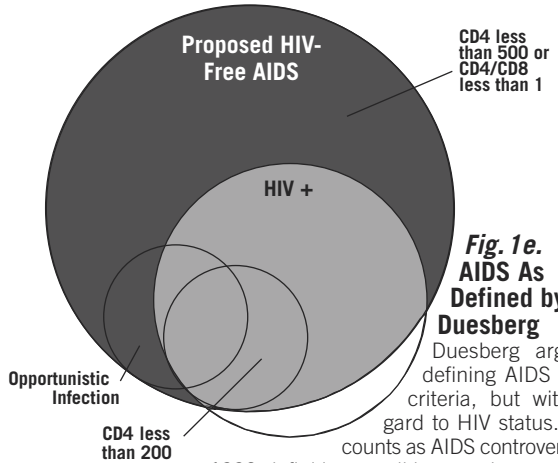


Fig. 1e. **AIDS As Defined by Peter Duesberg**

Duesberg argues for defining AIDS by 1993 criteria, but without regard to HIV status. He also counts as AIDS controversial non-1993 definition conditions such as oral thrush (candida) in men, and a low CD4/CD8 ratio without infection—making, in all, for a much larger group of "HIV-free AIDS" cases by his criteria than by anyone elses.

When it comes to immune function, then, it is better to have a direct test which is not subject to uncontrolled variables such as which microbes happen to be in the air or drinking water, and how many. Such a test exists. Quite early in the history of AIDS, it was found that the immune defect in this disease is peculiar, and that it most visibly involves a particular kind of cell in blood and lymphatic tissues (lymph "nodes"), called "T-lymphocytes." In the syndrome of AIDS, certain T-lymphocytes gradually disappear from both blood and lymph tissues, and a simple T-lymphocyte count in the blood can tell how serious the reduction has been in both places (since blood lymphocytes come from the lymphatics). The arm of the immune system which is controlled most directly by T-lymphocytes (the body's defense against viruses and fungi) is what is most defective in AIDS, and viral and fungal infections are the main opportunistic infections which appear and cause death in AIDS.

AIDS is so specific in its attack that scientists eventually found that only one *subset* of T-lymphocytes was initially hardest-hit. This was the so-called CD4+ or "helper" T-lymphocyte, which has the job of stimulating the immune system. The other major type of blood T-lymphocyte, the CD8+ or "suppressor" lymphocyte, is involved in shutting the immune system down; in AIDS, CD8+ lymphocyte blood numbers increase early in the disease, and are not decreased until near the very end of the disease process, when they may also disappear.

CD4+ lymphocyte blood counts tell much of the story in AIDS and other immunodeficiencies involving the T-lymphocyte immune system. A healthy adult might have a CD4+ lymphocyte count of 800 to 1000, with a CD8+ count half of this. These are normal values. Under physical stress, injury, or chronic infection, CD4+ lymphocyte count might drop to 500 (to even less than the CD8+ count), and mild, non-fatal opportunistic infections might be the result. A CD4+ count less than the CD8+ count was once used as a crude marker for AIDS, but today with progress we know that this immune state is non-specific. In AIDS, things eventually become much worse than this, and the worse things get, the fewer possible alternative causes are possible.

In full-blown AIDS, as defined by opportunistic infections and other problems, the CD4+ count is usually below 200. It is at such count levels that Kaposi's sarcoma (a tumor perhaps caused by a virus) and life-threatening infections begin to appear, although approximately 95% of AIDS patients survive beyond this level of decline.[2] Another feature of AIDS, however, is that inevitably the count grows worse over time. Today, in the modern era of antibiotics and more knowledgeable care, 85% of AIDS patients live to see their CD4+ lymphocyte count drop below 50.[3] Famous AIDS sufferer Kimberly Bergalis, for instance, had her CD4+ count drop to 41 before her disease was even diagnosed.[4] Many AIDS patients today go all the way to CD4+ counts of zero before the inevitable final infection or other complication. It is because of the implacable and more or less irreversible loss of vital T-cells that AIDS remains a fatal condition, with an average time span of less than two years between the first opportunistic infection and death.

If we wish to define AIDS in terms of immune failure, the essential question is where do we draw the line, so as to include almost all people with the new immunodeficiency epidemic, who are going to die from it, but exclude everyone else? If we simply define "immune deficiency" as a sustained CD4+ lymphocyte count of less than 200 (where death begins to become more likely), we will capture about 95% of people who die of what the C.D.C. now defines as "AIDS" (***Fig. 1b***).

> "Science, we are happy to report, still works, and it is making progress with AIDS. That some critics have failed to recognize this only highlights the fact that science is only partly an empirical enterprise, and that it also has an intuitive and aesthetic side which is subject to arguments over taste."

Previous to the epidemic of AIDS, of course, people did die of immune failure with low T-lymphocyte counts (including low CD4+ counts) for other reasons, and they continue to do so now. Thus, we must also exclude from our AIDS definition all those people who have one of the classic reasons for a very low T-lymphocyte count—reasons which were well-known before the AIDS era (cancer, malnutrition, tuberculosis, radiation, chemotherapy, etc). These people do not have AIDS, because the historical epidemic of AIDS consisted of people with no T-lymphocytes, and yet no known reason for it. These people had appeared newly on the scene in the 1980's with evidence of a fatal kind of immune failure which was *acquired,* meaning that it was an epidemic problem of something "picked up" by previously healthy people.

So let us simply collect all the people we can find with CD4+ counts remaining below 200 (for a few months) without known reason, and test them for HIV. When we do, we find that essentially all are HIV infected, and any who are not do not look at all like typical AIDS patients (as we will see). This, despite the fact that only 0.3% of the general population carries this virus. Thus, at this point we have no evidence yet to directly contradict the simple theory that HIV causes 100% of our conservatively defined "AIDS." AIDS skeptics will need different definitions in order to find HIV-free AIDS. (***Fig. 1d and 1e***).

Enter the AIDS Skeptics

The view that HIV plays no role in AIDS has been most notably put forth by Peter H. Duesberg, professor of molecular and cell biology at the University of California at Berkeley. A German emigree, he was originally trained in chemistry. On

arriving in the U.S. in 1964 he began work in the field of viral molecular biology at Berkeley, where in 1970 he co-discovered the genetic basis for the carcinogenic action of the Rous sarcoma retrovirus. In 1987 he began publicly questioning the role of HIV in AIDS, a stand which has made him the center of the present HIV/AIDS controversy. Duesberg's most recent book is called *Why We Will Never Win the War on AIDS* (1994), co-authored by a Berkeley graduate student and one-time protege Bryan J. Ellison. The book has been plagued by trouble. According to a message issued October 13, 1994 by the Group for the Scientific Reappraisal of the HIV/AIDS Hypothesis, this manuscript was published unilaterally by Ellison without Duesberg's consent, following failed editorial negotiations with the original contracting publisher (St. Martin's Press). According to Duesberg, the editor had asked for additional documentation, clarification, and elimination of material which might be considered unfair to individuals. Duesberg was willing to cooperate but Ellison was not. Following Ellison's publication of the manuscript at *Inside Story Communications* (a newsletter edited by Ellison), Duesberg severed relations with Ellison and is seeking an injunction against further publication of the book. The cooperation of James Tabulse, publisher of the Group's newsletter *Rethinking AIDS,* with Ellison, has meant that the Duesberg's Group has decided to severe relations with this publication as well. They now publish a new newsletter called *Reappraising AIDS.* Since Duesberg has questioned only publication and editorial rights for the new book and has not repudiated any of its contents, the book is used in this essay (see page references) as a source of Duesberg's views. A major Duesberg essay is also used.[5]

At the other end of the skeptic spectrum are hybrid arguments raised by Robert Root-Bernstein, an associate professor of physiology, winner of a MacArthur "genius" award, and author of *Rethinking AIDS*[6], the most carefully-documented work to yet assail the prevailing medical views on HIV and AIDS (see page references). Root-Bernstein is less radical than Duesberg, arguing for a somewhat less central role for HIV in AIDS than is generally given it, but still allowing for the virus to have some part in the etiology of the disease.

Since Duesberg's original challenge, which has been the cause of much formal debate in the literature[7], a number of scientists, physicians, and lay persons have taken up the cause for a "re-appraisal" of the idea that HIV is *the* major causal factor, or even *one* of the major causal factors, in AIDS. Most respectable is the Group for the Scientific Reappraisal of the HIV/AIDS Hypothesis, which has collected over 200 signatures of physicians and scientists, including those of Nobelists Walter Gilbert and Kary Mullis. This group has campaigned to remove the requirement for HIV infection from any medical definition of AIDS, feeling that using this criterion is at best premature, and prejudices any hunt for alternative explanations for the disease.

Almost all critics of the AIDS/HIV hypothesis have one thing in common: they insist on using a much broader definition of AIDS than we have proposed, a definition which virtually guarantees that some people who fit the critics' AIDS definition will *not* be HIV infected.

To be fair, there is some historical precedent for using a definition of AIDS which relies solely on the patient developing one of a certain list of the most serious and specific opportunistic infections, since this was the way the disease was diagnosed before HIV testing became available in 1985 (compare ***Fig. 1a*** and ***ld***). Today we know that almost all such people with pre-1985 defined "AIDS" are infected with HIV—indeed this was known in late 1983, before the official announcement of viral cause was made the following year. But today we know this figure would not quite be 100%.[13] As we will see below, there is evidence that the few HIV-negatives in this group will be people with lesser degrees of immune suppression (higher CD4+ counts), who will *not* progress to worse immune function, or quickly die. (***Fig. 1c***). It seems reasonable, then, with what we know today, to simply exclude them—since we know that this is not the characteristic picture of AIDS. Again, it is most reasonable for our purposes to diagnose AIDS on the basis of immune function (CD4+ levels) only, since it is immune function, not infection status, which correlates with short-term prognosis in CD4+ immunosuppressed people.

The skeptics, however, will have none of this, and in their definitions are seemingly less interested in clinical utility than they are in collecting ammunition for an argument. The more broadly AIDS is defined, the more "HIV-free AIDS" cases skeptics can assemble, and these, in turn, can be used as evidence to the lay public that HIV cannot be the cause of AIDS.

Duesberg, for instance,[5] has insisted upon retaining the early 1980's observation that a CD4+/CD8+ lymphocyte count ratio of less than 1.0 is often seen in AIDS, and he has decided that such a ratio, even in the absence of opportunistic infection, is synonymous with AIDS (p. 260). Duesberg now calls this ratio an "AIDS-defining immunodeficiency," and counts people with this lab result as part of "HIV-negative AIDS," in his shocking and too-often repeated statistic that there are "3,000 documented HIV-free AIDS cases."[8] Here again, Duesberg's chosen definition of AIDS is less than useful because people with such mild immunosuppression as he uses to define "AIDS" are not the people who are dying, or are shortly destined to die. AIDS is nothing if not a fatal epidemic, and insisting that mildly compromised persons who may or may not eventually get any worse be labeled as having "AIDS," as Duesberg routinely does, only serves to confuse the issue (***Fig le***).

There is a general trend for AIDS skeptics to overdramatize levels of immune deficiency which are not clinically very significant. For example, Root-Bernstein (p. 262), in characterizing a study of HIV-negative men newly infected with CMV virus, notes that for a time, some of the men had CD4+/CD8+ cell ratios of less than 0.4, a figure which he claims "represents extreme immune suppression." During viral infections such CD4+ depressions are transient. In

AIDS, however, this ratio would typically be far less than 0.3, and thus these men would not be mistaken for the current C.D.C. immunological definition of AIDS, even if they were HIV-positive.[9] The level of immunosuppression associated with a ratio of only 0.4 is not associated with significant risk of death by opportunistic infection. You might wonder how we are justified in calling a ratio of 0.4 "extreme immune suppression," if people rarely die from it, as they are known to do in AIDS. Root-Bernstein does not say—indeed, does not even raise the issue. The AIDS skeptics' overdrawn interpretation of the clinical significance of lab results is one of the places in which absence of medical training shows most clearly.

Indeed, Duesberg's paper[5] and Root-Bernstein's book[6] each contain descriptions of groups of HIV-free people who are somewhat immunosuppressed due to low CD4+ counts, or low CD4+/CD8+ ratios, but not severely so, as defined by our straightforward criteria of having a significant risk of infectious death due to T-lymphocyte loss. These immune deficient patients in the AIDS skeptics' literature are presented along with the inference that perhaps somewhere there exist people with these immune suppressive factors, or combinations of them, who are *severely* T-lymphocyte immunosuppressed for long periods of time (as AIDS patients are), and yet still without having HIV. Duesberg and Root-Bernstein only have one difficulty in this argument—neither has been able to actually *find* any such people.

"Almost all critics of the AIDS/HIV hypothesis have one thing in common: they insist on using a much broader definition of AIDS than we have proposed, a definition which virtually guarantees that some people who fit the critics' AIDS definition will *not* be HIV infected."

HIV-Free AIDS?

Hypotheses may be disproved by the right data with relative ease, and cases of HIV-free AIDS would disprove the idea that HIV causes AIDS, in proportion to how often these are found (i.e., if 10% of AIDS cases were HIV-free, this would prove that HIV is not the cause of *at least* 10% of AIDS). Thus, Duesberg and Root-Bernstein are not the only ones who have been looking for HIV-free people who are badly CD4+ lymphocyte immunosuppressed without reason (i.e., good candidates for HIV-free AIDS). Very recently the C.D.C. reported that after a massive search it had only been able to find less than 100 people without HIV infection across the country whose CD4+ counts were at one time less than 300 (not quite in the AIDS-class immunosuppression range of 200, but drawing close). This syndrome was named "ICL" (idiopathic CD4+ lymphocytopenia), meaning "people with low CD4+ lymphocyte counts without a medically-defined disease."

Why was ICL not simply called "HIV-free AIDS?" Critics have darkly suggested that the reason is politics, but in fact there were problems with considering these people as AIDS cases which had nothing to do with AIDS politics or the HIV theory. One difficulty was that people labeled as having "ICL" were found not to come from the AIDS risk groups. They did not use illicit drugs, had not been exposed to blood products, and had no evidence of sexual behavior which would have exposed them to a special infection risk. Thus, as we will see, the most popular alternative AIDS hypotheses did not explain these people *either*—a fact which did not keep them from being mentioned in nearly every skeptical treatment of the HIV/AIDS issue. What the skeptics had forgotten (or hoped their readers would not notice) was that the immune deficiency of people with ICL did not seem to be *acquired*.[10] What justification was there, then, for calling it AIDS?

Moreover, people with ICL were not only epidemiologically, but often immunologically distinguishable from AIDS cases: their CD4+ lymphocyte counts swung widely, and transiently, in response to infections, and were often much higher than 300 (in contrast to people with AIDS, whose CD4+ lymphocyte counts tend to stay low and heading on an ever-downward trend). ICL people also often had low total lymphocytes or low CD8+ lymphocyte counts, again indicating that their immune failure did not make much distinction between CD4+ and CD8+ lymphocytes, as classic AIDS does. Clearly, these people did not belong to the classic AIDS groups which began suffering with epidemic immune problems about 1980. They are not part of the new phenomenon of AIDS, and although sometimes suffering from opportunistic infections, did not even seem to share the implacable death rate of AIDS.[10]

Searches for HIV-negative people who have AIDS-type severe immune suppression have also been taken specifically within AIDS risk groups. Vermund reported in the United States Multicenter Cohort Study that of the 2,713 persistently HIV-negative homosexual men in the study, who had had a total of 22,643 blood tests, only one significantly immunosuppressed man (CD4+ lymphocyte counts persistently less than 300) was found. This man was taking chemotherapy and radiation for cancer, and thus had a very good reason other than his lifestyle to explain his lab results.[11] If this study is indicative, then most, if not all, male homosexuals with sustained AIDS-range immune failure are HIV-positive, since it has proved very difficult to find any who are HIV-negative.

Much the same seems to be true in IV drug users: in a study of 1,246 HIV-negative injecting drug users in New York City from 1984 to 1992, for example, only four were found with CD4+ lymphocyte counts less than 300 (if IV drug use per se was a major cause of AIDS, the number should have been far higher). In this small group of four people, even though infected with multiple non-HIV viruses, and with a history of heavy drug use, immune function was stable and without the steady decline in CD4+ lymphocyte counts over a time span of years which is characteristic of all unselected HIV-positive cohorts.[12] Thus, in this study also, the few HIV-negative people who could be found with even near-AIDS range immunodepression, were

What Is a Retrovirus?

A retrovirus is a virus which has its genetic structure encoded into RNA, but which reproduces by turning it back into DNA during an infection. Once inside a living cell, retroviruses are able to synthesize virus DNA-copy molecules using the virus's RNA genetic molecules as a template, or "master" (this process proceeds *retrograde* to the normal "DNA—>RNA" information flow in cells, hence the name). To do this job a unique enzyme molecule called "reverse transcriptase" is used by the virus. Since this enzyme is not found in normal cells the virus itself must carry it. This enzyme and the process it catalyzes are so unusual in biology that H. Temin and D. Baltimore were awarded the 1975 Nobel Prize in Medicine for discovering it.

Once the DNA-copy of a retrovirus (called a pro-virus) is made, it is often inserted into the DNA of the cell being infected. Now an actual part of the genetic code of the cell, the retrovirus genetic information is hidden from the immune system, which would otherwise destroy the virus inside the cell, or destroy the entire cell. All humans harbor some foreign retroviral DNA actually integrated or inserted into the DNA in most of their body cells. In this sense, we all share some of the fate of the scientist in the remake of the movie *The Fly,* a matter-transporter victim whose DNA is not pure and not entirely human, but who cannot do anything about it because there are no "tweezers" fine enough, or discriminating enough, for the job. Some of the foreign DNA in each of our cells is from retroviruses which went into hiding eons ago in our ancestors, and are now reproduced automatically along with our normal cells, and have long since "forgotten" how to get themselves back out of our DNA.

still not behaving medically like people with AIDS.

So far as we know, then, in the United States *all* people who are a part of this new phenomenon of sustained very low (and declining) CD4+ cell counts in high risk groups, have been infected with HIV. This does not prove that HIV causes AIDS, but it is surely an important clue.

Why Not AIDS Without HIV?

A persistent suggestion by skeptics is that it would be proper to use as an AIDS definition the current C.D.C. definition (which includes all HIV-infected people who have a much expanded list of infections and other problems), but with the HIV criteria removed. (***Fig. 1d.***) The problem with this suggestion is that definitions of diseases are chosen by the C.D.C. for maximum clinical utility, and HIV criteria in the C.D.C. AIDS definition was not put there only to insure that there would be no HIV-free AIDS. Rather, HIV infection in a person with opportunistic infection is known to be (alone among all other viral infections) a very good predictor of whether immune status will continue to decay until the person eventually succumbs to opportunistic infections. In people with mildly compromised immune systems, the prognostic importance of an HIV infection (which even critics admit, without admitting causation) is large. Thus, we cannot simply remove HIV status from the C.D.C. definition and still have the definition do what it was designed to do, which is predict impending death by immune failure.

AIDS skeptics know that if "AIDS" is defined only in terms of today's much broader list of "AIDS-defining" diseases and infections (which are meant to be used only in conjunction with HIV status), it is sure to be quite true that the definition will be far too broad to be prognostic. Such opportunistic infections, as critics well know, sometimes happen in the population occasionally even without the most severe CD4+ immunosuppression which is characteristic of people who die with AIDS.

A study by Salvato illustrates this point.[13] In the study, medical records over six years for 1500 HIV-positive patients were compared with records for 1,000 HIV-negative patients who had Chronic Fatigue Immunodeficiency Syndrome (CFIDS) and evidence of immune suppression. It was found that the CFIDS patients had fatigue, lymphadenopathy (swollen lymph "nodes") and low grade fevers—but that over the course of six years their problems were not severe. Only one of them developed CD4+ lymphocyte counts less than 300 ("ICL"). Still, two had yeast esophagus infections, a severe opportunistic infection rarely seen other than in AIDS and other people severely immunosuppressed. Three had active CMV virus disease of various tissues—another disease very often seen in AIDS. A total of 486 patients had evidence of yeast infection of the mouth on exam, a condition suggestive of mild immune problems but one not limited to AIDS. The average CD4+ lymphocyte count in these patients (not including the single ICL patient) ranged from 500-1400, with an average of 650. This was significantly lower than normal, but much higher than typical for AIDS.

In this study, 95% of the HIV-negative patients had previously been infected with the EBV, CMV or HHV-6 viruses, and 48% had evidence for continued viral infection (skeptics such as Root-Bernstein have suggested that these viruses have roles in AIDS at least as important as that of HIV, but this study provides evidence against this idea). Most interestingly, these immunocompromised HIV-negative patients were followed from two to six years, and none experienced progressive CD4+ lymphocyte decline (except for the one patient with ICL, who, with treatment of CMV infection, showed increased CD4+ lymphocyte counts again). Such CD4+ count stability is never seen in any random group of HIV-positive

people, where average CD4+ count decline with time would be inevitable. The authors conclude:

> Even after a methodical search in a practice that sees a large number of patients with immune problems, only 1 patient was found to have ICL. However, this study demonstrates that patients with normal CD4 counts can develop AIDS defining opportunistic infections . . . Upon long-term follow-up these patients do not appear to experience progressive CD4 depletion.

Most importantly, no HIV-negative person died in the study, which illustrates the extent to which chronically virally infected, immune-suppressed people can *approach* the clinical picture of AIDS (see dark area ***Fig. 1d***), without crossing into the permanent and deadly immune failure which is characteristic only of people with HIV infection.

The reader who is a bit confused at this point should keep in mind simply that the most important thing about the syndrome of AIDS is that it inevitably and rapidly destroys the immune system and kills people. Thus, mild CD4+ depression and opportunistic infections are not always AIDS, for only some of these people (as it turns out, the HIV+ ones) will progress to immune failure. It is immune failure (almost complete sustained CD4+ lymphocyte loss) and death by opportunistic infection which is characteristic of AIDS; and it is only these people who are *always* HIV infected.

"Do you know where the AIDS virus was developed? Right outside of Washington. It is my feeling that the U.S. government is deliberately spreading AIDS."
— Louis Farrakhan

Did the Government Create AIDS?

At the African-American Summit speech in New Orleans in 1989, Louis Farrakhan told his audience: "The spread of international AIDS was an attempt by the U.S. government to decimate the population of central Africa." Last year he told Barbara Walters on ABC's *20/20:* "Do you know where the AIDS virus was developed? Right outside of Washington. It is my feeling that the U.S. government is deliberately spreading AIDS." Such paranoid and conspiratorial thinking is not uncommon in history whenever a new and devestating plague destroys a community, as when the Jews were blamed for the Black Death in the 14th century. But this is not the form of AIDS skepticism which I am addressing in this essay, and needless to say there is not a shred of evidence for such an outrageous claim.[17]

But what if AIDS and immune failure are not really new—perhaps we just look harder for them now that we recognize them? Could our new theories be warping our views so completely that by now that we have made a new "plague" out of something that was here all the time? Epidemiologically, what can we fairly say about the period before 1980, keeping this possible bias in mind?

With the new ability to test old preserved tissue specimens for HIV, the first thing that becomes apparent is that AIDS is indeed older than 1981—perhaps far older. Deaths from what has since been recognized as HIV infection with immune failure have been seen clinically, without being understood, for at least 35 years, and probably much longer. An HIV-infected British sailor, who had traveled widely, is known to have died with severe immune deficiency and HIV infection in 1959, the earliest proven case of modern AIDS. The diagnosis was made by means of preserved autopsy tissue specimen HIV testing, 30 years after the fact.[17]

This man's death alone provides good evidence that HIV is not a product of deliberate (government or otherwise) genetic engineering, for in 1959 biologic science was simply too unsophisticated to work with lymphotropic (lymphocyte-infecting) retroviruses like HIV, let alone engineer them.[103] If it is anything at all, HIV is an accidental infection of humans with an African primate virus. The genetic material of the most common HIV-1 strain is most similar to that of a virus known to naturally infect chimpanzees, and it may be that HIV's ancestors have been present in Africa, perhaps even in humans, for a very long time—perhaps thousands of years.[18,121] In West Africa, a close cousin of the U.S. HIV-1 strain, called HIV-2, is almost identical to several indigenous African monkey viruses, and almost certainly has been derived from them quite recently in virus evolutionary time (less than several centuries).

The Origins of AIDS

The story of the detective hunt for the cause of AIDS is told with wit and clarity by Randy Shilts in the best-selling book *And the Band Played On.* (In 1994, Shilts, at the age of 42, became a casualty of the disease himself.) Other good histories of the early AIDS epidemic are also available.[14]

In the U.S., the first AIDS or AIDS-like death that we know for sure was also associated with HIV infection was that of a 17 year-old possibly homosexual male, who died of strange opportunistic infections in 1968, and whose preserved tissues also proved to be harboring HIV genetic material on testing decades later.[19] This early AIDS-sufferer had never been out of the country, showing that the virus was already active in the Western Hemisphere in 1968. In corroboration, a 4% fraction of preserved serum samples from IV drug users in this era (1971-2) in the U.S. have been found to be HIV-positive. Apparently HIV viral infection has been present in small contingents of both drug users and homosexual men for some time in the United States.[20]

Why, then, was the U.S. first hit with an AIDS epidemic only in the 1980s, with HIV infection quickly rising to 50% in some risk-groups? The answer may be that it was not the simple presence of HIV virus in the United States that changed; rather it was the social milieu.

In the late 1960s drug use became far more widespread in the U.S., and the invention of the disposable plastic injection syringe about 1970 made IV drug abuse possible for the first time on a large scale. Also beginning around 1969 (the

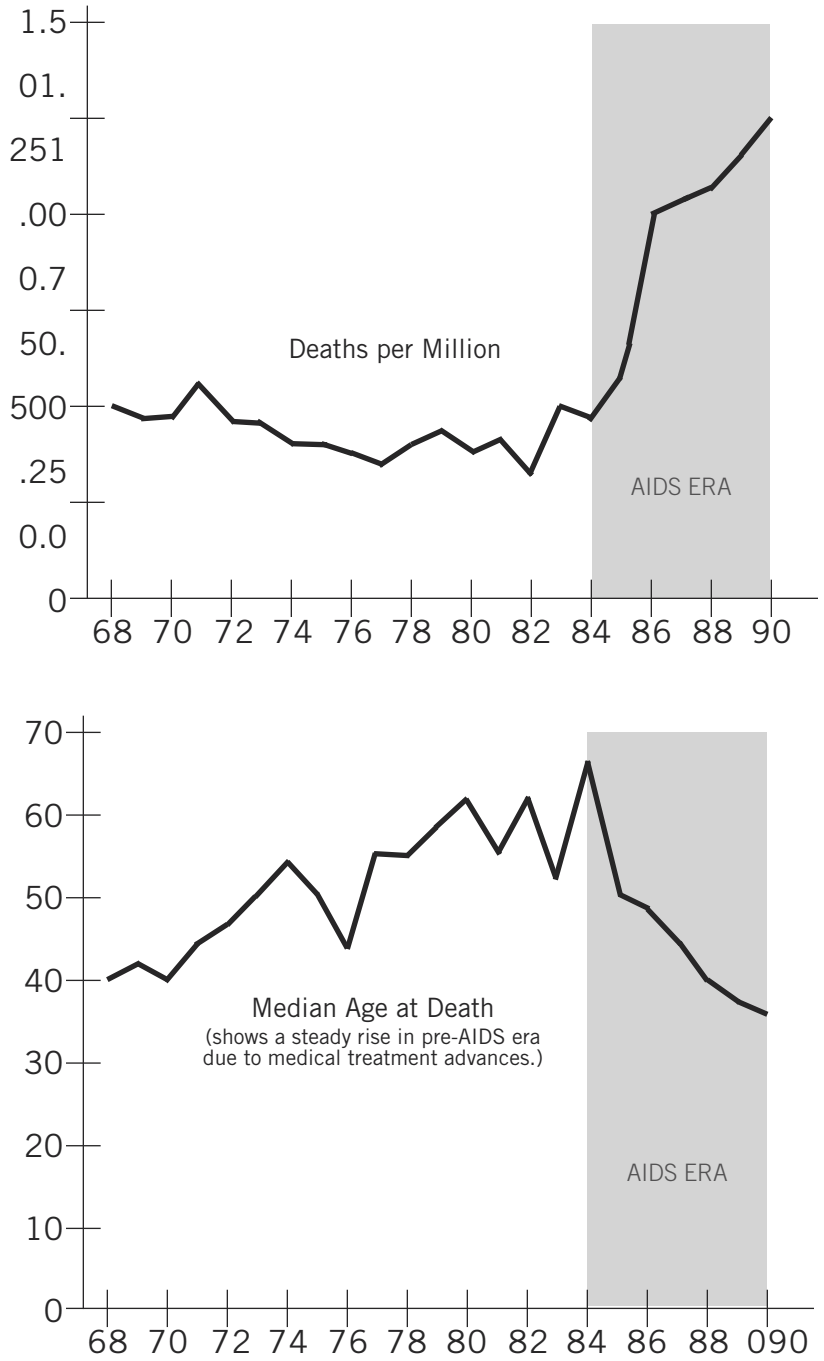


Figure 2, a and b

Hemophilia Mortality Rates Rose, and the Median Age of Death Dropped in the Years After AIDS Became Established—These graphs illustrate that people with hemophilia began to suffer an increasing chance of dying at every age (greater than age nine), starting in 1984, as compared with the era just before AIDS. (Redrawn from *Science.*[22])

date of the New York City "Stonewall" riots), homosexuals in the U.S. began to take open political power, and concomitantly one faction of male homosexuals began to engage in the high-infection risk "bathhouse lifestyle" chronicled by Shilts. In addition, the American homosexual-male community was apparently many times re-infected by many world-traveling disease "vectors" from other countries in the 1970s, including an airline steward named Dugas (described in Shilts as the C.D.C. *"patient zero")* who traveled widely in Europe, Canada, and the U.S., died of AIDS, and is known to have had sex with no less than 40 of the first 248 Americans to be diagnosed with AIDS by April, 1982.[14]

What happened in the late 1970s in the U.S. is that when a large enough fraction of the American homosexual-male population became infected with HIV, the U.S. blood supply, maintained with volunteer donations only, finally became contaminated with the virus. (This started in 1978, as we know from later testing of archived serum samples taken from homosexual men originally for hepatitis B studies). Similar archived samples tell us that in 1978 the U.S. plasma supply used to make clotting factor for hemophilia treatment became HIV contaminated, no doubt primarily by IV drug users selling plasma to support a drug habit. The dates are not coincidental—crossover between initial HIV infected groups occurred as some homosexual men experimented with IV drugs in the late 1970s, and male IV drug users in

large cities turned to homosexual prostitution in order to obtain drugs. The resulting new epidemic of transfusion and hemophilia-associated AIDS, beginning in 1982 and rising sharply in 1984, helped to bring the acquired nature of AIDS into focus.

The small incidence of AIDS in the American homosexual-male and IV drug-user communities before the late 1970s in no way subtracts from the reality of the dramatic increase in AIDS which took place in the early 1980s on the heels of exploding HIV infection rates in these groups. Although relatively mild immune suppression has apparently always been widespread in many AIDS risk groups, the more complete and devastating immune failure characteristic of AIDS itself has been sporadic and rare in young cancer-free people in any of these groups, until the 1980s.

It is, to be sure, difficult to retrospectively evaluate the health of male homosexuals before the first prospective studies of gay men's health were done in the 1980's AIDS era, but we can be reasonably sure that an epidemic of deadly immune failure among young American men before 1980 would have been duly noted by epidemiologists. AIDS skeptic Root-Bernstein documents a few cases of unexplained opportunistic infection deaths from the medical literature before 1980, but clearly an epidemic of immunosuppressive deaths cannot be seen in the historical record before 1980 by any act of imagination.

By contrast, at present AIDS shows a high and rapidly rising incidence among young men and women in the U.S., and these deaths cannot be simply a new label for an old problem. The reason is that *total* mortality and cumulated years of life lost to premature death in young persons are observed to be rising rapidly, with all of the change due to AIDS deaths, *at the same time* other leading categories of mortality remain stable. If mere re-labeling of deaths into different categories was a problem, these "newly recognized" AIDS deaths would come out of other previously defined mortality categories, and this clearly is not happening.[21] AIDS, the disease, may be old; but AIDS, the epidemic, is indeed something new.

People with hemophilia, unlike homosexual men, represent a well-defined group with long-term documentable changes in morbidity and mortality, since they had been well-studied as a group before the era of AIDS. This research shows that people with hemophilia began to die of dramatically different things, starting about 1982 (***Fig 2***).[22] A recent check shows little evidence of a special incidence of opportunistic diseases in people with hemophilia in the U.S. from the turn of the century up to 1979, although a low incidence of AIDS could not be ruled out in this study, mostly because some cases of fatal pneumonia had no identified infecting organism,[23] and because people with hemophilia as a group are immunosuppressed enough to be somewhat more susceptible than normal to bacterial infections. Significantly, however, in the years before AIDS, people with hemophilia had never been noted to be particularly susceptible to the more obvious *fungal* infections, such as candida esophagitis, common to AIDS patients and others with low-lymphocyte type immune deficiency. After 1984, however, this type of AIDS-associated opportunistic infection and immune failure rapidly became the single most common cause of death in people with hemophilia in the U.S.[24]

The rise in total mortality risk in people with hemophilia was sudden: total mortality in this population, which had been stable in 1982 and 1983, suddenly increased by a factor of approximately 900% in the first quarter of 1984.[25] Such an increase in raw numbers of deaths was consistent with an epidemic, or some new very toxic contamination of the clotting factor supply. It is not consistent with slower social changes, slower toxin or immune suppression models, multifactorial causation models, or the idea that people with hemophilia were actually at no greater risk than before (i.e., that again perhaps there had been some kind of "cause of death" re-labeling in response to AIDS hysteria). (***Fig. 2.***) Mortality figures in hemophilia patients also showed something else important, which was that the new deaths of the late 1980s, by virtue of all being judged "AIDS," demonstrated that most or all of them occurred in people with hemophilia who were HIV-positive. Since these deaths accounted more or less for the entire new increase in mortality, it could be inferred that the mortality rate for HIV-negative people with hemophilia did not increase much in the 1980s, if at all.

How significant was the increase in death rate for HIV-positives in this group? In one *Journal of the American Medical Association* study it was found that in a cohort of 111 people with hemophilia infected with HIV in the early 1980s, one third had died by 1992.[26] Imagine any group of this age (a high school class, perhaps) and imagine an overall 33% mortality rate in less than 10 years. Of the estimated 10,000 people with hemophilia to have been infected with HIV in the early 1980s in the United States, a quarter had been reported to the C.D.C. to have died of AIDS by July of 1993.

Such death rates were especially shocking in view of strides in hemophilia treatment which had been made in the years before. Total life expectancy in people with hemophilia had risen as clotting factor treatment became available through the 1970s, until by 1980 it was nearly normal.[23] After 1984, however, life expectancy in this group began a steep decline, and by the early 1990s was at a lower level than at any time since before World War II.[24] In the 1980s, total mortality for hemophilia increased in all age groups above nine years of age, and age at death shifted markedly to lower ages, decreasing from 57 years of age in 1979-1981 to 40 years of age in 1987-1989.[27] (**Fig. 2.**)

About 50% of people with hemophilia in the U.S. had been HIV infected by early 1986, when screening and treatment of the clotting factor concentrate stopped HIV spread.[28] Still, the long latency of the virus (as long as 15 years for 50% progression to AIDS in this group) caused death rates to rise for long after the window of new HIV infection closed.

The fact that there was a massive and silent HIV infection of half of the people with hemophilia in the early 1980s is beyond question, even for skeptics. The AIDS skeptics' quest to divorce this event from the epidemic of deaths by

AIDS in this same group over the next decade has resulted in some remarkable and curious statements about hemophilia mortality. Duesberg, for instance (p. 216) quotes only older statistics for hemophilia patients from the pre-1986 period, before AIDS deaths became very large. His practice of using randomly reported AIDS and mortality data for people with this disease (which is often notoriously unreliable in the best of circumstances[29]), instead of the much more reliable cohort study data, also results in figures which minimize the impact of AIDS. Cohort data shows mortality in hemophilia patients to be far higher than Duesberg acknowledges.[30]

Duesberg has not been alone in ignoring major trends in hemophilia mortality in the last decade. The very misleading statement that people with hemophilia are living "longer than ever" today is one of the standards among the HIV/AIDS skeptic community. Root-Bernstein does no better than Duesberg at providing updated information in this area, offering one paper's 1979 pre-AIDS statistics,[23] without update and without qualification, to represent *contemporary* life expectancy in people with hemophilia in 1993 (p. 247). This represents very sloppy scholarship (something which stands out particularly in Root-Bernstein), but the oversight does allow the author to skip discussion of the pronounced and otherwise awkward peak in life expectancy for hemophilia in the middle 1980s.

Duesberg, though he seems to believe that people with hemophilia have suffered no mortality increases in the age of AIDS, does suggest that people with hemophilia live longer than ever due to recent factor concentrate development, and thus live long enough to die of immunosuppression caused by longer treatments with clotting factor concentrate, instead of from hemophilia (p. 220). Although clotting factor does indeed appear to be mildly immunosuppressive (albeit in a different way than AIDS—CD4+ lymphocyte counts are not affected), the main problem with the hypothesis that clotting factor itself causes AIDS is that two studies of HIV-positive people with hemophilia have found that HIV infection, and not clotting factor use, is the critical risk for AIDS. These studies found that once a person is HIV-positive, risk of AIDS is *not* related to amount of clotting factor used or severity or type of hemophilia—effects that would have been expected if clotting factor carried a significant immune risk independent of its HIV content.[31] Available statistics thus strongly suggest that the known association of clotting factor use and AIDS risk is merely due to the increased risk of being infected with HIV the more clotting factor has been consumed; once HIV infection has occurred, it does not matter how much clotting factor is used.[109]

AIDS in the 80s

Historically, what happened in the U.S. in 1981 was that in increasing numbers homosexual men began coming to physicians with very, very low CD4+ lymphocyte blood counts (but not lowered counts for other subtypes of lymphocytes), a destroyed immune system with lymphatic tissue destruction, opportunistic infections, and Kaposi's sarcoma. No one who had treated diseases in the male homosexual community could remember having seen anything remotely like what had began happening on an increasingly large scale in the early 1980s.

The year 1981 was not (in retrospect) exactly when the problem started, but rather when the problem first grew large enough in the U.S. to be brought to the attention of the federally-run Centers for Disease Control in Atlanta. It was in the Summer of 1981 that alert physicians brought to the attention of the C.D.C. a mini-epidemic of immunodeficiency and pneumonia caused by unusual organisms (a fungus called *Pneumocystis carinii,* and a virus called CMV) in homosexual men in Los Angeles.

Because many of the first people to contract AIDS had had sexual contact with each other, C.D.C. researchers thought they might be looking at an unknown sexually-transmitted infectious disease. They also toyed for a time with the idea that sex-stimulant-chemical use or illicit narcotic use, both very common among the first cases of AIDS, might be somehow causing immunosuppression. Perhaps sexual contact was a red herring—or merely a marker for a small and fairly tight-knit sub-community of people who shared common interests in non-sexual activities which might be damaging their immune systems.

Those physicians treating infectious diseases in homosexual men thought not, however. Dr. Joel Weisman, one of the first doctors to put the AIDS puzzle together, noted that initially, within the male homosexual community, the disease seemed to follow lines of sexual contact more than it did drug or sex habits. Not all homosexual men were so promiscuous as to make contact-tracing impossible; Weisman observed that promiscuous men did not always contract the disease, but on the other hand, that even men with few sexual contacts were coming down with the disease if they had had sexual contact with the wrong person. In fact, men with severe immunodeficiency were eventually found to form sexual contact networks, of the kind that have always been seen by researchers using the classic epidemiologic tools for tracing sexually transmitted disease chains. The difference, however, was that for AIDS the contact networks stretched over years, indicating an infectious agent (if there was one) with a very long latency. Still, investigators found that of the first 19 cases of AIDS reported in Los Angeles, nine had direct or indirect (one intermediate partner) sexual contact with a single French-Canadian airline steward (previously mentioned), a man who was also sick with immunodeficiency.

Then, starting in 1982, reports began to come into the C.D.C. of the same CD4+ lymphocyte and lymphatic-tissue-destroying immune failure syndrome occurring this time in U.S. citizens who had received transfusions. Soon also came reports that an identical immune deficiency of a new severe variety was now being seen in men with hemophilia, a genetic disease in which sufferers must be injected with concentrates of protein clotting factors made from donated blood plasma.

Reports of the first people with hemophilia and AIDS emphasized that, in these people, none of the same drug or male-homosexual behavioral factors were present that had been seen in the first group of AIDS sufferers.[15]

Further, the same was true of those with "transfusion-related AIDS," who also did not fit into drug-using or male-homosexual lifestyles, and did not resemble them in sex or age either. Former tennis star Arthur Ashe is a well-known modern example. Ashe, like many of those with transfusion-related AIDS, had never had an intimate connection with anyone else with an immune problem, *except* for a history of blood transfusions years in the past, during the time in which transfusions were associated with AIDS.

In late 1982 all this worried epidemiologists as the reports continued to come in. They knew that another viral disease called hepatitis B ("serum hepatitis") was also transmitted epidemically as a sexually transmitted disease in homosexual men, but much more rarely in homosexual women or heterosexuals in the U.S. Hepatitis B had historically also shown up early in people with hemophilia, who because of their large pooled blood-product exposure have historically seemed to be first to suffer from any new organism infecting the blood supply. Hepatitis B had also been known to be one of the worst disease-causing contaminants in donated blood for general transfusion. Thus, the same three groups of people who had historically been infected with a new epidemic of hepatitis B in the 1970s, had now started coming down with AIDS. Hepatitis B was also a disease of IV drug users who shared needles, and it was not long before the first reports of IV drug users with AIDS came in.

By 1983, the C.D.C. was sure it had a new infectious disease on its hands, similar in epidemiology to hepatitis B but with a longer latency period. Analysis of the habits of donors of the blood components that went into those people who had later developed AIDS, indicated one thing different about the donors: it was found that blood products AIDS patients had received had more often come from people who themselves were at "high-risk" for AIDS due to promiscuous male homosexual behavior. On the other hand, matched case-controls who had been transfused identically from the same blood bank but had *not* developed AIDS after transfusion, were found to be not nearly as likely to have gotten blood components from anyone in a "high-risk group."

This initial study concluded that there was only a 1% chance that the statistical association of transfusion-associated AIDS with the lifestyle of the blood-donor would be as close as it was found to be, if only chance had determined the lifestyles of the donors of blood to people who later became sick. Such a chance association would have been expected if there was no contamination, and instead there was something about normal transfusion blood itself, or perhaps some other factor unrelated to transfusion, that was causing AIDS in transfusion recipients.[16] The remarkable fact—from which there was no escape—was that AIDS in a transfusion recipient *predicted* the lifestyle of a blood-donor he or she had never met (a donor which generally turned out to be a promiscuous homosexual man who had thought himself to be perfectly healthy). Nothing but an infectious agent could explain a statistical connection between a blood donor's sexual habits, and risk to the person receiving the blood. As for drugs or immune toxins, it was impossible to believe that any chemical toxin could be present in a relatively small amount of blood component coming from a single nominally healthy person, in sufficient quantities to cause total immune failure in the recipient, and do it years after the transfusion.

Eventually, with many cases like Arthur Ashe's on record (but showing up in the early 1980s, earlier than Ashe's did), AIDS looked epidemiologically *very* much like hepatitis B. The hunt was on for the microbe, or microbes, which caused the new syndrome. When the virus now known as HIV finally hit the world news in the Spring of 1984, there was a great deal of skepticism in the scientific and lay communities alike. With the ability to test for antibodies to HIV in 1985, however, there came a way of powerfully sifting through putative causal factors for AIDS, and comparing them with the factor of past HIV infection. HIV infection has emerged from these tests as the clear champion of competing AIDS-causation theories, convincing at present all but the most die-hard skeptics.[14]

Attacks on Straw Men

It is an unfortunate fact that a great deal of the debate over AIDS and HIV has been over what rhetoricians call "straw men." A straw man is an argument or viewpoint set up in a debate only for the purpose of being knocked down, and one which the opposite side never really defended or held; or one which is not very important to the central issue of the debate, even if it *has* been held. Straw man arguments often result from debaters talking "past each other," without understanding the opposing side's position. In the HIV/AIDS debate, straw men set up by heretics have most often been medical hypotheses which have previously been put forth in the context of the HIV theory and which have turned out to be wrong, but which were never important corollaries necessarily deduced from the idea that HIV causes AIDS. Other straw men are ideas that the orthodox scientific "establishment" never put forth seriously at all, though they may be attacked vigorously by heretics as though they are current medical dogma. We will presently see samples of both.

An example of an epidemiologic straw man is the timing of HIV arrival in the Western hemisphere. Root-Bernstein discusses cases of possible AIDS as far back as 1932, notes documented HIV infection with AIDS as far back as 1968 in the U.S., and argues that these data are anomalous (p. 2) if the virus was transferred for the first time to the Western hemisphere around 1978, as was originally thought. And so they are. But if the HIV virus was transferred much earlier than 1978 to the new world, and remained at low levels in male homosexuals and injecting drug users in America until changing social factors in the 1970s encouraged its spread (exactly as Root-Bernstein himself indirectly suggests), no real damage would be done to a suitably modified HIV/AIDS theory.

An example of a bad prediction made by the orthodox medical establishment which is not necessarily derivative of the HIV theory, was (or is) the official idea that AIDS is due to be a heterosexual pandemic in America *any time now.* It is

What Does "HIV-Positive" Mean?

Antibodies are blood proteins made by immune cells, which stick very specifically to microbial invaders, targeting them for destruction by the immune system. For many years after an infection by a microbe, antibodies specific to that microbe can be detected in the blood. A person who tests positive for antibodies to HIV by two different kinds of lab tests, is said to be "HIV-positive."

In the case of infection with the average microbe, a person may test antibody positive for years or even a lifetime after the microbe is completely gone from the body. For the chronic viruses which hide in cell nuclei, however (retroviruses like HIV; and also CMV, EBV, and other herpes-class viruses), the presence of antibody is generally a clue to the continued presence of the virus, active or inactive, somewhere in the body. In some cases modern sensitive tests for viral DNA can actually detect these hidden viruses directly.

Over the years since the discovery of HIV, critics of the HIV/AIDS hypothesis have had to struggle to keep up with sensitivity increases in HIV testing. Initially, critics complained that HIV virus was not present in most HIV-positive people. When it became clear that infectious virus could be found in almost 100% of such people (if cultures were done correctly) critics claimed that most HIV was dormant until reactivated in culture. With new sensitive tests for HIV RNA showing that HIV virus is active in the body's lymph nodes, critics have fallen back to the position that it may be active, but not active *enough.* This is a question which can only be answered indirectly, by other studies. Ellison and Duesberg assert (p. 124) that HIV is rarely to be found budding from cells in patients, and that "...in most individuals with AIDS, no virus particles can be found anywhere in the body," implying that this absolves the virus from any disease role. Actually, however, even actively reproducing HIV may spend very little of its total life-cycle budding through a cell membrane or floating free as a particle in the blood before being picked up by another cell. Studies of viral RNA in the body show that there may be anywhere from roughly 10 million, to as much as one billion particles or actively replicating HIV genomes in a gram of lymph tissue—a significant amount by the standards of most other kinds of virus.[122]

argued by Duesberg (p. 203), that the "viral hypothesis" has failed to predict the course of the AIDS epidemic—namely that AIDS has (at least so far) shown no clear inclination to spread rapidly by a complete heterosexual-sexual-transmission mechanism in the U.S., even though it apparently does so in Africa. It is also asserted in a related argument by Root-Bernstein that the HIV/AIDS hypothesis does not explain the generally-low measured levels of HIV virus in semen, the low (but not zero) rate of HIV infection in mates of HIV-positive men with hemophilia, or the nearly zero rate of infection in U.S. heterosexual prostitutes (unless they are drug users). If AIDS is an infectious disease, ask the skeptics, then why does HIV not infect very well?

All these arguments are against straw men. There is nothing in the HIV/AIDS theory which demands that any particular transmission mechanism be the chief cause of the spread of HIV infection in any given place, or which demands that the HIV virus be as infectious in one locality as another. For example, it now seems likely from many studies that sexual transmission of HIV often requires mucosal tissue trauma, which is much more likely with anal intercourse, and/or a concomitant inflammation or ulcer from a second sexually transmitted disease. Because transmission may be inefficient even so, promiscuity also greatly enhances the chance of HIV spread. These requirement(s) for efficient HIV sexual transfer easily explain the difference between spread of HIV in tropical Africa vs. the developed countries. They also adequately explain why a disease which spreads well sexually only in populations with an extreme level of both promiscuity and rectal mucosal trauma (i.e., one subsegment of American homosexual men) has not yet become a generally spreading sexually-transmitted disease epidemic in the U.S.

It is not that the HIV/AIDS heretics have not come across such explanations. Root-Bernstein, in a good discussion of the epidemiology of AIDS, admits that there is nothing especially strange about a sexually transmitted disease which spreads easily in homosexual males but not heterosexuals in the U.S. Both syphilis and hepatitis B in the 1970s have been examples of such a phenomenon, and the "odd" differential epidemiology of both diseases with regard to sexual-preference groups is easily explained by differential behavior in the homosexual and heterosexual populations in those years.

Duesberg argues that a disease which restricts itself to classes of people in America, but not in Africa, cannot be explained by a micro-organism. But while he is doing so, fellow heretic Root-Bernstein (pp. 281-303) is noting that infectious epidemiology in one group of American homosexual males, who might be sexually infected with giardia, parasites, amoebas, hepatitis A, and B, shigella, salmonella, etc., may resemble far more the disease epidemiology of some African countries than that of heterosexuals living next door (p. 290). In this, an AIDS caused by an infectious agent such as HIV may behave just as AIDS statistics suggest it does, and yet merely follow a pattern already amply demonstrated before AIDS, with many another infectious disease. Root-

Bernstein is sometimes too competent a scholar for his own good. His Chapters 8 and 9—which address the epidemiologic differences and commonalities of U.S. homosexual men and African heterosexuals due to sexual practices and social changes which appeared newly in the 1970s and 1980s—not only believably explains and refutes most of Duesberg's epidemiologic problems with AIDS (p. 209), but also does the same with many of Root-Bernstein's own epidemiological problems, raised in Chapter 1.

Unfortunately, Root-Bernstein is willing to let lifestyle and habit differences explain epidemiologic differences when it suits his argument's needs, but much less willing to consider them when they don't. An illustrative example occurs as Root-Bernstein discusses the rectal traumas and infections which occur during certain male homosexual practices, writing of these (p. 283-4): "It is now accepted that such injuries and infections greatly increase the risk of concurrent infections (HIV or otherwise) and of semen gaining access to the immune system following anal intercourse."

Yet when Root-Bernstein discusses the statistical association of AIDS with receptive anal intercourse (p.225) he shows an odd difficulty with the same concept: "One possibility is that it is much easier to transmit HIV to a receptive partner than from a receptive partner. No other sexually transmitted disease behaves this way, however . . . . HIV would be the first disease agent to be able to make the discrimination, unless some other factor is involved."

Here, unfortunately, Root-Bernstein is wrong, and wrong for the very reasons that he himself discusses in the quote preceding the last. Much like HIV, hepatitis B infection in homosexual men *also* correlates with rectal trauma and receptive anal intercourse,[32] and there is little reason to believe that the "other factor" is anything other than the fairly straightforward mechanical injury that Root-Bernstein has already helpfully identified for us (see reference 33 for statistical development of a "rectal trauma index" which partly predicts risk of HIV infection). It is a characteristic of Root-Bernstein's style of argument that it makes causal mechanisms as mysteriously complicated as possible—very often far more complicated than required to explain the facts.

Root-Bernstein, eager to draw attention to any factor other than HIV in the causation of AIDS, does not take into account the most obvious physical factors: "what is clear from existing studies," he asserts (p. 45), "is that HIV is extremely difficult to transfer to a healthy individual." In fact, existing studies establish no such thing. Studies quoted by Root-Bernstein never demonstrate that only "unhealthy" people in known risk groups contract HIV, only that certain traumatized risk groups (promiscuous gay men, hemophiliacs, transfusion recipients) are *on average* somewhat unhealthy to begin with. This, of course, is not the same thing. Indeed, there is evidence that within risk groups, even the healthiest of individuals (immunologically) are capable of contracting HIV. Although men with hemophilia and homosexual men are on average mildly immunosuppressed even in the absence of HIV, it is by no means true that all are. A study of army recruits (surely a carefully screened group for health) shows that those who seroconvert to HIV (demonstrating new HIV infection) may initially (by the criterion of CD4+ count) have immunity which is in the normal range. This is true in other groups as well.[34]

Perhaps the most bloated straw man assailed by Root-Bernstein (and the one that provides the major theme of his book) is the idea that the causal agent of an infectious disease such as AIDS must be both *necessary* and *sufficient* to cause the disease in every sense of the terms; and moveover that since Dept. of Health and Human Services Secretary Margaret Heckler's dramatic announcement in 1984, most scientists have considered HIV to play this very role for AIDS. Root-Bernstein spends much time attacking what he calls the "HIV-only" theory of AIDS, an idea which actually has never flown, except possibly in the popular press or the occasional scientist who expresses a rash opinion (Dr. Robert Gallo, official co-discoverer of HIV, must by now badly regret his hyperbole about HIV being able to cause AIDS in Clark Kent[35]). The subtitle warning of Root-Bernstein's book is *The Tragic Cost of Premature Consensus,* and it appears from the book that it is upon the "HIV-only" theory of AIDS that the "premature consensus" of the establishment is in dire danger of settling, if it has not already.

Fortunately, it can safely be said that no such thing is occurring in the biomedical consensus, or about to. This does not prevent Root-Bernstein (p. 331) from logically blasting the somewhat cartoonish view he attributes to medical science: "Two of the most important implications of the HIV-only theory of AIDS are that all the risk groups should develop AIDS at approximately the same rate following HIV infection and that the symptoms they manifest should, on the whole, be the same."

Alas for Root-Bernstein, however, since AIDS has from the beginning involved opportunistic infection organisms which vary in prevalence among populations, and since there has been reason to believe from the first that AIDS risk varies greatly with the biological *age* of the HIV-infected person, scientists have never, even at the beginning, seriously considered such a theory as Root-Bernstein here lays out:

> One logical implication is that the immunological status of an infected person should be irrelevant to susceptibility to contagion or to the progression from infection to disease. Acquisition of the retrovirus should be the sole factor determining whether an individual develops AIDS. Everyone should be at equal risk for AIDS, just as everyone is at equal risk for hepatitis B virus, syphilis, or measles.

The most troubling thing about such writing is that an unwary lay reader may leave Root-Bernstein's book with the impression that the author has single-handedly discovered that infectious disease risks depend partly on host immune defenses and host behaviors and environments. The reader might well decide further that the biomedical community today does not in general think in terms of individuals having differing resistances to various diseases, and is accepting such advanced ideas only under duress, due to political pressures resulting from the penetrating logic of popular writers such as Root-Bernstein, who are "re-thinking AIDS."

The facts are more mundane. Obviously, since no microbe infects 100% of people exposed to it, or even causes

disease in 100% of the people it infects (not even HIV has been shown to do this), there must be other factors to explain why some exposed people become ill with ANY infectious agent (viral, bacterial or parasitic), and some do not. Medical science certainly recognizes such factors, but does not use them to argue that there is in general something badly wrong with the germ theory of disease. Instead, as discussed earlier, medical scientists regard "causality" in infectious disease in merely the sense of "necessity" (i.e., the "causal" microbe is necessary, but not sufficient). Medicine has not regarded the pathogenesis of any natural infection in terms of a "germ only" theory such as Root-Bernstein describes, since Pasteur, referring to disease, said: "The seed is nothing, and the soil is everything." Thus, Root-Bernstein spends many chapters assailing an idea that physicians have not held since the late 19th century, and certainly have never generally held in the case of AIDS.

No infectious agent is usually "sufficient" to cause disease in a natural host, although in a laboratory (or perhaps very occasionally in nature) it may be sometimes true that the dose may be so high as to make host resistance almost irrelevant. Naturally-occurring infectious disease organisms at reasonable doses, however, always rely on a chink of some kind in host immunity with regard to that particular microbe (this is not to say that we must consider any host that is successfully infected to be "immunocompromised"—that would cheapen and overly broaden this useful term). The idea that deficiencies in host defense in some sense "permit" all or most infections is indeed a standard medical teaching,[36] although a lay reader of Root-Bernstein might be surprised to learn of it after Root-Bernstein finishes misrepresenting the standard views of modern medicine.

"Why is there such a huge and medically unprecedented variation in time between HIV infection and death from AIDS?" asks Root-Bernstein (p. 89). The answer to this rhetorical question is that such variation is *not* medically unprecedented. Other infectious diseases, from malaria to syphilis to tuberculosis to viral hepatitis, may kill years after initial infection—or within a much shorter time. In a cohort of newly-infected people, any study of a chronic infectious disease cannot help but produce steady increases in the "average" time between infection and death, as deaths accumulate slowly while the study follows the infected cohort prospectively onward in time.

"No theory based solely on HIV can explain the phenomenon of variable times of death," writes Root-Bernstein (p. 89). This is correct so far as it goes, but it says much less than it seems to, for this much is true of every infectious disease known, including other infectious diseases which may have latency times to death fully as long as those for HIV. Too much of Root-Bernstein's *Rethinking AIDS* consists of arguments that the HIV hypothesis needs to be rethought because HIV infection supposedly has strange properties—properties which on close examination turn out to be broadly similar to those of many other infectious diseases. □

PART II

HOW SKEPTICISM WENT ASTRAY

Drugs Don't Cause AIDS—HIV Does

The fact that the first AIDS cases were homosexual men who were heavy illicit drug users engendered a drug-use theory of AIDS which lasted for mainstream investigators only until it became clear that non-drug using recipients of blood products from many walks of life were developing the same immune unique problems. A few skeptics, however, refused to consider the drug theory falsified by the finding of many non-drug using AIDS patients, but instead began to postulate *additional* causes of immune failure for each additional "AIDS" group identified.

This group included Peter Duesberg, who believed that drug use caused AIDS, but postulated additionally that people with hemophilia had began to suffer immune failure in the early 1980s from long time clotting factor use, just at the same time as gay men and IV drug users began to suffer from a similar immune problem—and that the timing was purely coincidental. The fact that HIV infection was proved (by later stored blood sample testing) to have spread silently and largely concurrently though both gay men and people with hemophilia a few years before the AIDS epidemic, was explained as being merely an early warning of impending immune failure in these groups.

The process of multiplying causal theories in order to minimize HIV responsibility for AIDS culminated in the work of Root-Bernstein, which contains an eclectic "multifactorial" view of AIDS which is so formless and complicated as to be epidemiologically unfalsifiable, even in Root-Bernstein's view (p. 92).

At the time of the early drug/toxin theories of AIDS, the leading toxin candidates were the inhaled amyl and butyl nitrite street drugs ("poppers") used heavily and almost universally as sexual-experience enhancers in the 1970s and early 1980s by the same fraction of homosexual men who indulged in high risk, promiscuous sexual practices causing injuries to mucosal tissue, and who also historically were the

first U.S. group to develop AIDS as an "epidemic."[14]

Since this group was the one that suffered the first major impact of AIDS, a number of early studies found high statistical correlations between AIDS risk and nearly everything to do with this group's lifestyle. Later, after the HIV virus was identified, the C.D.C. found that HIV was universally present and active in such men who developed AIDS. Almost as prevalent were a number of other chronic viruses, such as CMV (cytomegalovirus), HZV (Herpes Zoster virus), EBV (Epstein-Barr virus), and HSV-1, 2, and 6 (Herpes Simplex viruses 1, 2, and 6). Many of these chronic viruses were found to be replicating actively in homosexuals with AIDS. This state of "viral re-activation" (a product of immune suppression) was less common in AIDS sufferers from other risk groups, mainly because other groups had not been infected with as many chronic viruses in the first place. Sorting through the drug and infection variables among promiscuous homosexual men with AIDS was a statistical nightmare, although it became easier to separate out important AIDS risks when AIDS in other groups with different lifestyles was considered.

Epidemiologists fought it out in scholarly journals. After the main battle was over, they even tried to decide who had not guessed from the beginning on epidemiologic grounds that the problem might be infectious, even before a specific causal virus was proposed—occasionally lambasting each other's past methods in print with words like "Neanderthal."[37,38] Before HIV was identified, however, the basic problem for epidemiologists was that statistical methods could not by themselves suggest which lifestyles or practices (if any) were causal for AIDS, and which were merely an associative marker for some other causal factor which (perhaps) had not been measured. *After* HIV was identified, however, a second statistical appraisal could be taken using HIV status as a statistical factor, in an attempt to see if HIV had a closer associational (and therefore presumably more likely causal) relationship with AIDS, than other previously identified factors.[39] It did.[40]

"Since no microbe infects 100% of people exposed to it, or even causes disease in 100% of the people it infects (not even HIV has been shown to do this), there must be other factors to explain why some exposed people become ill with ANY infectious agent and some do not."

Much the same thing happened with other viruses, especially when statistics were extended across different risk groups. Infectious HIV was finally found to be present in essentially 100% of AIDS cases in *all* risk groups—a higher proportion than was seen with any other virus.[41] Furthermore, most of the change in HIV infection status had occurred before 1984 in people with hemophilia,[28] long before the worst incidence of immunosuppression and increased death rate in this community, proving that HIV positivity was not derivative of *severe* immunosuppression, since it preceded it. As judged by CD4+ lymphocyte counts in people who were followed over time, most of the loss of immune function in *individual* HIV-positive people with hemophilia, came *after* HIV infection, as well.[42]

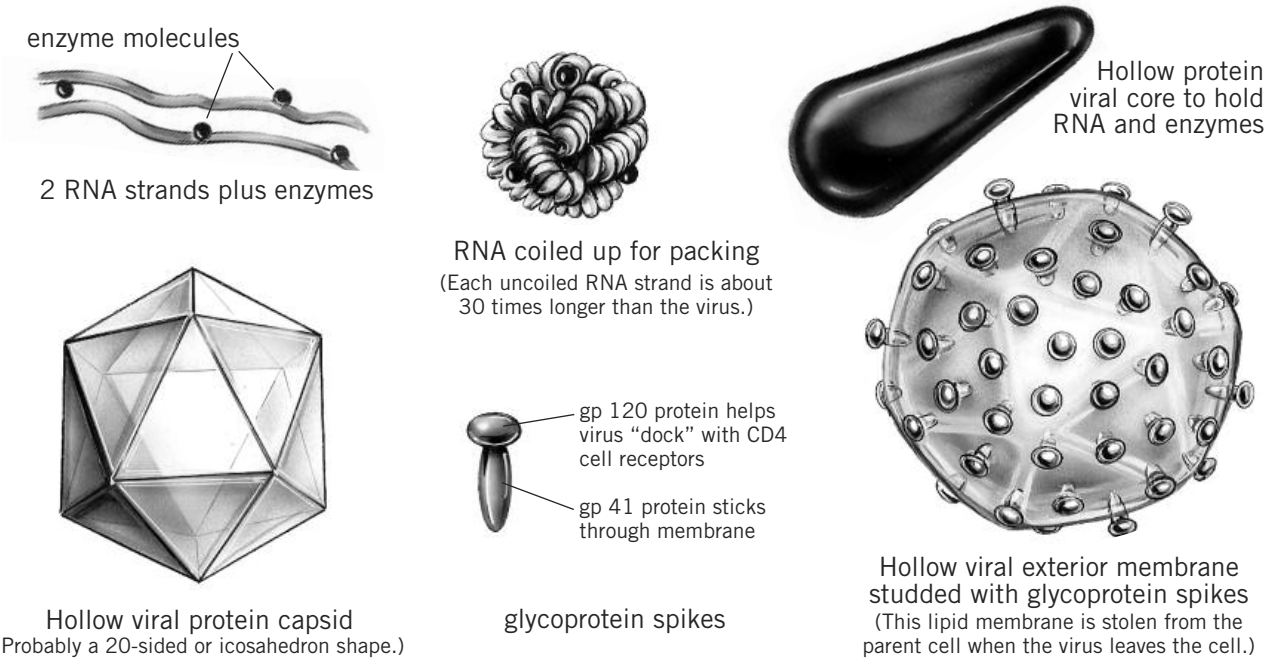
Finally, it was found in several studies that while HIV-negative homosexual males might be mildly immunosuppressed, their immune function was never seen to drop more than transiently as low as AIDS-class immunosuppression (immune failure), as defined by CD4+ lymphocyte counts below 200. Moreover, when followed over time, HIV-negative homosexual men did not become *more* immunosuppressed, but HIV-positive ones did. In prospective studies when men were followed by blood tests as they actually contracted HIV, this same slow and steady decay in immune status happened to the newly infected group after contracting HIV infection, starting immediately after infection. HIV, when contracted by men being followed in studies, was generally contracted during a time when immune status (CD4+ lymphocyte count) was reasonably good.[43] Men who were severely immunosuppressed with no other explanation (such as cancer), invariably had become HIV positive already, or in other words, had become HIV-positive *first*.[44] Such tight correlations between timing of immune failure and time of infection do not hold for any other known viral infection in immunosuppressed people. This is strong evidence that HIV is at least a primary causal agent of AIDS.

Lifestyle factors such as non-injected drug use and exposure to blood products (as in transfusions or hemophilia treatments) did correlate with risk of developing AIDS, but this association could be completely explained in the statistics by the fact that these behaviors (including even perhaps nitrite "popper" use[45]). also increased risk of contracting HIV. To discover which was most important to risk, HIV or drug use, epidemiologists statistically "controlled" for HIV status (i.e., compared people with each other only within HIV status groups), attempting to discover if drug use or blood product exposure was important to AIDS risk *after* the HIV virus was contracted, or independently of it. The answer, it turned out, was generally no. By and large (with two qualifications to be noted below), drug use and promiscuity were not independent variables after HIV infection was taken into account.[46-52]

Illicit drugs do not cause AIDS, with the qualification that injection of drugs has been implicated as an independent cofactor. In the end, the "drug-only" hypothesis of AIDS pathogenesis fails all careful epidemiologic scrutiny. Even among IV drug users, although short term overdose deaths tend to swamp any necessarily long-term consequences of HIV infection,[53] studies have generally shown that HIV infection is an additional mortality risk factor for IV drug users.[54-56]

Injected or IV drug use, of course, proved an excellent way to *contract* HIV, if needles were shared. There was no evidence, however, that injected drugs themselves ever led to severe AIDS-type immunosuppression in the absence of HIV. There was some evidence that IV narcotic use could be quite immunosuppressive (leading at least in part to fatal

How to Build an HIV (or FIV or SIV) Virus



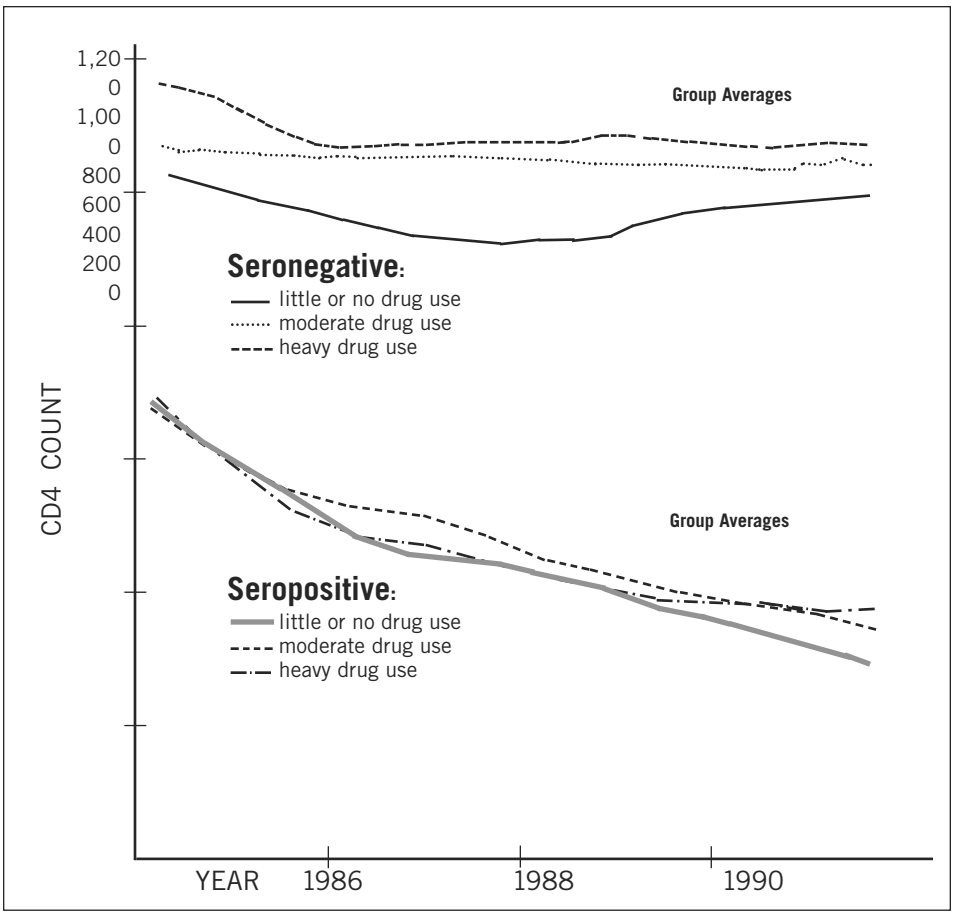
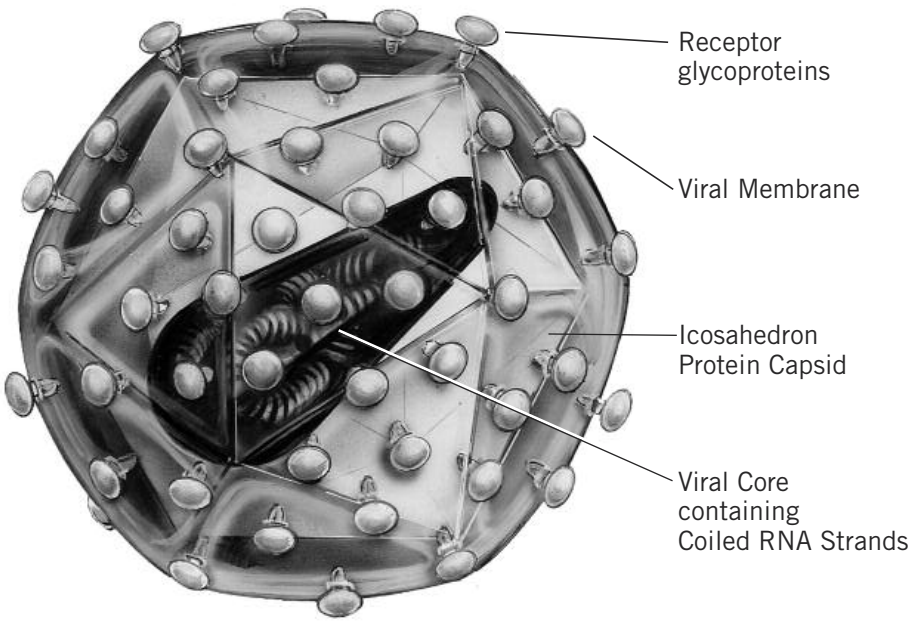


Figure 3:

Drugs Don't Cause AIDS—HIV Does

When HIV-positive and HIV-negative men are each divided into three groups according to intensity of drug use (total of six groups) and the men are then followed for a number of years, it is apparent that the decay in average CD4+ counts for groups, indicating immune status decline over time, is associated with HIV status, not drug use. These trends are well established before AZT became available in 1987, and thus are not due to AZT being given to HIV-positive men. Redrawn from *Nature*.[40]

The Complete HIV Virus



infections), and a co-factor for rapid AIDS development in people HIV-positive. Some studies found that continued IV injection of heroin, but not use of other drugs, hastened progression to AIDS in HIV-positive people,[57] but other studies have suggested that heroin does not decrease CD4+ counts as AIDS does, so the immunosuppression of heroin users may not be due to the drug itself.[22] One study[58] suggested that HIV-positive IV drug users who switch to methadone (an oral heroin substitute) may have slower progression to AIDS, but there was no mortality difference between using methadone and quitting narcotics completely, so IV injection per se, rather than narcotic use, is possibly the offending practice. Studies of IV drug users who continued IV drug might be implicating not drugs themselves in the rapid production of AIDS, but rather simply continued needle-sharing leading to acquisition of more virulent strains of HIV. The same was possibly true of extreme promiscuity, which also continued to be a risk factor after HIV-infection, in one study.[59] Acquisition of CMV was also a possible consequence of risky behavior, although the role of this virus as cofactor in AIDS is limited at best.[60]

The Skeptics Go Too Far

The above results have not convinced those who champion the drug hypothesis as the cause of much of AIDS. Duesberg, for example, accepts a causal role for drugs in AIDS on much the same grounds which he rejects for assigning a causal role to HIV—namely, epidemiological correlations and suggestive lab experiments. The irony of this position is that the correlations are not nearly as good statistically for drug use and AIDS as they are for HIV infection and AIDS, and the lab experiments with drugs are not as impressive either. Duesberg's standards of evidence change greatly with the hypothesis he likes, and he has even accused a group of scientists of data fabrication[61] after a paper in *Nature* reported findings not in line with his drug hypothesis.[40] Duesberg's letter was refused print by *Nature's* editor, with an accompanying editorial.[62] An independent institutional review board cleared the researchers of Duesberg's charges, which have been answered in print by the authors.[63]

In the study printed in *Nature,* the authors had found in the San Francisco cohort men no connection between the four most commonly reported kinds of illicit drug use and later progression to AIDS, after results were controlled for HIV status (i.e., heavy drug users had the same likelihood to progress to AIDS as light users, if HIV-positive, but HIV-negative men did not progress toward immune failure, no matter what their drug use). (***Fig 3.***) Moreover, these results held also for the 1985-1986 period before the drug AZT (the use of which Duesberg has suggested may cause AIDS to develop in HIV-positive people) was available.

Duesberg's objection was that the study had not controlled carefully enough for drug use between HIV-positive and HIV-negative groups. But Duesberg did not address the obvious question of why such considerable controlling for drug use as *was* done, had absolutely no effect on differential AIDS risk seen. Duesberg also complained after seeing the raw data that supposedly "AIDS-defining" diseases in the HIV-negative group had not been counted as "AIDS," despite the author's denial that this had happened. Here apparently much depends on a disagreement between Duesberg and others as to what constitutes clinical AIDS. A recent article in *Science* suggests that one difficulty is over the question of whether mild opportunistic conditions such as oral candida (thrush) constitute clinical "AIDS." Duesberg, ever ready to define AIDS broadly, argues they should.[22] In any case, the specifics of Duesberg's reanalysis of the *Nature* paper have never been printed, and death rates in this study again underscore the fact that Duesberg's broadly defined "AIDS" which strikes HIV-negative people, somehow does not kill nearly as well as the standard variety.

As for worsening immune failure in groups over time (seen as declining CD4+ counts in the HIV-positive men, independent of drug use, but not in HIV-negative men, no

AZT: Panacea, Plague, or Perfectly Pedestrian Pharmaceutical?[110]

Most new drugs go through three phases of introduction, in which they first appear too-good-to-be-true, then (as side effects are seen), as possible mistakes, then finally (as doctors learn to use them) join the ranks of ordinary mixed-blessing pharmaceuticals. But few drugs in history have been at first hailed, then vilified, to the extent of today's ordinary antiviral drug AZT.

AZT was first synthesized in the 1960s as a possible chemotherapeutic agent for cancer, but it proved too toxic to normal cells at doses that interfered with cancer. However, it proved less toxic at smaller doses which still inhibited HIV. The initial 1986 placebo-controlled trial of AZT in AIDS patients was so dramatic that the independent ethical monitors of the study stopped the trial early so that AZT could be given to all the participants. The study was halted when 19 people had died in the group of AIDS patients receiving placebo, but only one patient had died in the equal-sized group receiving AZT.[111] A second study of AZT vs. placebo in Europe also showed that AZT delayed progression of HIV-positives to AIDS.[112]

AZT was not benign, however. In the initial trial the 1500 milligram daily dose, three times what later became standard, was enough to cause some patients to require transfusions due to AZT's toxicity to their blood-forming bone marrow. The drug also caused side effects in the GI system and muscles. A number of placebo-controlled trials at lower doses showed that AZT did indeed delay the onset of AIDS and lengthened survival when given to immunosuppressed HIV infected men (male homosexuals and hemophiliacs[113]), although the earlier the drug was given in the course of the HIV disease, the more the toxicity of the drug counterbalanced any symptoms of immunodeficiency that were delayed.[114]

In the end, AZT alone turned out to represent a few extra months of life to the average AIDS patient, nothing more. Nor did early use of the drug before AIDS appeared seem to offer clear survival benefits over waiting until later stages of HIV disease.[115] Eventually it became clear that the reason for this was that the fast-mutating HIV virus was capable of evolving enough under the pressure of toxicity to escape the effect of AZT after approximately six months of treatment.[116] Because of this, many physicians began to suspect that these six months of viral suppression were probably best left until late in the course of the disease, when the virus was causing the most damage, since AZT itself could damage quality of life in HIV-infected people who still had good immune function and were feeling well.[117]

This suspicion was confirmed by the Concorde Trial, the largest trial of AZT ever done and one which had more patients and statistical power than all the other trials combined. When Concorde examined the benefits of AZT started quite early in the course of HIV infection, as opposed to waiting for AIDS or severe immune problems before starting AZT, there was a disturbing trend toward greater mortality on early AZT than deferred AZT. Some of the excess AZT group deaths, however, came from auto accidents, and it wasn't clear if these should be counted; AZT is accused of modulating immune problems, after all, not causing traffic accidents. However, with the study showing an 85% chance that the drug had done more harm than good when started earlier vs. later in HIV disease, it was finally apparent to most physicians that AZT was at best a short term drug, and a drug to be used later rather than earlier in HIV disease, at least when used alone.[118]

Critics had thus scored a point in suggesting long ago that immense political and economic pressures had introduced AZT too early into clinically well people, a group for whom overall benefit was never well documented, and who in fact (as now appears) were being very expensively treated without being helped. The Concorde trial, however, proved also a blow to the severest critics of AZT, since it made clear once and for all that AZT at the proper doses was not a very toxic drug, and certainly was not a major AIDS-producing drug.

Nevertheless, to this day many HIV/AIDS skeptics blame AZT, not HIV, for causing many HIV-positive people to develop AIDS.[119] Most famously, Duesberg has blamed AZT and related antiviral drugs for the AIDS of clean-living tennis star Arthur Ashe, who probably contracted HIV from blood transfusions in 1979 or 1983; and also for the AIDS of Kimberly Bergalis, a non-drug using Florida college student who contracted HIV by means still not clear (perhaps from her dentist). What Duesberg and other critics do not acknowledge in their carefully censored accounts of the illness of these AIDS celebrities (see Ellison and Duesberg pp. 217, 222) is that both Ashe and Bergalis clearly had badly compromised immune systems and clinical AIDS before being tested for HIV, or being given AZT. Before diagnosis, Ashe first became ill with toxoplasmosis of the brain, a disease never seen in men without severe immunosuppression. Ms. Bergalis developed Pneumocystis carinii pneumonia and a CD4+ count of 41, giving her AIDS by both classic and modern criteria, before being tested for HIV or given AZT.[4] Ashe survived more than 3 years and Bergalis 2 years after their first opportunistic infection and HIV diagnosis—in both cases considerably longer than the comparable figure (less than a year) for AIDS patients before AZT became available in 1987. There is no evidence that standard AIDS treatment shortened the life of either Ashe or Bergalis.

matter how much drug use), Ellison and Duesberg have noted that this phenomenon is not so clear before the data is reduced to averages. This, however, seems a strange complaint (making group trends clear is *why* scientists calculate group averages).

The bottom line is that, for now, the drug hypothesis of AIDS has no epidemiologic associational evidence behind it which is independent of HIV infection. HIV infection, by contrast, is heavily associated with AIDS risk, independent of drug use.

It's Not Only a Virus, It's the HIV Virus

Because Duesberg does not regard any virus as being capable of causing a fatal disease long after the body has generated an antibody immune response to the microbe, he rejects a causal role for any virus in AIDS. The evidence for multiple viral infections in many of the early victims of AIDS, however, has caused many such "non-HIV virus" theories to be generated and tested. For example, though Root-Bernstein does not regard HIV as always a bystander virus in AIDS, he does regard other viruses in AIDS to be just as important as HIV. Are the other viruses (CMV, EBV, Herpes, etc.), or at least their antibodies, present as often in AIDS as those of HIV?

Here statistics help. According to Root-Bernstein, evidences of replication of the viruses CMV and EBV "are just as frequent concomitants of AIDS as is HIV replication" (p. 260). Unfortunately, Root-Bernstein fails to note that this is true only in homosexual men with AIDS (where co-infection with EBV and CMV along with HIV is nearly universal). In science, situations in which several possible causes are all nearly 100% associated with a particular effect do not help us to differentiate causality, a point that Root-Bernstein makes (pp. 279-280) without taking the next logical step. What are needed with viral studies and AIDS, obviously, are AIDS groups where some of the putative viral causes are present less frequently than 100% of the time. Such groups are available. In both hemophilia and transfusion-associated AIDS, HIV infection is universal, whereas infection and reactivation with other viruses, such as CMV and EBV, is variable.[64] In short, some people with AIDS in these groups have never been infected with CMV or EBV viruses at all in the past—but all have been infected with HIV.[65, 66]

It is necessary for heretics to come to grips with the crucial point (hard to explain if HIV has no causal role in AIDS) that the utility of HIV antibody screening is *exactly* that a positive HIV screen, found in only 0.3% of the population, is predictive of risk for development of severe immunodeficiency, i.e., 50% risk of developing severe, life-threatening immunodeficiency within less than 15 years. By contrast, EBV and CMV viral immunity and antibodies are acquired by most (well over 50%) of any normal, healthy population of humans during a lifetime, and thus are not predictive of future severe immunodeficiency and death. Like many other factors, the association of viral antibodies with AIDS across risk groups disappeared when people were compared within groups—except for HIV, where the association persists. As any life or medical insurance company knows, HIV infection status is more surely predictive of future death due to future severe immune failure than any other known piece of medical information related to viral infection.

Historically HIV was implicated as the most probable causal agent in AIDS by a similar statistical process. The standard method of trying to identify a new virus in a new disease suspected of being caused by a new virus is to attempt to culture a new virus from an infected person, then show that antibodies to this virus are present in all people with the disease, but less often in people who are not ill. It is also helpful to show that persons develop antibodies to the virus during the acute illness.

Sometimes viruses can be very difficult to culture in lab glassware. This is especially true of viruses which grow in human T-cells—cells which could not be grown well without certain growth factors only discovered in the 1970s. In 1980, Robert Gallo of the NIH formally reported isolating a virus he named "Human T-cell Leukemia Virus," (HTLV) which infected T-cells and which was thought to cause some cases of T-cell leukemia in humans. This virus was a retrovirus and it was a distant relative of the "Feline Leukemia Virus" (FeLV) which caused leukemia in housecats.

Because the transfusion results had shown that AIDS could be infectious, and because AIDS patients had abnormal-looking T-cells which looked something like those from retrovirus-infected animals, or T-cells in cultures infected with retroviruses, early AIDS researchers began hunting a T-cell retrovirus. In early 1983, a team of French scientists led by Luc Montagnier isolated a new retrovirus which they reported in May of that year, calling it eventually Lymphadenopathy-Associated Virus (LAV), because it had been isolated from tissues of a French patient with enlarged lymph tissues, or "lymphadenopathy" (this man died of AIDS in 1988). The French had been alerted to the possibility of a retrovirus in AIDS patients by the American team, led by Gallo, which was convinced that the AIDS virus was another variety of HTLV. It was not.

The new virus discovered by the French was a tiny, spheroidal, membrane-coated, protein-studded virus 1/100th the diameter of a lymphocyte, with an inner protein viral core shaped like a truncated cone, with a dense base. Under the electron microscope it did not look like the feline FeLV or the human HTLV leukemia viruses (***Fig 4***), which had no distinct cores. Eventually, the LAV virus was correctly understood that summer by the French team not to be a leukemia virus as they had thought, but rather to be the first human "lentivirus." This hypothesis was first formulated when Montagnier, at a suggestion from a colleague, began reading about "lentiviruses" or "slow viruses"—a class of animal retroviruses of which he was previously unaware. In one book was an electron micrograph of the "equine infectious anemia virus," a virus which sometimes produced a familiar-sounding immunodeficiency and lymphadenopathy disease, after long latencies, in horses. Montagnier found himself looking at a tiny membrane-coated virus shaped like a sphere,

Montagnier, Gallo, Slip-Ups and Wrong Paths

In the first weeks after the first AIDS cases were reported in 1981, the brilliant Don Francis of the C.D.C. (played by actor Matthew Modine in the TV-movie version of Shilts' *And the Band Played On*), a scientist who had spent years working with the FeLV virus, hypothesized that AIDS was "feline leukemia in people."[14] This was an inspired guess, but as it turned out, not quite correct (FIV, the actual cat analogue of HIV, would be discovered only in 1986). Sometime later Bob Gallo of the NIH (Alan Alda) would at Francis' suggestion make essentially the same assumption, thinking that AIDS was caused by a human leukemia retrovirus in the family that he himself had discovered. He would prove wrong.

The French researcher Luc Montagnier isolated the correct virus in early 1983 from a French patient who later died of AIDS. However it was not until Gallo's lab cultures were contaminated with one of Montagnier's generously provided virus strains, which was then mistakenly identified as coming from an American AIDS patient, that the Americans were ready to also announce in 1984 that this virus (Montagnier's virus) was the AIDS virus.[67] Incredibly, the French-provided virus was also "re-isolated" after a similar lab contamination in England, as well. These fortuitous lab incidents, which tended to rob the French of sole credit and sole patent rights, were later proven by genetic fingerprinting of viruses; but government hearings failed to convict Gallo or anyone else of any misconduct. Meanwhile, however, Americans had shared formal credit in 1987 with the French for the discovery of what became known as HIV, and by international agreement shared royalties for the HIV antibody test as well. The Americans and Gallo have since made far more money at this than the French, and thus, particularly in the eyes of HIV/AIDS skeptics who see a capitalist conspiracy in AIDS, have emerged as the clear villains of the tale.

containing a protein viral core in the shape of a narrow cone.[67] Antibodies against the horse virus cross-reacted with Montagnier's new virus, but not with Gallo's HTLV.

Most importantly, coded AIDS patient serum provided by the C.D.C. contained antibodies to LAV, but not HTLV-III, and Montagnier proved his lab could easily pick out AIDS samples from normal samples in the C.D.C. material, without knowing the codes. Thus, Montagnier had the answer, but nobody would believe him for almost a year.

Cold Sores and Slow Diseases

Most readers will remember that viruses in some sense are not complete living organisms. Animal viruses when outside cells do not metabolize, and cannot reproduce or grow by themselves. Instead, most viruses are little more than tiny floating packages of genetic material, sometimes without much other equipment. Viruses can reproduce themselves only by entering a living cell and commandeering the cell's synthetic machinery to subvert it into making more virus particles, which are then, in turn, released to infect more cells.

A metaphor for a virus would be a truck-load of blueprints which rolls into a completely automated factory, and once there, is somehow able to use the blueprints to control the factory's machinery to cause it to make more sets of blueprints and more trucks to carry them, all of which are then assembled and sent out to take over more factories.

Members of one class of viruses use RNA as their genetic material, and are called "retroviruses," because their synthesis of DNA from RNA proceeds retrograde, in the opposite direction to what is "normal" in the rest of biology. Retroviruses avoid the body's immune system by inserting themselves into the DNA of the host cell.

The virus which produces "cold sores" on the mouth and lips (a type of herpes simplex virus) is a familiar example of the virus which uses the trick of getting into the nucleus near the DNA, and which the immune system, despite all efforts, sometimes can never get rid of. Many people who are afflicted with a cold sore propensity are afflicted for life because there is no known way to remove herpes virus DNA chromosomes from association with the DNA of nerve cells, with which it is sequestered. Each outbreak of cold sores represents an event in which "sleeping" herpes DNA, hiding in nerve cells near the base of the brain, re-activates and directs the cell's biochemical machinery to now produce more virus DNA. The newly-made virus DNA then uses the nerve cell's inner transportation machinery like a subway train to move down through a long branch of the cell to the mouth, where it breaks free of the cell to infect and destroy skin cells to form a blister. Such outbreaks may occur sporadically for life. Each time the normal immune system stops an outbreak, the virus simply goes back into hiding inside the nerve cells.

Most retroviruses cause no major disease, but not all are harmless. A sub-class of retroviruses, called "lentiviruses" is capable of slow infections resulting in death. Lentiviruses typically spend lengthy waiting periods in hiding in the cell nucleus (music lovers will recognize the same root as in *lento,* meaning "slow"), and lentiviruses may never cause overt disease in their natural hosts. Sometimes, however, the lentivirus disease produced after a latency period can be devastating, though sometimes difficult to detect epidemiologically due to the delay between initial infection and death.

Lentiviruses were named in 1954 in honor of several very slow-acting brain infections of farm animals. The classic

example was a sheep disease with a latency as long as a decade, called "visna" (an Icelandic word for "shivering"). Visna wiped out most of the sheep population of Iceland in 1939 because it had not been realized in 1933 that apparently-well sheep brought to the island from Germany had actually been carrying a latent disease. The ability of visna to cause disease many years after infection has since been demonstrated in a series of controlled experiments with sheep.[68] The visna agent proved eventually to be a retrovirus and a lentivirus, and the ominous pattern of the visna epidemic will become familiar to the reader during the course of this essay, as we discuss other better-known viruses in this unique class. HIV, our main subject, is a lentivirus. It is clearly related to the visna sheep lentivirus in structure and genetics, and even more closely to "equine infectious anemia virus" and several other immunosuppressive lymphocyte-infecting (lymphotropic) animal lentiviruses we will now introduce.

As further support for the HIV-AIDS connection, we will examine two very similar animal lentiviruses called FIV and SIV, and will note something of their effects in different animal hosts.[69-71] The details about these two virus/host systems are given because all are crucial to a pattern which will be apparent by the end of our survey. The two viruses we are about to describe were actually discovered several years *after* HIV, but it is more illuminating to tell about them first, for nature seldom provides her good clues in proper order.

The reader should again bear in mind that our modern idea of the cause of AIDS is based on induction and inference, and inference depends on recognition of common *patterns.* Some of the crucial information for one of these patterns follows. By the end of the discussion, the reader should have some idea for why the "odd" effects of HIV in humans are no longer a surprise or shock to most scientists who study the matter. They have seen it all by now in animals, under controlled conditions, and realize that the way HIV works is much the way other viruses in its family work.

"The reader should again bear in mind that our modern idea of the cause of AIDS is based on induction and inference, and inference depends on recognition of common *patterns.*"

Cat AIDS

The feline immunodeficiency virus (FIV) is a lentivirus discovered in Petaluma, California, in 1986, where it was first obtained from the blood of two domestic cats living in a household in which there had been a number of deaths of cats from a strange immune deficiency disorder. The virus was isolated from the housecats by experimentally infecting special disease-free laboratory cats with their blood, then isolating the resulting infectious virus in tissue culture. The FIV microbe, once characterized, has since been identified in many species of cats around the world.

The FIV virus is a tiny ball of lipid and protein four millionths of an inch in diameter, which is less than the span of 1000 hydrogen atoms laid next to each other in a line. An FIV virus particle is thus 1/10th the length of a small bacterium, or 1/100th the diameter of a white blood cell. The electron microscope shows the virus to be composed of a roughly spherical coat of phospholipids stolen from the host cell membrane when the newly made virus particle leaves or "buds" from the cell. This outer membrane is studded with protein molecule spikes, a bit like cloves stuck in a Christmas orange. The membrane closely covers a protein shell which is a sphere or icosahedron (20-sided object made of triangles). The shell, in turn, contains within it a protein lozenge (called the viral core) in the shape of a blunt or "truncated" cone—a cone which has a base which shows up noticeably darker (denser) in the electron microscope views. The final result is a complicated structure not seen in any other virus class but the lentiviruses (***Fig. 4***).

Inside the hollow protein cone which makes up the core of FIV are packaged two identical (or close to identical) coiled strands of viral genomic RNA, each containing nine genes. Also present along with the RNA in the FIV viral core are molecules of a particular variety of reverse transcriptase enzyme peculiar to several previously known lentiviruses, including HIV. This reverse transcriptase functions best with a particular concentration of magnesium ion, and does not work (as this enzyme from other retroviruses sometimes does) with ions of the chemically somewhat similar mineral manganese.

The RNA molecule genome of FIV is organized very closely along the lines of several other lentiviruses and is clearly related to them, with most genes and proteins having identifiable analogues from one strain of lentivirus to another. FIV, however, infects only the cat family. It causes disease in domestic cats but apparently infects lions without causing disease. Not surprisingly, once FIV infects a cat, a DNA virus copy finds its way into the cat DNA, and stays with the animal for life.[72]

It is what happens to FIV-infected domestic cats, however, that makes the FIV virus most interesting. Late in life, apparently many years after being first infected, some FIV-infected cats come down with an immune deficiency syndrome. Older cats infected with the virus are most severely affected. The presence in the cats' blood of antibody is not protective against late disease, since the presence of FIV antibody made no difference in later development of severe symptoms and death in older cats. Indeed, even with antibody present, the immune system of infected cats was found to be declining in a peculiar way—CD4+ lymphocytes were disappearing while CD8+ lymphocytes were relatively unaffected.[72]

The lymphocytes of cats also happened to be the cell preferentially infected by the FIV virus in cell culture. FIV virus infection sometimes killed cells in culture and sometimes not, depending on the strain of the virus and the type of cat cell. In FIV-infected cats, immune systems began to malfunction (sometimes years after infection) as CD4+ lymphocytes numbers declined. As scientists followed naturally-

infected older cats, they saw some cats begin to waste away and develop lymphadenopathy (swollen, enlarged lymphatic organs or "nodes"—the filtering structures which hold immune cells and trap invading microorganisms). Infected cats also developed fevers, diarrhea, and chronic neurological dysfunction—the last a result of direct brain infection by the FIV virus. Finally, after a year or two of being ill, the unfortunate cats usually died of opportunistic feline infections.[73]

Naturally, scientists wished to prove once and for all that FIV was the entire cause of the disease syndrome which they were seeing in FIV-infected cats, now informally dubbed "feline AIDS." With experimental cats in the laboratory setting, experimenters were able to do what could not be done in humans, which was to cause deliberate infections in an animal with a lentivirus. FIV experiments with cats have taught us much, and allowed us to infer still more.

When young cats were infected with FIV by injection in the laboratory, they suffered lymphadenopathy, coat and skin problems, and lethargy. They also developed very slow and progressive and specific loss of CD4+ lymphocytes and a decline in immune response over a period of years. The FIV virus was also active in the brains of deliberately infected cats, and they suffered various abnormalities in neurological function.[74] Older cats were most affected, just as with HIV in humans.[75] Cats experimentally infected with FIV were observed to sometimes enter a carrier phase after infection, but this might progress to lymphadenopathy, wasting, and death as long as three years after infection. It did not happen in uninfected control cats. Experimentally infected specific-pathogen-free lab cats often developed lymphomas. "Random-source" domestic cats, exposed to and carrying many more normally-present "cat germs" from the outside world, not surprisingly, were more likely to develop immunodeficiency and AIDS-like opportunistic cat infections when brought to the lab and given FIV.[71,76] Domestic cats infected with FIV are known to develop candidiasis and cryptococcosis, rare cat microbial infections also seen in human AIDS. Toxoplasmosis, a common cat parasite usually benign in both cats and people with good immune systems, was another organism deadly in both human and feline retrovirally acquired immune deficiency.

In all FIV-infected cats, destruction of lymphatic tissues in a manner similar to that seen in AIDS patients (but no other human infectious disease) was found, with FIV virus growing actively in the lymphatic tissues.[76] What was really needed for further study, however, was an animal even more closely related to man, which could be infected with a similar immunosuppressive lentivirus.

Monkey AIDS

The needed non-human animal model of AIDS arrived by chance a decade before it could be recognized or put to use. In 1976, a colony of stump-tailed macaque monkeys at the California Regional Primate Research Center in Davis developed a disease epidemic—an infectious syndrome of immunosuppression, lymphocyte loss, lymphadenopathy, wasting, and death. Scientists at that time had no idea what kind of infection was killing the monkeys, but they did preserve some of the obviously diseased lymphatic tissue of one dead monkey in 1977. Many years later, in the mid 1980s, they isolated from this frozen tissue a virus which was by then familiar in both structure and function. In 1977, however, nobody recognized simian AIDS.[77]

Macaque monkeys infected with the new agent developed a peculiar and severe immunodeficiency, and sometimes they developed it after unprecedented delays, causing mistakes to be made in assuming that monkeys were recovered and well, when they were in fact chronically infected and doomed. At the primate colony at the Yerkes Primate Center in Atlanta, which had previously been "closed" to contact with other lab primate colonies since 1964, four apparently healthy stump-tailed macaques were introduced from the apparently "clean" California Regional Primate Research Center in 1981.[78] In retrospect this was to prove as much a disaster as the visna-infected sheep which passed the quarantine in Iceland. The California Primate Center colony was not discovered to be still infested with its old 1970's immunodeficiency plague until 1986, when the plague broke out in California again. At that time, newly available antibody survey tests showed that two of the animals previously transferred to the Yerkes colony in 1981 were indeed infected with the latent retrovirus, but (in 1986) were still without symptoms after five years in their new home.

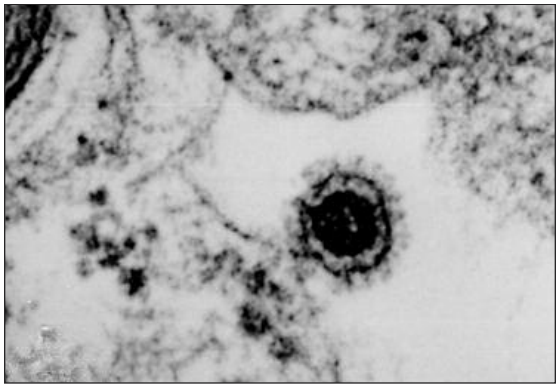
It was not until 1988 that much of the Yerkes colony, still "closed" to other contact with other lab primates, began to die of an immunodeficiency syndrome, with loss of half of the animals in the colony over the next year. Many of the Yerkes macaques, including the two infected transferred animals, began to develop immunodeficiency more than seven years after first being exposed to the infectious agent from the other colony, and their disease syndrome consisted of opportunistic infections, lymphadenopathy, and selective loss of CD4+ lymphocytes. Scientists found that all the dead adult animals (including the transferred monkeys) had antibody in their blood to the newly identified viral agent, so again, antibodies had not conferred immunity to the immunodeficiency disease.

The agent responsible for the Yerkes disaster was by this time known to be a lentivirus, a virus that has since become known as Simian Immunodeficiency Virus, or SIV. Eventually, a number of different SIV strains were isolated from both captive and wild African monkeys, each with its own story of detection, and sometimes also disaster in an expensive commercial colony.[79]

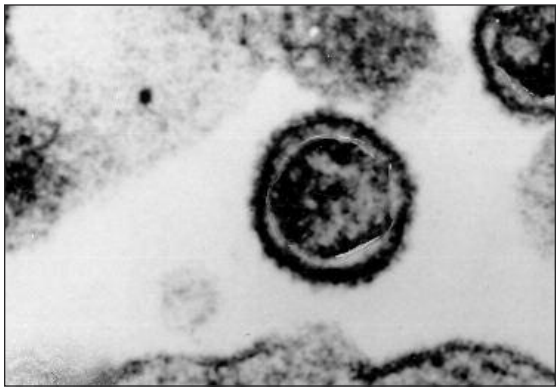
The SIV virus strains, like FIV, turned out to be interesting in a number of ways. SIV was, by the mid- 1980's era of AIDS, also a horribly familiar-looking virus. It was a tiny sphere, 1/100th the diameter of a lymphocyte, and it had a lipid membrane studded with proteins, and an inner protein core that was a truncated protein cone with a dense

Figure 4: **High Magnification Micrographs of Six Retroviruses**
The family resemblance for FIV, SIV, and HIV is clear

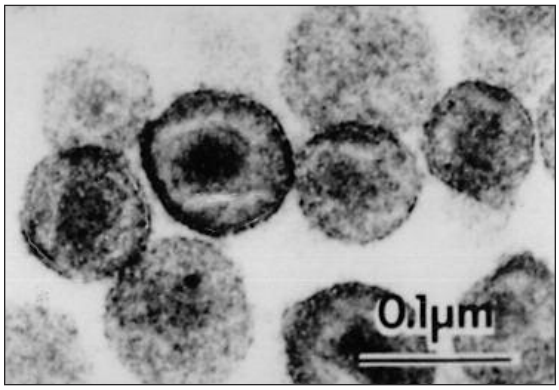
Viruses related less closely to HIV—Feline syncycium-forming virus and feline leukemia virus cause retroviral diseases in cats. They are not lentivirues, and (like the human leukemia retroviruses) do not show a distinct conical viral core. A third virus, the ovine lentivirus, is a lentivirus causing a slow disease called "visna" in sheep. It is a "slow virus," but does not attack the immune system. Its core has an intermediate appearance.



FeSFV—feline syncycium-forming virus.

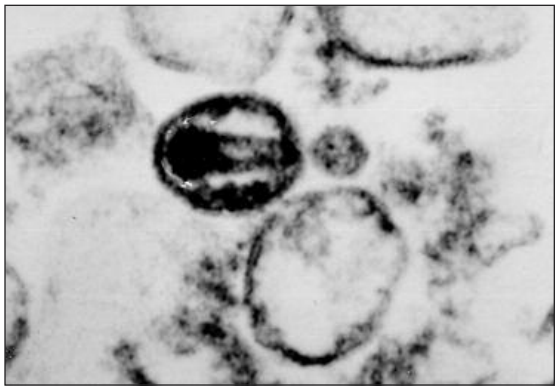


FeLV—feline leukemia virus.

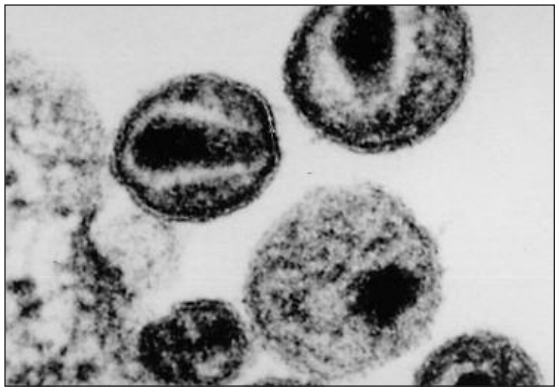


MVV—visna virus.
(also called maedi-visna virus, or ovine lentivirus)

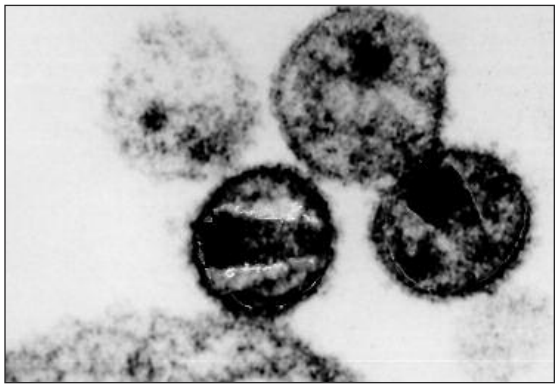
Close cousins—the three viruses below, the lymphocyte-infecting lentiviruses of cats, monkeys, and humans known as FIV, SIV, and HIV, have a characteristic cone-shaped viral core with a dense base, and are visually almost identical. Gene and protein analysis also indicates that these viruses are closely related. FIV and SIV cause fatal, CD4+ depleting, long-latency immunodeficiency diseases in animals, as proven in direct lab experiments. HIV is isolated from humans dying with a new and similar epidemic.



FIV—feline immunodeficiency virus.
(formerly called FTLV—feline T-lymphotrophic virus)



SIV—simian immunodeficiency virus.
(formerly called STLV—simian T-lymphotrophic virus)



HIV

Electron micrographs used with permission, courtesy of Dr. Niels C. Pedersen, School of Veterinary Medicine, U.C. Davis.

base. Inside were two identical or near-identical RNA molecules, associated with a peculiarly magnesium-dependent reverse transcriptase enzyme. The organization of its 9-gene genome was similar to other lentiviruses, and much like that of FIV and HIV.

Like many other viruses in many classes, SIV turned out to be very host-specific in its ability to cause disease. SIV infected its natural hosts (apparently a number of species of *African,* not Asian, monkeys) without causing any obvious sickness or immunosuppression in them. The hosts developed antibodies to the virus, but in the case of SIV, like FIV in cats, these antibodies did not signal immunity, since the virus went on quietly hiding in the nuclei of cells until ready to reproduce and infect other animals.

Only when transferred to genetically different *Asian* species of primates did SIV cause illness. It killed animals quickly when antibodies did not develop, but of more interest was that it was quite capable of killing monkeys after more than a year, long after a strong antibodies response did appear. SIV had originally been transferred to Asian macaques perhaps by housing primates from Africa and Asia in the same cage. Apparently, the African SIV virus did not know quite how to behave in the Asian macaques, and in these monkeys SIV caused both rapid and slow syndromes of immunosuppression and death, depending on the host's immune response. If the virus from a dying macaque was transferred back into African monkeys, however, it went right back to being benign—infecting and reproducing without causing sickness.

"The comparison leads to an obvious inference—FIV causes Cat AIDS; SIV causes Monkey AIDS; HIV causes Human AIDS."

Again, all this was an old story to virologists, who had long known that severe viral disease and death syndromes usually result from mismatched duets between a virus and a "new" species of host for which the virus is not yet adapted. Viruses, after all, do not evolutionarily "want" to make their hosts deathly ill—they want their hosts to be up-and-about, and spreading the virus. Generally, a virus does not kill its normal host.

For SIV, the consequences of maladaption to Asian monkeys caused the scientific interest—for SIV infection in macaques caused what looked more like human AIDS than anything seen yet. Again, in SIV infection, T-lymphocytes were infected, and CD4+ lymphocytes were preferentially killed, leaving CD8+ lymphocytes. Again, simian lymphatic tissues became swollen, and were eventually destroyed during SIV infection. Again, the disease progressed inexorably in some infected animals, even in the face of antibody "immunity," and without showing much active virus in the blood (progression was in the lymphatic tissues, which became damaged in a way sometimes indistinguishable from the stereotypically-destroyed lymphatic tissues found in human AIDS patients).

Again the SIV virus paradoxically caused little damage to lone CD4+ cells in culture, but obviously also did something in the host which totally destroyed the CD4+ system in the living animals. At the end of the SIV disease course, the CD4+ lymphocyte-depleted primates developed not only a few monkey-specific diseases, but also an eerie number of the same opportunistic fungal and parasitic infections that were familiar from human AIDS: oral candidiasis (yeast infection of the mouth), *Pneumocystis carinii* pneumonia (a fungal pneumonia), cryptosporidium diarrhea (a protozoal intestinal infection), cytomegalovirus (CMV) retinitis (a herpes-type viral eye disease), and *Mycobacterium avium* (a tuberculosis bacterium relative). SIV also caused a "retroviral encephalitis"—a brain infection caused directly by the SIV virus which was microscopically similar to the disease changes seen in human AIDS brains. Macaques with SIV also developed lymph-cell-associated tumors (lymphomas), a frequent AIDS complication in humans.[80-82]

The comparison leads to an obvious inference—FIV causes Cat AIDS; SIV causes Monkey AIDS; HIV causes Human AIDS.

Skeptics Dig In

Dr. Peter Duesberg spends very little time on the monkey SIV experiments in his writings, and what time he spends is spent on select experiments. Concerning SIV, Duesberg notes that in one experiment lack of good antibody response to a cloned strain of SIV in monkeys predicts simian death, suggesting that the virus is powerless against a good immune response. Unfortunately, Duesberg fails to note that this finding applies only in the short term in a paper where animals were not followed for the long term.[81] Thus, while it is true that experimentally infected monkeys die quickly of SIV in the short term if they cannot mount an antibody response, it is also true that they can also often be expected to die of SIV-caused immune suppression after one to three years of infection, despite good antibody response.[83] This has also been seen in naturally transmitted infections: a long SIV infection progressing to AIDS even with good antibody response has been observed after experimentally-monitored sexual transmission of SIV from animal to animal.[84]

Duesberg believes that the presence of antibodies to a retrovirus confers immunity on the host (p. 233), and thus that it is unlikely that those people infected by HIV who develop antibodies (making them "HIV-positive"), should develop active, damaging HIV infection later on. But it has long been known in general that antibody response does not protect against long delayed immune failure in the slow but fatal immune deficiency disease caused not only by SIV and FIV, but also by many retroviruses, such as the simian leukemia virus and feline leukemia virus.[85] Nor does it against the persistent and

sometimes later damaging infection in lentiviral diseases in sheep and goats.[86]

In writing of SIV infection, Duesberg is also at great pains to emphasize differences between the infection and human AIDS, pointing out that SIV infected monkeys do not get dementia (how would we know if they did?) and Kaposi's sarcoma, but failing to note that monkeys do get most of the other human AIDS infections, and have much the same basic pathology evident in their destroyed lymph tissues and immune systems as do human AIDS patients.

If Duesberg fails to discuss the relevant animal work with any degree of care or detail, Root-Bernstein does not even try. Any argument based on induction must turn on standards of evidence, and bias in standards of evidence abounds in arguments about the cause of AIDS, just as it does in all scientific arguments (the arguers being human). Thus, Root-Bernstein (p. 330) asserts: "The entire case for HIV as the cause of AIDS rests upon epidemiologic correlations . . . ." He knows better. Root-Bernstein himself is willing to use a wide range of animal experimental evidence in indirect support for his own multifactorial AIDS hypotheses, yet he steadfastly maintains a peculiar blindness for the same kind of evidence when it supports the HIV/AIDS hypothesis.

For instance: Root-Bernstein is quite capable of noting for purposes of inference many instances where a possible non-HIV causal factor of AIDS, either drug or virus, causes relatively mild unselective lymphocyte suppression, or even relatively mild selective CD4+/CD8+ ratio suppression, in laboratory animals (pp. 117-138). Yet there is total silence from Root-Bernstein about the immunological effects of infection by animal lentiviruses like SIV and FIV. Indeed, the "retrovirus gap" in Root-Bernstein's discussion of causes of immune suppression is so glaring that one is left wondering how it is that a literature search as careful as that represented by his book entirely failed to note the effects of certain viruses on immune parameters.

Nor does Duesberg mention such effects, except in one instance in which he makes an observation that SIV retrovirus "barely reduces the T-cell levels of ill monkeys" (p. 232), a statement which is false as a generalization, since there are in fact a number of studies which have found significant T-cell and CD4+ lymphocyte depletion in some SIV-infected monkeys.[80] Note that it is not that the effects of retroviruses on immunity are discussed and dismissed in heretical literature; rather, they are generally not discussed at all. In reading the AIDS heretics—even those heretics doing detailed surveys of the biomedical literature about AIDS—it is as though information on the effects of lymphotropic retroviruses on animal immune function did not exist.

Human Experiments

SIV clearly caused immunosuppression and death in monkeys, but no such simple answer was forthcoming with humans when it came to the question of what was causing AIDS, although certain lab and blood donation incidents came close to being controlled experiments with HIV. At the NIH, three workers have so far been accidentally infected with pure molecularly-cloned HIV, with the result that two are running abnormally low CD4+ counts some years later, and the third has lost almost all CD4+ cells, and developed opportunistic infections. (Though many of Duesberg's "HIV-free" AIDS cases are based on nothing more than slightly abnormal CD4+ counts, in a display of double standards he reportedly refuses to acknowledge two of the lab HIV infections as AIDS by the same criteria.[8,22])

In another example, an African study found that children who had been HIV infected by blood transfusion given for malaria and other reasons, had a far higher death rate than matched children who had received the same amount of blood for the same illnesses but did not contract HIV.[87] In this study, 6% of patients who received HIV-positive blood had been infected, but no HIV-negative transfused controls, had developed clinical AIDS after one year. Such studies underscore the close relationship between HIV-positivity of blood and risk to the recipient of dying. Duesberg has claimed[88] that no study shows a higher death rate in HIV infected people than in matched HIV-uninfected people—yet here is such a study.

Since HIV was discovered before the many careful studies with FIV and SIV, the progression of HIV infection to serious illness in the face of serum antibody "immunity" to it, puzzled some scientists quite a lot. Today, we know from much closer experimental study that lentiviruses are routinely able to mutate to escape host antibodies, so that antibodies found in the same blood with these viruses often do not neutralize them, especially late in the course of disease.[86]

The HIV virus proved to have a special affinity for CD4+ lymphocytes, the very cells which disappeared in AIDS patients. The HIV virus grew readily in CD4+ lymphocytes in culture (not usually causing them harm, but sometimes doing so[89]), and with the ability to grow the HIV virus in cultures of cells and to detect antibodies to it, came the ability oBecause HIV infection almost always resulted in HIV antibody, but since the antibody did not signal cure or the end of virus infection, the HIV antibody test was later used to track cases of transfusion-associated AIDS. In nearly all cases where archived samples of transfused blood could be tested later, people with transfusion AIDS were found to have gotten units of "HIV-positive" blood. In the U.S., 28,000 people received HIV-positive blood products before testing halted such transfusions in 1985. Of these, 5,879 have developed AIDS as of July, 1993. These figures, allowing for less than 100% transmission of HIV by this route, are quite similar to the AIDS rate in HIV-infected people with hemophilia. HIV-positive blood was later shown to hold not just antibodies to HIV, but also the infectious HIV virus itself.

From HIV to Full Blown AIDS

Although people could not be deliberately infected with HIV for ethical reasons, antibody testing to see who had been infected with HIV suggested that HIV was indeed transmitted sexually (though with very low efficiency), and also through contaminated blood products. In time, the virus was "caught in the act," as a number of people were identified by antibody

testing and viral culture as they were first undergoing HIV infection. This "primary" infection turned out to sometimes be rather like an attack of infectious mononucleosis ("mono")—a long and severe sore throat, swollen lymphatic tissues, fever, and tiredness for weeks. Sometimes it was less severe, and was not even noticed. After the initial onslaught, however, the infected person developed HIV-antibodies (i.e., become "HIV-positive") and then began recovering.

Occasionally a person newly infected with HIV would rapidly seroconvert, lose most CD4+ lymphocytes in the blood, and go on to develop full-blown AIDS in as little as eight weeks,[90] so scientists knew this could happen. Most people, however, apparently recovered completely after initial HIV infection, and felt well.

But only apparently. The virus was not gone, but was hiding in the DNA of many of the host's cells. Even years after infection viral DNA could still be detected essentially 100% of the time in an HIV-positive person's CD4+ lymphocytes, and other cells as well. Especially easily infected were immune system cells called monocytes and macrophages. In a person with AIDS, up to 13% of lymphocytes and monocytes in the blood were found infected.[91] From 93% to 100% of the time (depending on the study), infectious virus and viral DNA could be recovered from the blood of asymptomatic people who were HIV-positive, and 100% of the time from people with AIDS.[41] Higher levels of virus could be cultured from the lymphatic tissues of such people, where it was multiplying actively, even in people who appeared healthy.[92,122]

Like SIV-infected monkeys and FIV-infected cats doomed to future immune failure, HIV-positive people were still infected, and most were still slowly losing immune cells in lymphatic tissues. In some sense they were still "sick," even though they might feel and appear healthy. By following large groups of HIV-positive volunteers with blood tests and exams over more than a decade, scientists began to piece together what was happening. Over time, the average numbers of CD4+ lymphocytes in the blood of groups of such people were slowly falling at a steady rate, although not at the same rate in everyone. At the same time, until late in the disease, levels of CD8+ lymphocytes actually rose.

The lymphatic tissues of some infected people were found to be under viral attack, and after some years began to show this by enlargement, as was also often seen in lentivirus-infected animals. Eventually, in an HIV-positive person with lymphadenopathy, most of the CD4+ lymphocytes in the lymphatic organs (where 98% of the CD4+ lymphocytes in the body were normally to be found) were gone. Exactly what had happened to them was not clear, but they had disappeared from the blood as well, and had obviously been destroyed.

At about the time the lymphatics were reaching the end stage of destruction, the HIV virus, escaping filtration by the now-destroyed immune system in the lymphatics, began to enter the blood in larger numbers once again. The largely asymptomatic and reasonably healthy latent period was now at an end.[93] Levels of CD4+ lymphocytes had been falling at an average rate of 60 per year, and when levels of CD4+ lymphocytes in the blood reached the critical count of 250 to 200 (about a quarter of normal levels), fevers and other symptoms began. Opportunistic infections often also appeared, such as candida yeast infection in the throat (often the first infection), or unusual fungal pneumonias in the lungs. In homosexual men, but much more rarely in other AIDS patients, a peculiar vascular tumor called Kaposi's sarcoma might appear on the skin. (This disease has long been thought to be caused by a second infectious agent, which only has been detected by DNA sequencing and suggested to be a new virus in the herpes class). With the appearance of these markers of secondary disease, now the infected person was said to have "full-blown AIDS," or simply, AIDS.

Estimates of the time between initial HIV infection and later AIDS were found to vary strongly with the age of the person, and to a lesser extent on the group infected (homosexuals, with many other concurrent infections, developed opportunistic infections sooner, and also Kaposi's sarcoma). The latency time did not depend heavily (if at all) on the sex of the infected person. Generally, the period taken for half of a given infected group to become sick with full-blown AIDS was about 10 years—with perhaps a few more years for younger people, and a few less for older people.

Before scientists became acquainted with the lymphotropic (lymphocyte-infecting) lentiviruses, they had never before seen *any* disease, toxin, or condition specifically destroy nearly every CD4+ lymphocyte in an animal, while leaving CD8+ cells relatively untouched until near the end. The specificity of lentiviruses in causing destruction of one part of the immune system, while leaving another part relatively intact, was awesome and very strange.

It remains so today, not least because scientists still have not discovered exactly why it happens. One good guess is that the body's immune system somehow destroys infected CD4+ lymphocytes (as it does other virally infected cells) before they have time to make it into the blood, until eventually they are all gone. Many other possible mechanisms for destroying these cells have been proposed, and limited evidence for each proposed mechanism exists. That infection with a lentivirus can destroy an immune system is not the issue, since lentiviruses are known for certain to have this capability in animals, and thus a mechanism for this certainly exists. The only issue left is what this mechanism is.

Telling Nature How Her Viruses Must Behave

It is unfortunate that HIV/AIDS skeptics spend so little time on the behavior of lentiviruses in animals, for HIV is a typical lentivirus, and many of the things critics are saying HIV cannot do in humans are things which lentiviruses are known quite well to do in animals. The inference is not difficult to draw. It is one thing to assume that HIV cannot cause disease long after there has been a good antibody response to its initial infection, and another thing to assume this even though many examples are known in animals of the viruses' cousins

operating in exactly this way. Animal models quite often provide "existence proofs" of mechanisms which overconfident scientists might otherwise dismiss as being unlikely or impossible. That is one important function of animal models: to provide humility to biologists. Usually models are success-
The status of Peter Duesberg as a leading retrovirologist has made it easier for him to be taken seriously when he expresses disbelief at the way in which HIV is hypothesized to damage the immune system. Duesberg's objections of disbelief are made possible by the fact that we do not presently understand every step in the process by which lentiviruses (or indeed most viruses) cause disease. This does not prevent Duesberg, however, from dictating how it should behave. "If HIV were the cause of AIDS," writes Duesberg, "T-cells would drop and AIDS would appear during the primary infection, when HIV titers [amounts of HIV-antibody] are high and there is no viral immunity."[8] Unfortunately, based on the way both FIV and SIV are documented to kill animals after long intervals with good antibody production responses, it would appear that Duesberg has no good grounds to believe that HIV should not, or could not, do the same as a pathogenic agent in humans.

Similarly, a great number of other properties of HIV, which Duesberg believes argue against HIV's pathogenicity, also happen to be properties of the demonstrably pathogenic "simian-AIDS" virus SIV, which closely resembles HIV. There is, for instance, no question that SIV infection alone is sufficient to cause simian CD4+ cell-loss immunodeficiency and death, and that this may happen with delays of up to three years in experimental infection.[81,83] In short, much of Duesberg's inference that HIV is probably harmless is built upon the very shaky proposition that HIV-l is not likely to be able to do in humans what FIV, SIV, and (as we will see) HIV-2—all very similar retroviruses—are already known both observational and experimentally to do, without assistance, in animals.

Properties of SIV infection, in common with HIV, include: similar low level viral titers in animals which are doomed to die later of retrovirus infection, lack of pure CD4+ lymphocyte cell killing by SIV in culture,[89] with paradoxical profound loss of CD4+ lymphocytes and lymph organ destruction in SIV-infected animals,[94] and finally, absence of any obviously special SIV genes which might confer virulent properties with regard to other retroviruses. All these viral properties or infection characteristics have been claimed by skeptics to indicate that HIV is probably harmless, and yet we know that their presence with both SIV and FIV certainly does not indicate harmlessness for these organisms. By analogy it would seem, if anything, that HIV is not necessarily harmless either.

The Koch Postulates of Disease

The parallels between SIV and HIV turn out to be useful also in an odd debate involving the "Koch postulates" of disease causality, which has lately been resurrected by HIV/AIDS skeptics. Duesberg, almost alone among virologists, believes that viruses must fulfill these postulates to be proven to cause disease. Koch's postulates, named after the 19th-century physician Robert Koch, date from a time before viruses or antibody testing was known, and have been discarded by most scientists in the modern era, since they can lead to bad inferences.

As an example, there are many people with sore throats who are not infected with the micro-organism popularly known as "strep," and many people are infected with strep for decades who do not have sore throats. However, we could not legitimately conclude from these data that strep does not cause *any* sore throats. Rather, the issue is what fraction, if any, of sore throats are caused by strep. In order to even begin to answer this question, we need to know at minimum how "tight" mathematical correlations between the presence of the putative infectious agent (strep), and the disease syndrome (sore throat) we think it may cause.

Dr. Koch postulated some simple rules which he felt should be fulfilled for an organism to be proven to cause a disease:

(1) The organism be findable in essentially all cases of the disease. Strep would fail the first Koch test as the "cause" of the syndrome of sore throat, but today we would not say that this was proof that strep did not cause sore throats. Rather, we would measure the prevalence of strep in various populations of asymptomatic and sore-throated people, and then employ statistical methods in order to arrive at a probabilistic estimate of what fraction of sore throats strep was likely to cause. Koch, too, would use such statistical methods later in life when he was forced to abandon his own rules in order to inductively guess the cause of cholera. In short, the world has moved beyond Koch's postulates, and even Koch in his own life time did so. But not Duesberg. Duesberg's attempts to define AIDS in such a way that many AIDS cases would be HIV-free, are misguided because they are based on Koch's simple un-statistical laws. Another of Duesberg's arguments relating to the first Koch postulate holds that HIV is not present in *sufficient quantities* to cause disease in humans who have AIDS. But how do we know what "sufficient quantity" is, when it comes to lymphotropic lentiviruses? This ought to be a case where animal models should help. HIV is in fact present in the blood of AIDS patients in quantities very similar to the amount of SIV in the blood of SIV-infected monkeys, and we know that without doubt SIV is sufficient to cause severe immune deficiency disease leading to death in monkeys.[82] We also know active HIV virus is present in large quantities in lymphoid tissues in HIV-positive humans.[122]

(2) A second Koch postulate requires that an organism be isolated in pure culture and that this culture then be used to transmit the disease to a susceptible host. Duesberg has pointed out that HIV does not cause disease in non-human primates, and has not been demonstrated by deliberate and controlled direct transfer to cause disease in man. However, we should note that failure to cause disease by experimental transmission is true only for HIV-1, since recent experiments have now succeeded in reproducing animal disease with another strain of HIV, called HIV-2. (HIV comes in two strains. HIV-l does infect and replicate in chimpanzees, but except for lymphadenopathy does not cause noticeable illness in them. Quite recently, however, when researchers were able to

isolate a different lentivirus from AIDS patients in West Africa they found that the new virus, eventually dubbed HIV-2, was only 50% identical in genome to the more familiar HIV-1, but was genetically almost indistinguishable from the SIV family of monkey viruses.)

Since HIV-2 is the only retrovirus isolated from some West African AIDS cases,[95] it was natural for researchers to see if the HIV-2 virus, so similar to SIV, killed Asian monkeys (but not African monkeys) in the manner of SIV. They found, by injecting HIV-2 into Asian monkeys, that this virus does indeed behave like SIV.[96] HIV-2 destroys the immune system in Asian monkeys by giving the monkeys the simian version of AIDS.[97] Further, the longer the chain of infection in monkeys, the more deadly the human virus becomes for them. In all this work, clues have emerged about where the HIV-2 virus came from originally. Humans appear not to be the natural hosts of this virus, just as they are not the natural or earliest reservoir for HIV-l.

The result of this work is a chain of inferences, but with help of the new HIV-2 results, not a difficult chain to follow. The retrovirus known as HIV-2 has been found by direct experiment to cause low CD4+ lymphocyte counts in animals, destruction of animal immune systems, opportunistic infections, and death. This HIV-2 virus had been isolated from humans dying in Africa from an epidemic of something that destroyed CD4+ lymphocytes, destroyed immune systems, and as a result allowed opportunistic diseases resulting in death (in other words, AIDS). If HIV-2, which causes AIDS-like CD4+ immune destruction in monkeys, is not causally involved in the severe human immune problems in West Africa where it is isolated from AIDS cases, it would rank as one of the greatest scientific coincidences of all time.

The art of scientific inference lies in deciding how many coincidences it is wise to accept. □

PART III

LESSONS ON HOW SCIENCE WORKS

The Ultimate AIDS Test

Since the HIV/AIDS hypothesis has not been proved by experimentally infecting completely healthy humans deliberately with HIV under controlled conditions, many of the standards of proof required by those who are skeptical of the HIV hypotheses would seem to be impossible. Apparently no organism but man becomes significantly ill with HIV-l. Root-Bernstein notes that human-specific viral diseases satisfy Koch's postulates only by being transferred deliberately and experimentally from a sick person to a healthy one (p. 95), and sometimes such a trial appears to be what skeptics demand for HIV. Root-Bernstein states: "correlation, no matter how good, is never grounds for asserting causation. One must have experimental control over the disease" (p. 101). Does he mean by this that scientists should inject themselves with HIV, much as did the famous surgeon Dr. John Hunter (who died after inoculating himself with syphilis) or Walter Reed's brave colleagues James Carroll and Jesse Lazear (who allowed mosquitos carrying yellow fever to bite them, resulting in the death of Dr. Lazear)?[1] Perhaps. Peter Duesberg has indicated unwillingness to be inoculated with HIV, saying it would prove nothing if he survived in good health, as he expects to.

Duesberg is probably right in this, but since HIV is thought to cause steady and implacable immune decline in more than 90% of people infected with it, highly significant results would be generated if even two healthy skeptics infected themselves with HIV, and both survived for five years without any evidence of increasing immune deficit. In fact, one Florida physician named Robert E. Willner, author of an amazingly misinformed AIDS heresy book called *Deadly Deception,98* has already performed two televised needle inoculations on himself with the blood of an HIV-positive man with hemophilia![22] There is no word yet on Willner's HIV antibody status, but from what we know of viral blood burdens, he is inoculating with too little blood to realistically be of much risk from a non-ill HIV-positive person. Such cases will probably remain too scarce for conclusions, especially if the adequate pre-testing necessary for good science is not done. Still, if any self-inoculating heretic does contract HIV, and then AIDS, it will certainly make news.[98] I formally propose that Willner and Duesberg make a pact between themselves to get appropriate pre-studies done, then each self-inject enough pure molecularly cloned HIV to seroconvert to HIV-positive. If both are healthy with no significant CD4+ loss in 5 years, I will campaign for the Nobel Prize for both.

When Does Causation=Correlation?

How much can we know about causation from mere observation, without experimentation? Since the writings of the 18th-century philosopher David Hume it has been known that certainty about physical causes and effects is

not to be had from mere association, even if the temporal sequence is correct. Hume is at least correct that to some extent the causal conclusions of science are always uncertain, because they involve mechanisms and rules we can never be completely sure of understanding, even if we had some way to guarantee that future events will continue to be bound by any "rules" we *could* be sure we understand now. A favorite fable which philosophers tell features a turkey on a family farm who observes that every time the farmer comes to his turkey-run, he comes to feed the turkey. The turkey thus hypothesizes a causal connection, and predicts feeding each time the man comes, and as time goes on, sees this theory "verified" many times. But on the third Thursday of November the turkey's well-verified theory suddenly becomes mal-predictive, because the universe is a much more complicated place than turkeys can comprehend. Unfortunately, the universe is such a complicated place as to sometimes make turkeys of scientists as well.

Nevertheless, to the extent that today's future, which we cannot know, continues to be like "yesterday's future," which we can check, progress can be made. A turkey's existence is made easier for a time by having at least an incomplete model of reality, and we may ourselves say that even partial understanding of causes brings partial "knowledge." Inductive knowledge is uncertain in the same way a weather forecast is uncertain, but this does not mean that science does not uncover a certain kind of truth. A weather forecast may not guarantee the future, but the point is that it is usually better than guessing. Probabilistic knowledge is still genuine knowledge of a special kind. Such knowledge is the only kind of knowledge we can have about the future.

Because the association of events may be always controlled by a third factor we do not suspect, the problems with induction become most acute in trying to tease out causal relationships in systems where we cannot experimentally influence events in order to rule out possible causal relationships. In such systems, statistics help us tell which factors are important and independent of each other in predicting future events, but such associations only suggest causation when present. This is because any factor "predictive" of an event may still only be merely a good "proxy," or marker, for an even more predictive, mechanistically causal factor. Thus, the strength of statistical associations between events and possible causes are far more helpful in ruling out possible causes than ruling them in. The reason is that it is rare for a factor to be causal of an event if its presence is not independently predicative of the event.

Here an example may be helpful: Let us pretend that we discover that weekly ice cream sales during a calender year predict juvenile delinquency arrests from week to week, but spaghetti sales do not. This is reasonably good evidence that spaghetti sales are *not* causally connected to juvenile delinquency. On the other hand, for ice cream and juvenile delinquency, the associative connection found by the statistics is merely suggestive—here we may be looking at cause and effect, *or* we may be looking at a variable which is a proxy for something else which is more directly causal of delinquent behavior. But if find that the daily average *temperature* predicts juvenile delinquent behavior as well as ice cream sales do, and ice cream data adds nothing, then we now have evidence that ice cream is not causal, but is *merely* a proxy, or marker, for *temperature* during the year. Even with this better association, we are still not assured of the causal role of temperature, although we might guess that we are closer to the right track for temperature than we were with the ice cream sales. This story illustrates a major path by which science in general makes progress.

"I formally propose that Willner and Duesberg make a pact between themselves to get appropriate pre-studies done, then each self-inject enough pure molecularly cloned HIV to seroconvert to HIV-positive. If both are healthy with no significant CD4+ loss in 5 years, I will campaign for the Nobel Prize for both."

Sharpening Occam's Razor

Statistics cannot do our thinking for us. We must rely on something else to come up with our list of possible causal factors to test with our statistical methods. This is the business of the human imagination. Karl Popper, the noted philosopher of science, observed that almost no theory is ever ruled out by experiment because with enough imagination, nearly any theory can be tinkered with so that it continues to "explain" all data. Thus, if one causal factor does not explain results statistically in a given situation, it is not necessary to drop it—one may instead postulate an additional factor which explains results in the case where the first one fails. In fact, if one persists in hypothesizing new factors each time an old factor fails, one need never drop any old hypotheses at all. At some point, however, doing this makes any theory simply too ugly and ungainly to be believed, and at that point (if a better alternative is in view) many scientists may decide to discard the old theory,[99] though many do not, as Max Planck pointed out. Only death removes the last die-hard believers in *some* theories.

In this manner it is indeed possible to construct a theory in which AIDS is *not* caused by an infectious agent. To do so, however, requires that a newly emerging simultaneous and significant cause of mortality in many diverse groups of people be explained rather "unnaturally" in a great number of different ways. For example, Duesberg suggests that AIDS in Africa is caused by malnutrition and tuberculosis and new misclassification, in U.S. male homosexuals by a new habit of recreational nitrite use (p. 248), in female IV drug abusers and their newborn children, by newly popular drugs other than nitrite (p. 215), and in many of those HIV-positive people who do not use illegal

drugs, by use of prescription AZT since 1987 (p. 241), etc.[100] Deaths in non-drug-using groups like people with hemophilia in the era before 1987 are explained as being due to immune suppression and extra life extension by clotting factor concentrate, new since the early 1970s (p. 219).[101]

For none of these suggested causes of AIDS is there any mechanistic or experimental evidence, since none of the agents proposed, or anything related to them, causes in animals the severe and specific suppression of CD4+ lymphocyte numbers characteristic of AIDS. In Duesberg's theory, AIDS deaths from transfusions are argued to be non-existent (p. 214), rejecting the orthodox idea that simple transfusion or trauma-associated mortality usually covers them up.[87] AIDS deaths in contaminated hospital workers are rejected as anecdotal and perhaps due to something else, such as personal drug abuse (p. 211). AIDS deaths in wives of men with hemophilia (and their children) are dismissed as being due to normal aging and misclassification (p. 219), etc. The Duesberg theory is here becoming rather ungainly.

To make progress in science requires that we continue to propose new and better causal factors for effects and then test these causal factors statistically and experimentally. Independent prediction serves as the best statistical test for factors which we cannot vary experimentally. The problem with Duesberg's theories is that they are retrodictive, but not predictive. If HIV is only a proxy factor, or marker, for a number of habits or practices which are supposed to "explain" immune failure better than HIV infection does, then it follows that the presence of such problems should be able to predict future development of AIDS in asymptomatic people, to even better accuracy than HIV status does. Nothing of the kind has been shown, however. On the contrary, cohorts of HIV-positive people have been shown to develop AIDS at a predicable rate, fairly *independently* of most of the factors that have been suggested by skeptics to be the real causal factors for which HIV is merely a marker.[100, 102]

Duesberg's hypothesis, as compared with Root-Bernstein's, actually has the charm of a certain simplicity, since in Duesberg's theory immune failure is said to be due to only two categories of toxins: foreign blood proteins or drugs. In Duesberg's view, these two causal factors are supposed to have independently (and, apparently, coincidentally) begun producing an epidemic of immune deficiency in: 1) people with hemophilia; and 2) everyone else—both starting in 1982 or so.

"Multifactorial" hypotheses such as Root-Bernstein's, however, posit so many different contributing causes of severe immunosuppression that one or more of the additional risk-factors identified by Root-Bernstein is likely to be present in addition to HIV, in almost every AIDS case. *Rethinking AIDS* argues the case that besides HIV infection, AIDS might be caused by blood product infusion (both whole blood infusion and clotting factor concentrate injection), by surgery and/or anesthetics, by accidental trauma, by age (both young and old) by use of any and all common illicit drugs and most pharmaceuticals, by concurrent infection with any of dozens of microorganisms, by rectal insemination, by malnutrition, and even by sunlight exposure. Considering all these hypothetical cofactors, Root-Bernstein writes (p. 92): "If such agents exist…it is not enough to demonstrate that HIV is present and highly correlated with AIDS. It is also necessary to demonstrate that these other agents are not present in AIDS patients. That is impossible."

Here Root-Bernstein misses the point. In general, it is not necessary statistically to find cases where each factor which is a possible cause of a disease is totally absent, in order to amass evidence that the factor in question is not causal. It is merely enough to show that the increasing or decreasing *quantitative* presence of the factor has no independent statistical effect on probability of the disease. Such a demonstration never rules out causation completely, but it does make causation much less likely for those who like their hypotheses as simple as possible.

Such statistical tools (i.e., multivariate analysis) are among the most powerful which scientists can use for exploring initial possibilities for causation, in complicated and difficult-to-manipulate systems. Without such statistical tools it would never be possible to exonerate any one of any common set of behaviors from a causative role in *any* disease. The reason is that we live in a complicated world, and participation to some extent in one or more of a certain set of behaviors describes *all* of us. But we are fairly certain that walking and driving a car do not contribute to lung cancer, for instance, because of multivariate analysis of life-style, *not* because somebody has described a group of lung cancer sufferers who never drove cars or walked.

Formless hypotheses involving large numbers of unknown etiologic factors which will be prohibitively expensive to search for do not help the cause of human knowledge. When considering complicated multi-factorial hypotheses, where most of the multiple factors are unquantified, missing, or un-named, one is reminded of the great physicist Wolfgang Pauli being asked if he thought the theory in a new scientific paper was wrong. He said "wrong" would be too kind. "It isn't even wrong."[99]

In the case of the HIV/AIDS skeptic proposals for AIDS cofactors, a great many studies have indicated that many proposed cofactors (such as non-injected drug use, clotting factor use, and AZT use) are proxy variables for acquisition of HIV, like ice cream use and temperature in the example. Their predictive power in telling AIDS risk disappears completely when HIV status is controlled as a variable. There is thus very little justification in continuing....

In the case of the AIDS skeptics, all these proposed cofactors are merely proxy variables like ice cream sales and temperature. There is thus very little justification in continuing to advance hypotheses which involve them, since none have passed even the most basic initial statistical standards used by epidemiologists.

So Many Theories, So Little Time

There are of course many gaps in our understanding of the causal sequence in AIDS. An examination of the virally-caused CD4+ immune failure and slow death in animals infected with viruses related to HIV demonstrates that it is quite possible biologically that HIV operates in humans to cause the same sequence of pathologic events as we see in AIDS, but we do not know exactly how this works even in animals, let alone humans.

Let us frankly admit it: we know very little of the actual molecular mechanisms behind *most* of the causal sequences which we have identified by experiment in biology. Thus, at this point the fact that we do not yet know exactly how HIV and the other retroviruses work is no more and no less odd than the fact that we do not yet know exactly how cancer, or fetal development, or memory, or the aging process works. Complaining in 1995 that we have spent a decade and lots of money on AIDS (or for that matter cancer) and only gotten more bogged down, is childish.[103]

This does not mean progress is not being made in identifying cofactors for acquisition of HIV, and also cofactors for developing AIDS after HIV infection.

It is generally assumed by orthodoxy that risk of HIV infection is influenced by such standard infectious disease variables as virulence of the HIV strain, amount of the HIV virus inoculated, and route of inoculation into the body (related to amount inoculated). The role of none of these is fully understood for HIV infection, but the idea that there is a large role to be found for each of them is not really controversial. Possible cofactors in the acquisition of HIV and development of AIDS have been discussed in the mainstream scientific literature for years, and are not in any danger of being dismissed any time soon. The real *controversy* in the treatment of AIDS is almost entirely centered about the role of conjectural cofactors which are manipulatable *after* the time of HIV infection, and thus not related to sexual mechanics, the genetics or age of the host, or the inoculum and virulence of the HIV strain in question.

In *Rethinking AIDS Root*-Bernstein ironically quotes Einstein's version of William of Occam's philosophic razor: "Keep hypotheses as simple as possible, but no simpler." Failure to follow this maxim can be very costly in the real world. Resources for research are not infinite, and in practice, diversion of resources toward experiments to test *a priori* epidemiologically unlikely hypotheses, can result in much wasted time and lives lost. One can imagine for instance, how long-delayed might have been the program to control polio (a disease which was also, for a long time, refractory to the "one agent—one disease" approach criticized by Root-Bernstein) had multifactorial theories of disease been pursued on all fronts for polio paralysis. To this day we still cannot explain why the polio virus causes paralysis in some few, but not most, infected people—yet science succeeded in finding an effective preventive strategy for polio paralysis, nevertheless. We long ago stopped polio by simply stopping the polio virus, which we had found was a necessary element in the disease. We *ignored* the other cofactors (whatever they were) which caused some people to be paralyzed, and not others. There is perhaps a simple lesson here.

Root-Bernstein, in the concluding paragraphs of his book, brings us to the crux of this practical issue (p. 372): "Assurance in science," he writes, "comes only through elaborating as many possible explanations as can be imagined for a phenomenon and eliminating all that can be possibly eliminated." A historian of science ought to have inserted major qualifications in such a statement. There are actually an infinite number of possible explanations which can be imagined for any phenomenon, and trying to eliminate them all would leave both science and funding agencies paralyzed and bankrupt.

In practice, only a certain relatively small segment of possible kinds of theories are accepted or acceptable in science, and these are based mostly on the success of previous small classes of theories. As both evolutionary biologists and successful businessmen know, no efficient search of any large set of possibilities proceeds by random search of all possibilities, but rather must succeed by exploration of a much more limited set of combinations of previously successful possibilities. Major hypotheses worthy of the expense and time of experimental testing in science are not generated by elaborating every possible explanation. Rather they come through a still mysterious process of mentally narrowing down certain classes of possible explanations to a few "good ones," and then testing those. (If there were no mystery about this process of narrowing down millions of theories into a few good candidates, it would not be necessary to speak of scientific "genius.")

At present, there is no getting around the fact that the HIV-infection theory of AIDS is the leading and most predictively successful causal hypothesis for AIDS. Progress is thus most likely to be made by continued testing of this theory, and likely variations of it suggested to us by various kinds of statistical evidence. A theory is not "tested" by requiring that it provide the route to a successful treatment for disease as well. Our present failure to cure either AIDS or lung cancer does not speak to the truth or usefulness of theories about their causation.

Allocation of resources for the testing of more radical causal theories for any disease must be made on the basis of some prior likelihood of their being more useful or more explanatory (our current tests for "truth"), since otherwise much money would be spent uselessly chasing moonbeams and bad guesses.[104] When a new causal theory "predicts" a phenomenon only after the fact (retrodiction), and predicts it no better than our current best theory, which is much simpler and already available for no more money, then our current theory is to be preferred. On the public level of funding, there would seem little reason to waste money on the infinite number of alternate theories of disease which may be more comforting than the standard one, but which have too little chance of being true to bet much money on. It is to this point that we have come with AIDS.

The Future of AIDS—Are We Doomed?

The HIV viral plague is the great plague of the 20th century, infecting as many as a million people in the U.S. alone, with 1/3 of a million people already having developed AIDS. Almost all of the people with AIDS now alive can be expected to die within a few years, barring some immediate major technical advance or discovery. What about the rest of people with HIV? If there is no evidence that converting to a drug-free, medication-free lifestyle assures the harmlessness of subclinical HIV infection, then what can be done? And what about those people who are still HIV-free? Are they destined to see the disease sweep through their communities, eventually catching everyone who is not perfectly chaste, careful, and lucky?

Let us, for the moment, follow William of Occam and assume that there are no important post-HIV-infection modifiable cofactors for AIDS left to identify, since at present we really do not have much reliable AIDS epidemiologic data that cannot be explained in broad terms under the headings of host and behavioral cofactors that we assume exist already. Suppose HIV is indeed the major culprit for development of AIDS, exactly as it appears, and that risk of AIDS, once HIV infected, is more or less predetermined already by the virus and host, with only minor modifications in AIDS risk possible though modifications of the most extremely risky behavior (IV drugs and promiscuous sex). Studies show that very long-term HIV survivors are *not* saints,[46] the long-term healthy HIV-positive men (8% of the total) in the longest and best study so far done (14 years) were as likely to have had non-HIV sexually transmitted diseases, or been users of non-injected illegal drugs, as the other HIV-positive men in the study (92% of the total) who had become more immunocompromised or died with AIDS during that time.[46] As we have noted, only the most extreme infection-risking behavior, such as IV drug use or a high degree of promiscuity, correlates with increased AIDS risk after HIV infection. Science so far provides no evidence that saintly behavior, once a person is HIV-positive, adds anything significant to survival time.

Is there much hope for the population of the world, even on these grounds? Perhaps. I believe there is reason for optimism, even if the simplest AIDS hypothesis which fits the facts (which is the one now commonly accepted) turns out to be substantially correct.

The first bit of optimism is on behalf of people who do not have HIV yet. It appears that the HIV virus is very hard to catch, with favorable odds seen so far, even for U.S. call-girls who report that even they do not use condoms with some trusted regular customers. The risk for transmission from a woman to a man is particularly low in the absence of other sexually transmitted diseases—so low, in fact, that when American women contract HIV from men, the men they contract the virus from almost never contracted the virus themselves from other women, but rather from needle-sharing during injected drug use, or from male homosexual contact. Since it is difficult to hide the scars and the lifestyle which are corollaries of the kind of illicit drug use which involves drug injection equipment-sharing, it follows that a discriminating American woman's major risk of AIDS is from heterosexual contact with a secretly bisexual man. Even this risk can be greatly reduced by avoidance of anal intercourse, and sexual contact with men who do not appear perfectly healthy. As for men's risks, exclusively heterosexual men in America who have sexual partners at low risk for other concomitant sexually transmitted diseases, have a very low risk of acquisition of HIV.

"It appears that the HIV virus is very hard to catch, with favorable odds seen so far, even for U.S. call-girls who report that even they do not use condoms with some trusted regular customers."

These facts alone are probably enough to insure that in the present sexual climate, condom use or not, HIV will not spread to any great further extent by exclusively heterosexual transmission in the U.S. The heterosexual AIDS pandemic we have been warned of for a decade, in other words, is not coming at all.[105] Indeed, there is every reason to believe that such an epidemic would be here already if it was destined to arrive soon. Constant numbers of HIV infected persons in the U.S. for the last several years point strongly to the probability that at an infection prevalence of only 0.3% of the total U.S. population, HIV has largely run its course in most subpopulations susceptible to it in this country.[101] (Because of latency delays between infection and disease, new yearly AIDS cases will continue to rise rapidly for years, even so). In the future, sexual mores may yet change greatly—and it may be that even now, among select groups of heterosexuals (e.g., inner city teens) promiscuity and lack of treatment for other sexually transmitted diseases will allow for a future small heterosexually-transmitted AIDS mini-epidemic. Much remains to be seen. What does seem likely, however, is that for the near future, most of the U.S. population will escape AIDS—even should no vaccine or treatment be found.

For any individual, use of a condom during heterosexual contact further greatly decreases the odds of HIV transmission, so much so that the odds of HIV transmission after condom failure with a carefully-chosen heterosexual partner, are probably on the order of the risk of dying on a routine freeway excursion. In short, conservative protests that use of condoms gives heterosexuals a "false" sense of security, are incorrect. For the American heterosexual, use of a condom and common sense probably results in at least as much security from accidental fatality as is the norm for participation in many other activities such as driving, swimming, skiing or boating. Certain homosexual behaviors, by contrast, are

indeed considerably more dangerous, unless extraordinary precautions are taken.

The estimated risk of transmission of HIV from male to female during vaginal intercourse in the absence of other sexually transmitted disease is estimated to be about one in 250 to 500 per act of intercourse, and around 50% of this risk for transmission from female to male. This data comes from married couples discordant for the virus. If a properly used condom fails 1% of the time, this figure would result in an infection risk of one in 50,000, even with an HIV-infected partner. (These figures are consistent with studies of HIV-discordant married couples which show that consistent condom use even over several years time reduces HIV infection rate to essentially zero.) Since far less than 1% of non-IV drug using women will be infected with HIV, total HIV-infection risk of heterosexual contact for an American man should be less than one in five million, which is the range for mortality-risk on an average commercial jet airline flight.

Concomitant sexually transmitted disease other than HIV does contribute to HIV transmission risk in a significant way. Studies of healthy Thai soldiers who acquire HIV heterosexually from prostitutes suggest that transmission risk odds for HIV in the presence of other sexually transmitted disease(s), may approach 1 in 12 per sexual encounter. In light of such facts the Surgeon General would of course remind us that limiting one's number of lifetime sexual partners is a time-honored (if not always followed) way of decreasing one's chance of acquiring sexually transmitted diseases, including HIV. Statistically, however, this strategy works only if one's partner(s) are doing the same. Requiring formal HIV testing before the beginning of any monogamous sexual relationship helps these statistics, and a rapid saliva HIV test is under development in Thailand and soon may be available on the U.S. market.

For those people already infected with HIV, there is much hope as well. Very long-term HIV survivors do tend to be people who have avoided long-term early treatment with AZT alone,[46] but it is hard to know if this is a cause or effect of good health. In any case, although it seems likely that AZT monotherapy for long periods (greater than 12 months) is worth avoiding, the same does not necessarily follow for combinations of anti-retrovirals. New antiviral drugs are being developed at a rapid pace, and even a mutating virus may have difficulty keeping up with many different antiviral drugs administered at a time, or in combinations in a rotating fashion.

As long-term animal and human survival with retroviruses demonstrates, immune failure as a consequence of retroviral infection is a host-specific response to infection, and has little to do with any property of the virus itself. Almost certainly, AIDS is an evolutionary "mistake," caused by a particular (and perhaps unnecessary) interaction of HIV virus and host.[106] We know that retroviruses survive well in many of their natural hosts without causing illness. It is thus very probable that HIV will be successfully dealt with eventually by finding a way to turn it into the kind of harmless infection it is in chimpanzees, long before a way is found of removing the virus wholesale from the body. In Australia, scientists have followed for some years a group of five people who are HIV-positive but healthy (save for one who died of AIDS after being treated with immunosuppressant drugs for lupus erythematosus), after all being infected by a blood donation from a single healthy HIV-positive donor who may harbor a more or less harmless strain of HIV.[107]

There is also much to learn from the 8% of HIV-positive people harboring conventional strains of HIV, who are still healthy after 14 years of infection, with no sign of becoming more immunosuppressed.[46] Do these people (who may be HIV long term survivors) have less pathogenic strains of HIV, or are their own immune systems simply better? Recently identified is an interferon-like factor made by CD8+ cells in these and other healthy people, which suppresses HIV infection in CD4+ cells without killing the cells. The factor is being intensively studied, and should it prove useful, may one day be commercial produced by genetic engineering techniques.[108]

Of all examples of evolution we know of, viruses are the most spectacular, since they evolve so quickly that new species are seen on Earth regularly on the scale of a human life-time, and some of these newly "emerging" viruses emerge as plagues. Indeed, with HIV, there is good reason to think that the average human HIV host is infected by not one, but rather many closely related strains or subspecies of the HIV virus, all evolving furiously in parallel. During the asymptomatic phase of HIV infection, virus cultured from the host reproduces slowly in culture, but at the end of the disease when the virus is more active, cultured viruses have often turned into strains that are able to reproduce rapidly in culture. Usually, after a long time, the virus gains the upper hand in this battle with the immune system, but it does so only because it infects the host slowly enough to give the virus time to evolve over a decade into something the host's defenses finally cannot handle. Even so, the virus can win only by slowly destroying the body's ability to deal with any invader, including itself.

What will the future bring in the way of new diseases like AIDS? To the question of whether or not we will see more viruses newly evolving to be able to infect humans with new plagues, the answer is that no doubt we will. We know that a virus can be as deadly as HIV without needing a latency period. But a short incubation and less than maximum infectivity has been the undoing of viruses, or otherwise modern world civilization might indeed have been destroyed already.[121] The real question is: what kind of viruses can manage greater spreading capability by having a long infectious latency period, yet be able to cause high mortalities as well?

Let us hope that lymphotrophic retroviruses are all forever somehow necessarily constrained in communicability, and that biotechnology progresses rapidly enough to find a way of suppressing our current crop of these microbes. Finally, let us also hope biotechnology does not progress in such a way as to let molecular bioengineering of such a virus become a possible basement hobby project (as it surely will one day) before we understand how to protect against the possibility of such a deliberately-caused, or deliberately-modified plague—a disaster that could resemble the Black Death that once eliminated almost half the European population. □

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102. *AIDS* 7:231 -239, 1993; also see *AIDS* 8:803-810, 1994. From these papers and others it is apparent that yearly risk of progressing to AIDS is far from constant for either persons or populations. Instead, risk in a population rises almost linearly from the date of infection for at least seven years, toward peaks of as much as 7% per year. This does not prevent Duesberg from routinely treating AIDS risk rates in populations as constant.
103. The necessary technology to grow the HIV virus in culture and thus identify it, preceded the main onset of the AIDS epidemic by only 5 years, so in this sense things might have been much, much worse. HIV, dispite many attempts, could not be grown in the lab until 1983. Genetic engineering of viruses also dates only from the 1970s.
104. According to the Bayesian analysis of scientific induction, it is necessary to first have some *a priori* idea of the likelihood of the truth of a proposition, before one can properly evaluate the helpfulness of new evidence which supports it.
105. *Lancet* 341:863-864, 1993.
106. As Ewald (note 18) argues, promiscuous behavior, or rapid experimental passages of a virus from one lab animal to another, may select for more virulent strains, since in such conditions viruses do not need to keep their hosts alive for as long.
107. *Lancet* 340:863, 1992.
108. *Hospital Practice* 29(10):41-52, 1994.
109. *AIDS* 8:564-5, 1994.
110. I am indebted to Dr. Louis Goodman, late professor of pharmacology at my medical school, for this alliterative description of the three sequential social phases in the introduction of the average medicinal drug.
111. *N Engl J Med* 317:192-7, 1987; *Am J Med* 85(2A):208-13, 1988.
112. *JAMA* 262(17):2405-10, 1989; *AIDS* 8:313-321, 1994.
113. *J Acquir Immune Defic Syndr* 5:120-126, 1992.
114. *N Engl J Med* 322(14):941-949, 1990; *N Engl J Med* 326(7):437-43, 1992.
115. *JAMA* 272:437-442, 1994.
116. *N Engl J Med* 328:1686-1695, 1993.
117. *N Engl J Med* 330:738-743, 1994.
118. *Lancet* 341:889-890, 1993.
119. *Am J Med* 85(2A):208-213, 1988.
120. *CalReport, U.C.* Berkeley newspaper, Fall 1991. Interview with P.H. Duesberg; See also Lauritsen, J. *Poison by Prescription—The AZT Story.* Asklepios Press, NY, 1990.
121. Preston, R.M. *The Hot Zone.* Random House, NY, 1994.
122. Int Conf AIDS. 1994 Aug 7-12;10(2):80 (abstract PA0200).