Infectious AIDS

Have We Been Misled?

A collection of thirteen articles originally published in scientific journals that call into question the dogma of infectious AIDS

Peter H. Duesberg

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North Atlantic Books
Berkeley, California

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Published by
North Atlantic Books
P.O. Box 12327
Berkeley, California 94712

Cover and book design by Paula Morrison
Typeset by Catherine E. Campaigne

Printed in the United States of America

Infectious AIDS: Have We Been Misled? is sponsored by the Society for the Study of Native Arts and Sciences, a nonprofit educational corporation whose goals are to develop an educational and crosscultural perspective linking various scientific, social, and artistic fields; to nurture a holistic view of arts, sciences, humanities, and healing; and to publish and distribute literature on the relationship of mind, body, and nature.

Library of Congress Cataloging-in-Publication Data

Duesberg, Peter.
Infectious AIDS : have we been misled? / Peter H. Duesberg.
p. cm.
Includes bibliographical references.
ISBN 1-55643-204-6 (cloth). — ISBN 1-55643-195-3 (pbk.)
1. AIDS (Disease)—Etiology. 2. HIV (Viruses) I. Title.
RC607.A26D838 1995
616.97'92071—dc20 95-32937
CIP

1 2 3 4 5 6 7 8 9 / 99 98 97 96 95

Infectious AIDS: Have We Been Misled? is a collection of thirteen articles originally published in scientific journals between 1987 and 1995, that call into question the dogma of Infectious AIDS.

Contents

Preface

> It is easy enough to find a theory, logically harmonious and with important applications in the regions of fact, provided that you are content to disregard half the facts. . . . An unflinching determination to take the whole evidence into account is the only method of preservation against the fluctuating extremes of fashionable opinion.
>
> —Alfred North Whitehead

If ever there was a rush to judgment with its predictable disastrous results it has been the HIV/AIDS hypothesis and its aftermath. Announced at a press conference prior to the publication of any scientific proof, complicated and confused by early legal arguments concerning theft of the "French" virus by American researchers, the continuing inability of a worldwide scientific effort to muster clear proof for causality of AIDS by HIV, the inability—after 10-plus years and billions of dollars—to generate any progress in prevention or therapy, and amid growing controversy about effectiveness of drugs like AZT to have any benefit, the HIV/AIDS hypothesis remains simply that: a theory with erratic correlation, but no proof of causality, between HIV and AIDS. I say "erratic," because of the many HIV-positive cases with no AIDS and of the many AIDS cases with no HIV (see Chapter Seven), and also because the circular definition of AIDS (no HIV = no AIDS) makes any correlation meaningless to begin with (AIDS patients without HIV are not officially listed by the CDC as having AIDS).

The collected works of Peter Duesberg is the closest thing we have—in the HIV/AIDS controversy—to a steadfast refusal to disregard uncomfortable facts. No one can know all the facts, and the science of HIV/AIDS is fractured among many disciplines so that few scholars can barely keep up with any one of them. This collection of publications, however, leaves out very little. Even so, it can only suggest the staggering amount of work the author has actually done over the years since this effort began in 1987. It is, in its depth and breadth, a magnificent effort dealing with subjects ranging from molecular biology of viruses to immunology, cell biology, and epidemiology. In this age,

when even the best of us find it impossible to keep up in our own narrowly-defined fields, the fact that he has kept a careful watch on the literature of the breadth indicated is simply astounding. Since 1987, I have watched Dr. Duesberg spend virtually every day, twelve hours each day, month after month, year after year—at first having some staff, but very soon with none—trying to make sense out of what was, and remains, a scientific enigma: the HIV/AIDS hypothesis.

In 1987 Peter Duesberg was at the top of his career and the future was promising. He was, and is now, a full professor of Molecular and Cell Biology at UC Berkeley, and a member of the National Academy of Sciences (1986). He was the recipient of a seven-year Outstanding Investigator Award Grant from the National Institutes of Health that provided him with hundreds of thousands of dollars to conduct his research on the molecular biology of viruses. His brilliance as an experimental virologist was acknowledged around the world and his prizes for leadership work are many. Now, in 1995, he has no grants from the National Institutes of Health and, therefore, his research has come to a halt. Peter Duesberg is fifty-eight years old, vibrant, capable, full of research ideas, and wants to do much more. What happened?

In 1986 and 1987, Peter was on leave from Berkeley at the National Institutes of Health in Bethesda where he was a prestigious Fogarty Scholar-in-Residence. During his sabbatical time there he had many conferences with his host, Stuart Aaronson, and with Robert Gallo, and other leaders in cancer research and virology. After all, he was himself one of the leaders in molecular biology and the time there was pleasant, provocative, and productive. He had gone there to sit in the magnificent library, to gather his thoughts on the future of virological research, and to ponder what his own contributions might be in the years ahead. One of his interests was cancer biology . . . he had isolated the first so-called cancer gene in 1970, and had worked out the genetic structure of several retroviruses. But after more than fifteen years of intensive work he had become convinced that viruses had little to do with human cancer. His conclusions were summarized in a "Perspective" article commisioned by Peter Magee, editor of the prestigious journal *Cancer Research.*

His article was published 1987 under the title "Retroviruses as Carcinogens and Pathogens: Expectations and Reality" (Chapter One). In

this review he made the case *against* retroviruses (without oncogenes) as cancer-causing agents. While we continue to hear much publicity about cancer genes, many thoughtful biologists and medical researchers agree that the war on cancer, fought mostly on molecular genetic grounds, has not been won and that the strategy needs fundamental change. But that is another story. Peter's case was a strong one and I remember discussing it with some of my own friends at the NIH who were quite surprised that someone of Peter's stature would basically declare obsolete one of the mainstream approaches to such an important disease. That paper still stands with fundamental questions about viruses as carcinogens unanswered. The most fundamental of these was: Why are cancers not contagious if they are caused by viruses? An alarmingly simple question when you think about it; perhaps too simple for a cancer establishment already fully committed to a virus hypothesis.

The last four pages of this review were devoted to HIV and its role in AIDS. It appeared to Peter that many of the same contradictions that appeared in the retrovirus/cancer hypothesis also appeared in the HIV/AIDS hypothesis. He systematically began to discuss the weaknesses in HIV as a retrovirus causing immunodeficiency. Included in his criticism back in 1987 were the following crucial points that stand against the hypothesis and that remain completely unanswered by the scientific orthodoxy in charge of AIDS research:

1. There is HIV infection and low or no risk of AIDS; therefore, something other than HIV must be involved.
2. The long latent period between infection and clinical disease is inconsistent with the short generation time of retroviruses which is only 24–48 hours and with everything known about experimental retroviral disease. AIDS remains as the only claimed retroviral disease outside of the laboratory!
3. The levels of actual HIV found in the blood of AIDS patients is too low to account for observed loss of immune function.
4. There is no animal model for AIDS.
5. HIV is not directly cytocidal; it does not kill T cells.

All of these points were then, and are now, defended by a close analysis of available data, as you will see. As the reader goes through this

collection, it will become clear how steady are these points and how they remain critical and unanswered. The last point is of special interest since, in 1995, eight years later, we find in *Nature,* arguably the leading science weekly journal in the world, the commentary that, at the same time (a) confirms Peter Duesbereg's contention (point number 5, above) that the evidence could never have supported direct viral killing; and (b) shifts the standard hypothesis around 180 degrees. The *Nature* commentary, in an article dealing with HIV, said that: ". . . an intrinsic cytopathic effect of the virus is no longer credible." (Wain-Hobson, S. *Nature,* 373: 102, 1995).

What very few people realize, including most professors of molecular biology that I know, is that this shift has occurred: that the orthodox view of HIV as a direct killer of human immune cells has been thrown out. This is a crucial issue since the experiments surrounding this new view, while they have received wide acclaim by the AIDS orthodoxy, are seen to be flawed by many other experts (see *Nature,* Scientific Correspondence 375: 193–198, 1995).

The new view is that the source of trouble is not direct killing by HIV but rather a cell-mediated killing of HIV-infected cells by the immune system itself (Wei, *et al.,* and Ho, *et al. Nature* 373: 117–126, 1995). This turn-around was necessitated by the fact that Duesberg's third point (above) was also true. How could HIV kill so many T cells if one could not detect significant numbers of free HIV in a patient's blood? This question has remained unanswered until these recent reports. Using new amplification methods to detect HIV, Wei and Ho conclude that, indeed, free virus is found after all. However, as Duesberg and Bialy, have pointed out (see Chapter Twelve), the new method (PCR) does not measure free virus but only highly amplified amounts of viral RNA. This method amplifies an original HIV-RNA signal by many thousand times so that error becomes a major problem in quantitation. That is, it is extremely difficult to know with any precision exactly what the level of starting material might have been. It is one of the problems in HIV/AIDS and other disease research that highly sophisticated molecular measurements are used as surrogate markers for infectious virus units, the only significant units in biological measurements of this kind.

Kary Mullis, the inventor of PCR, takes a dim view of using PCR

in the above manner indicating that it is a very poor substitute for identifying "live" virus (replicating virus) in the blood of an AIDS patient. Most people, including most biologists, do not know that it is almost impossible to isolate live virus from AIDS patients; a crucial point that Duesberg has been making for almost ten years.

A careful reading of Dr. Duesberg's criticisms, and the papers themselves, reveals that when one establishes standards to convert PCR results to actual viral numbers, those numbers reflect the same old low levels of infectious HIV (Duesberg and Bialy, see above). That is, there are still no valid measurements that lead one to the conclusion that AIDS patients have high levels even of infectious HIV. But let us suppose the PCR studies are correct and that AIDS patients actually harbor high levels of infectious HIV and that a war of attrition against the immune system, after ten years, finally takes its toll. But it is precisely because of the fact of latency—Duesberg's second point, above—that such a war is so unlikely. With the high (PCR) viral numbers reported (100,000 HIV per ml blood) every cell in the body would soon be infected. But with this level of infection it becomes impossible to explain the lag period; such an infected person would surely be dead within days or weeks if HIV truly caused AIDS. This is just one of many contradictions present in the latest claims from *Nature* that the critics of the HIV hypothesis have finally been silenced. In fact, the editor of *Nature* has, in a flagrant act of censorship, called for Peter Duesberg to quit his role as critic, and he has stealthily used his power as editor to enforce Duesberg's silence in the journal ("Has Duesberg a right of reply?," *Nature* 363: 109, 1993)

This new research, together with its contradictions and false claims, are just surfacing as the Duesberg collection goes to press. But the reader will get some accurate sense of the state of confusion generated by this research from the recent "Scientific Correspondence" in *Nature* (375: 193–198, 1995) and from a full discussion of the HIV numbers game by Duesberg and Bialy in *Genetica* (Supplement, in press,1995), reprinted in Chapter Twelve in this volume.

This change of purported mechanism of AIDS causality is just the latest example of flip-flopping by the HIV/AIDS research orthodoxy where the emphasis on direct HIV killing needs to be modified in order to accommodate the reality of AIDS natural history. The other most

recent "shift" in emphasis involved discarding what was the earliest and most telling characteristic of AIDS, Kaposi's sarcoma. Kaposi's sarcoma is no longer considered to be caused by HIV (see Chapter Ten). But very few people take note. Few have the time to follow even the highlights of this enormous literature. Of course, we also are reminded by Dr. Duesberg that the definition of AIDS is completely circular and makes a mockery of its scientific pursuit. If you had Kaposi's sarcoma, or any other AIDS disease, but no HIV, then you would not receive a diagnosis of AIDS. You would simply enter the hospital record book as a patient with Kaposi's sarcoma, or with whatever other disease you actually had. No HIV, no AIDS . . . very simple, but also impossibly irrational since causality is built into the definition

The first paper in this collection begins with a quotation from Sherlock Holmes: "How often have I said to you, that when you have eliminated the impossible, whatever is left, however improbable, must be the truth."

What is left, for many of us, is the clear truth that after more than a decade of intensive research and billions of dollars spent, we have not moved the HIV/AIDS hypothesis from the realm of correlation to the realm of causality. At best, what we have is circumstantial evidence for a theory born under most unfavorable circumstances. We also have, as Peter Duesberg shows us, strong conflict between the HIV hypothesis and reality. The truth is that we really still do not know what causes the immunodeficiency behind AIDS. In view of this, Duesberg has proposed that recreational drugs and AZT cause AIDS. Although the HIV establishment gives him full credit for "the drugs hypothesis," the fact is that such a hypothesis is nothing new. It was, in fact, the first AIDS hypothesis formulated by the CDC. In the early days, many independent investigators called it the "lifestyle" hypothesis. If it were not for Peter Duesberg, and a few others, with the rush to judgment about HIV causality, even this much of the truth would be hidden from us.

What should we do with the information he has given us? AIDS research focuses almost entirely on HIV. For any other disease of this importance, and with an analysis like the one before us in this collection, we would immediately begin to diversify our research portfolio and begin to include lines of inquiry into the vast number of possible

causes of immunosupression in addition to HIV that we know about. This is what we should do now.

What should we do about what has been called the "Duesberg phenomenon" (Chapter Ten)? With him we have a wise and dedicated analyst and critic of one of the most important developments to come onto the public health scene in over fifty years. If he is correct—or even partially correct—he will have already provided us with invaluable alternative rationale and directions. He has done what *Nature* editor John Maddox once recommended, and he has lost his research grants and with them, the power to do the kind of work that needs doing. Maddox said,

> Is there a danger, in molecular biology, that the accumulation of data will get so far ahead of its assimilation into a conceptual framework that the data will eventually prove an encumbrance? Part of the trouble is that excitement of the chase [for molecular answers] leaves little time for reflection. And there are grants for producing data, but hardly any for standing back in contemplation. *Nature* 333: 11, 1988.

Peter Duesberg *has* stood back in contemplation and concludes that AIDS has been forced into a monolithic pattern of viral causality. The physicist Freeman Dyson recently argued in the *New York Review of Books,* May 25, 1995, that: "Science flourishes best when it uses freely all the tools at hand, unconstrained by preconceived notions of what science ought to be."

Peter Duesberg argues against a preconceived viral causality, and for pluralism in the science of AIDS. The argument that AIDS research is already a wide-spectrum effort is specious. Of course, funded projects range over a wide variety of disciplines; but all disciplines focus on a single idea—HIV. The expectation is that the more the better, and that sooner or later the details will make the preconceived picture clear. Peter Duesberg argues that we need a new picture, or several pictures. His own alternative view that drugs, and not HIV, cause AIDS, is one of many reasonable possibilities not considered by our present monolithic research establishment centered on a "virus only" approach. Peter Duesberg should be given a medal and a large grant simply to continue this invaluable service of critic-at-large. Instead, he is ignored and discredited by the mainstream scientific community, including Maddox himself (Chapter Twelve).

This collection of scientific analyses of the HIV/AIDS hypothesis will provide the reader with a basis for judgment about this most important public health issue and about the appropriateness of its current research strategy. It will also provide an essential background for an understanding of the ways in which science goes wrong in dealing with internal controversy. There used to be a place for criticism of mainstream thinking, especially from old hands like Peter Duesberg who were recipients of NIH Outstanding Investigator awards that are supposed to encourage "innovative" thinking. It is suggested that it is simply a fantasy to think that open criticism is welcomed within scientific inner circles; for example do not *Nature* and *Science* continue to run articles and scientific correspondence on the HIV/AIDS and other controversial issues? The answer, is of course, that yes, they do. But with HIV/AIDS, any reading of these major scientific journals reveals a deep-seated reluctance to engage in an evenhanded exchange (see Chapters Ten and Twelve). What is also revealed is that dissent within the accepted paradigm *is* allowed; but woe to those who question too deeply and with steadfast commitment the scientific basis of that paradigm. In January 1995, *Nature*'s editor, two years after calling for Peter Duesberg to cease and desist, thought (wrongly) that the HIV/AIDS question had been settled in favor of the HIV hypothesis (the Wei and Ho papers mentioned above) and he confidently reversed himself and publicly requested a scientific response from Duesberg. That response was promptly prepared and offered (see Chapter Twelve) but, as mentioned above, was rejected. Apparently, it was, at 2,000 words, too long and raised too many fundamental questions. As the leading critic, Duesberg was instead offered 500 words with which to mount a critical evaluation of highly technical research results presumably of decisive importance in settling an issue of great scientific and human importance.

Critics in a free society that cares, especially about the existence of an unfettered science, deserve better treatment. We all suffer when they are treated in such a shabby manner.

Richard C. Strohman
UC Berkeley
May 1995

Chapter One

Retroviruses as Carcinogens and Pathogens: Expectations and Reality[1]

Cancer Research, Vol. 47, pp. 1199-1220,
(Perspectives in Cancer Research), March 1, 1987.

Abstract

Retroviruses (without transforming genes) are thought to cause leukemias and other cancers in animals and humans because they were originally isolated from those diseases and because experimental infections of newborns may induce leukemias with probabilities of 0 to 90%. According to this hypothesis viral cancers should be contagious, polyclonal, and preventable by immunization. However, retroviruses are rather widespread in healthy animals and humans where they typically cause latent infections and antiviral immunity. The leukemia risk of such infections is less than 0.1% and thus about as low as that of virus-free controls. Indeed retroviruses are not sufficient to initiate transformation (*a*) because of the low percentage of symptomatic virus carriers and the complete lack of transforming function *in vitro*; (*b*) because of the striking discrepancies between the long latent periods of 0.5 to 10 years for carcinogenesis and the short eclipse of days to weeks for virus replication and direct pathogenic and immunogenic effects; (*c*) because there is no gene with a late transforming function, since all genes are essential for replication; (*d*) because host genes, which do not inhibit virus, inhibit tumorigenesis up to 100% if intact and determine the nature of the tumor if defective; and above all (*e*) because of the monoclonal ori-

1. Supported by (OIG) National Cancer Institute Grant CA-39915A-01 and Council for Tobacco Research Grant 1547 and by a scholarship in residence of the Fogarty International Center, NIH, Bethesda, MD.

gin of viral leukemias, defined by viral integration sites that are different in each tumor. On these bases the probability that a virus-infected cell will become transformed is estimated to be about 10^{-11}. The viruses are also not necessary to maintain transformation, since many animal and all bovine and human tumors do not express viral antigens or RNA or contain only incomplete proviruses. Thus as carcinogens retroviruses do not necessarily fulfill Koch's first postulate and do not or only very rarely (10^{-11}) fulfill the third. Therefore it has been proposed that retroviruses transform inefficiently by activating latent cellular oncogenes by, for example, provirus integration. This predicts diploid tumors with great diversity, because integration sites are different in each tumor. However, the uniformity of different viral and even nonviral tumors of the same lineage, their common susceptibility to the same tumor resistance genes, and transformation-specific chromosome abnormalities shared with nonviral tumors each argue for cellular transforming genes. Indeed clonal chromosome abnormalities are the only known transformation-specific determinants of viral tumors. Since tumors originate with these abnormalities, these or associated events, rather than preexisting viruses, must initiate transformation. Therefore it is proposed that transformation is a virus-independent event and that clonal viral integration sites are consequences of clonal proliferation of transformed cells. The role of the virus in carcinogenesis is limited to the induction of hyperplasia which is necessary but not sufficient for carcinogenesis. Hyperplasia depends on chronic viremia or high virus expression which are very rare in animals outside the laboratory and have never been observed in humans. Since latent viruses, which are typical of nearly all natural infections, are neither direct nor indirect carcinogens, they are not targets for cancer prevention. Viruses are also not targets for cancer therapy, since tumors are not maintained and not directly initiated by viral genes and occur naturally despite active antiviral immunity.

Lymphotropic retrovirus has been proposed to cause AIDS because 90% of the patients have antibody to the virus. Therefore antibody to the virus is used to diagnose AIDS and those at risk for AIDS. The virus has also been suggested as a cause of diseases of the lung and the nervous system. Promiscuous male homosexuals and recipients of frequent transfusions are at a high risk for infection and also at a relatively

high annual risk for AIDS, which averages 0.3% and may reach 5%. Others are at a low risk for infection and if infected are at no risk for AIDS. AIDS viruses are thought to kill T-cells, although these viruses depend on mitosis for replication and do not lyse cells in asymptomatic infections. Indeed the virus is not sufficient to cause AIDS (*a*) because the percentage of symptomatic carriers is low and varies between 0 and 5% with the risk group of the carrier, suggesting a cofactor or another cause; (*b*) because the latent period for AIDS is 5 years compared to an eclipse of only days to weeks for replication and direct pathogenic and immunogenic effects; and (*c*) because there is no gene with a late AIDS function, since all viral genes are essential for replication. Moreover the extremely low levels of virus expression and infiltration cast doubt on whether the virus is even necessary to cause AIDS or any of the other diseases with which it is associated. Typically, proviral DNA is detectable in only 15% of AIDS patients and then only in 1 of 10^2 to 10^3 lymphocytes and is expressed in only 1 of 10^4 to 10^5 lymphocytes. Thus the virus is inactive or latent in carriers with and without AIDS. It is for this reason that it is not transmitted as a cell-free agent. By contrast, all other viruses are expressed at high titers when they function as pathogens. Therefore AIDS virus could be just the most common occupational infection of those at risk for AIDS because retroviruses are not cytocidal and unlike most viruses persist as latent, nonpathogenic infections. As such the virus is an indicator of sera that may cause AIDS. Vaccination is not likely to benefit virus carriers, because nearly all have active antiviral immunity.

Introduction

> How often have I said to you, that when you have eliminated the impossible, whatever remains however improbable must be the truth.
>
> —Sherlock Holmes

The irreversible and predictable courses of most cancers indicate that cancer has a genetic basis. In 1914 Boveri (1) proposed that cancer is caused by chromosomal mutations. This hypothesis has since received ample support (2–4), although a cellular cancer gene has yet to be iden-

tified (5). In the light of the spectacular discovery of RSV[2] in 1911, which proved to be a direct, infectious carcinogen, the hypothesis emerged that viruses may be a significant source of exogenous cancer genes (6). The virus-cancer hypothesis has since steadily gained support because retroviruses and DNA viruses were frequently isolated from animal leukemias and other tumors, and occasionally from human leukemias, in efforts to identify causative agents (7–16). However, once discovered in tumors and named tumor viruses, most of these viruses were subsequently found to be widespread in healthy animals and humans (8, 12–18). Thus these viruses are compatible with the first but apparently not necessarily with the third of Koch's postulates[3] as viral carcinogens. Only a few of the many tumor viruses are indeed directly oncogenic, such as RSV and about 20 other types of retroviruses (5, 13, 19, 20), and hence compatible with Koch's third postulate. Therefore, if we want to assess the role of viruses in cancer, there must be a clear separation between those viruses which are directly oncogenic and those which are not.

The directly oncogenic retroviruses owe their transforming function to a particular class of genes which are termed *onc* genes (20). These are as yet the only known autonomous cancer genes that can transform diploid cells *in vitro* as well as in animals susceptible to the particular virus (5). Since susceptible cells are inevitably transformed as soon as they are infected, the resulting tumors are polyclonal (13, 16). Nevertheless, directly oncogenic retroviruses have never caused epidemics of cancer. The probable reason is that *onc* genes are not essential for survival of the virus and hence are readily lost by spontaneous deletion or

2. The abbreviations used are: RSV, Rous sarcoma virus: AIDS, acquired immunodeficiency syndrome; HTLV-I, human T-cell leukemia virus; MMTV, mouse mammary tumor virus; ATLV, adult T-cell leukemia virus; STLV-III, simian T-cell leukemia virus; ATL, adult T-cell leukemia; MCF, mink cell focusforming; HIV, human immunodeficiency virus; ARV, AIDS-associated retrovirus.
3. Koch's postulates define the steps required to establish a microorganism as the cause of a disease: (a) it must be found in all cases of the disease; (b) it must be isolated from the host and grown in pure culture; (c) it must reproduce the original disease when introduced into a susceptible host; and (d) it must be found present in the experimental host so infected.

mutation (5). Indeed, *onc* genes were originally discovered by the analysis of spontaneous *onc* deletion mutants of RSV (21). Moreover, because *onc* genes typically replace essential genes (except in some strains of RSV) these viruses cannot replicate unless aided by a nondefective helper virus (5, 13).

The vast majority of the tumor viruses are retroviruses and DNA viruses that do not contain *onc* genes. The RNA genomes of all retroviruses without *onc* genes measure only 8 to 9 kilobases (13, 22). They all encode three major essential genes which virtually exhaust their coding capacity. These are in the 5' to 3' map order *gag* which encodes the viral core protein, *pol* which encodes the reverse transcriptase, and *env* which encodes the envelope glycoprotein (23, 24). Although these viruses lack *onc* genes they are considered tumor viruses, because they were originally isolated from tumors and because experimental infections may induce tumors under certain conditions. However, in contrast to tumors caused by viruses with *onc* genes, such tumors are always monoclonal and induced reproducibly only in genetically selected animals inoculated as newborns after latent periods of over 6 months (see below). Because of the long latent periods, these retroviruses are said to be "slow" viruses (13, 16), although their mechanism of replication is exactly the same as that of their fast and efficient relatives with *onc* genes that transform cells as soon as they infect them (5, 19) (Table 1). The retroviruses are also considered to be plausible natural carcinogens because they are not cytocidal and hence compatible with neoplastic growth and other slow diseases. Indeed, retroviruses are the only viruses that depend on mitosis for replication (13, 25).

However, the retroviruses without *onc* genes are also the most common and benign passenger viruses of healthy animals and humans probably because of their unique noncytocidal mechanism of replication and their characteristic ability to coexist with their hosts without causing any pathogenic symptoms either as latent infections, which make no biochemical demands, or even as productive infections. Based on the permissiveness of a host for expression and reproduction, they have been divided into exogenous viruses which are typically expressed and hence potentially pathogenic and endogenous viruses which are typically latent and hence nonpathogenic (16–18). Because they are so read-

ily suppressed in response to as yet undefined cellular suppressors (8, 11, 12, 16–18), endogenous viruses are integrated as proviruses into the germ line of most if not all vertebrates (8, 13, 16–18). Nevertheless, the endogenous and exogenous retroviruses are entirely isogenic and there is no absolute biochemical or functional distinction between them except for their response to suppressors of a particular host (13, 16–18) (Part I, Section A). Therefore the association of these viruses with a given disease is not sufficient even to suggest a causative role in it. Indeed there is as yet no direct evidence that retroviruses play a role as natural carcinogens of wild animals and humans. Thus the critical expectations of the virus-cancer hypothesis, namely that RNA or DNA tumor viruses would be direct carcinogens, that viral tumors would be polyclonal because each virus-infected cell would be transformed, and above all that viral carcinogenesis would be preventable by immunization, remain largely unconfirmed.

Recently retroviruses without *onc* genes have been isolated from patients with AIDS and those at risk for AIDS and have since been considered the cause of AIDS (26). In contrast to other retroviruses, the AIDS viruses are thought to act as direct, cytocidal pathogens that kill susceptible T-cells (13, 27).

Here we discuss how the retroviruses without *onc* genes fit the role of viral carcinogens or AIDS pathogens and whether these viruses are indeed the vessels of evil they have been labeled to be. Above all we hope to identify transformation-specific or AIDS-specific viral and cellular determinants and functions. Since the genetic repertoire of all retroviruses without *onc* genes, including that of the AIDS viruses (28), is exhausted by genes that are essential for virus replication (13, 24), a hypothetical oncogenic or AIDS function would have to be indirect or it would have to be encoded by one of the essential genes. In the second case the virus would be oncogenic or cause AIDS whenever it replicates. A survey of the best studied animal and human retroviruses demonstrates that these viruses are not sufficient to cause tumors and not necessary to maintain them. Most likely these viruses play a role in inducing tumors indirectly. Indeed transformation appears to be a virus-independent, cellular event for which chromosome abnormalities are the only specific markers. Likewise the AIDS viruses are shown

not to be sufficient to cause AIDS, and the evidence that they are necessary to cause it is debated.

I. Retroviruses and Cancer

A. Retroviruses Are Not Sufficient for Transformation Because Less Than 0.1% of Infected Animals or Humans Develop Tumors

Avian lymphomatosis virus was originally isolated from leukemic chickens (29). However, subsequent studies proved that latent infection by avian lymphomatosis viruses occurs in all chicken flocks and that by sexual maturity most birds are infected (30–32). Statistics report an annual incidence of 2 to 3% lymphomatoses in some inbred flocks. Yet these statistics include the more common lymphomas caused by Marek's virus (a herpes virus) (33, 34). The apparent paradox that the same virus is present in most normal and healthy animals (30) but may be leukemogenic in certain conditions was resolved at least in descriptive terms by experimental and congenital contact infections. Typically experimental or contact infection of newborn animals that are not protected by maternal antibody would induce chronic (31, 32) or temporal (35, 36) viremia. The probability of such animals for subsequent lymphomatosis ranges from 0 to 90% depending on tumor resistance genes (Section C). However, infection of immunocompetent adults or of newborn animals protected by maternal antibody and later by active immunity would induce latent, persistent infections with a very low risk of less than 1% for lymphomatosis (32).[4] Thus only viremic animals are likely to develop leukemia at a predictable risk.

Viremia has a fast proliferative effect on hemopoietic cells and generates lymphoblast hyperplasia (Fig. 1) (32, 36, 37). Hyperplasia appears to be necessary but not sufficient for later leukemogenesis because it does not lead to leukemia in tumor-resistant birds (36) (Section C) and because removal of the bursa of Fabricius, the major site of lymphoproliferation, prevents development of the disease (9, 32).

The murine leukemia viruses were also originally isolated from leukemic inbred mice (9) and subsequently detected as latent infections

4. Rubin, personal communication.

in most healthy mice (8, 13, 16, 17, 38). Indeed, about 0.5% of the DNA of a normal mouse is estimated to be proviral DNA of endogenous retroviruses, corresponding to 500 proviral equivalents per cell (18). Nevertheless leukemia in feral mice is apparently very rare. For instance low virus expression, but not a single leukemia, was recorded in 20% of wild mice (38) probably because wild mice restrict virus expression and thus never become viremic and leukemic. However, in an inbred stock of feral mice predisposed to lymphoma and paralysis, 90% were viremic from an early age, of which 5% developed lymphomas at about 18 months (39).

Experimental infections of newborn, inbred mice with appropriate strains of murine leukemia viruses induce chronic viremias. Such viremic mice develop leukemias with probabilities of 0 to 90% depending on the mouse strain (Section C). However, if mice that are susceptible to leukemogenesis are infected by the time they are immunocompetent or are protected by maternal antibodies if infected as neonates, no chronic viremia and essentially no leukemia are observed (although a latent infection is established) (41). Thus leukemogenesis depends on viremia (40) as with the avian system. However, viremia is not sufficient, because certain tumor-resistant strains do not develop leukemia even in the presence of viremia (42) (Section C). Again viremia has an early proliferative effect on lymphocytes which has been exploited to quantitate these viruses *in vivo* within 2 weeks by the "spleen-weight" or "spleen-colony" assay (18, 43–47). This hyperplasia of lymphocytes is necessary for leukemogenesis, because the risk that an infected animal will develop leukemia is drastically reduced or eliminated by thymectomy, which is a major source of cells for prospective leukemogenesis (9).

The AKR mouse is a special example in which spontaneous expression of endogenous virus and the absence of tumor resistance genes inevitably lead to viremia at a few weeks after birth and, in 90% of the animals, to leukemia at 6 to 12 months of age (9, 41, 48). This also shows that endogenous viruses can be just as pathogenic or leukemogenic as exogenous viruses if they are expressed at a high level. Likewise, endogenous avian retroviruses are leukemogemic in chickens permissive for acute infection (49, 50).

The evidence that mammary carcinomas are transmissible by a milk-

borne virus, MMTV, indicates that the virus is an etiological factor (51, 52). However, the same virus is also endogenous but not expressed in most healthy mice (16, 53). Since no mammary tumors have been reported in wild mice the natural incidence must be very low, but in mice bred for high incidence of mammary carcinomas it may rise to 90% (13, 16, 54, 55). As with the leukemia viruses, the risk for tumorigenesis was shown to depend on a high level of virus expression from an early age and on the development of hyperplasias that are necessary but not sufficient for carcinogenesis (56, 57). For example, BALB/c mice that express over 100 μg virus per ml milk all develop tumors after latencies of over 12 months, but mice that express 3 μg or less virus per ml develop no tumors at all (54, 58).

Feline leukemia virus was originally isolated from cats with lymphosarcoma (59) and subsequently from many healthy cats. It is estimated that at least 50 to 60% of all cats become naturally infected by feline leukemia viruses at some time during their lives (60, 61). However, only about 0.04% of all cats develop leukemia on an annual basis (62), which is thought to be caused by these viruses (13, 61, 63). Most natural infections cause transient virus expression which is followed by an immune response, after which little virus is expressed (60, 64, 65). Such infections do not induce leukemias at a predictable rate (61). However, 1 to 2% of the naturally infected cats become chronically viremic (66). About 28% of the viremic cats develop leukemias after latent periods of 2 years. Thus viremia indicates a high risk for the development of leukemia (66). Viremia may result from a congenital infection in the absence of maternal antibody or from a native immunodeficiency. As in the avian and murine systems, experimental infection of newborn, immunotolerant cats produces early viremia and runting diseases and late leukemias at a much higher incidence than natural infections (63, 64, 67, 68). The gibbon ape leukemia virus was also initially discovered in leukemic apes and was later isolated from healthy gibbons (13, 69). Again, only chronically viremic gibbons were shown to be at risk for leukemia (70).

The bovine and human retroviruses associated with acute leukemias are always biochemically inactive or latent (Section D). Viremia, which is frequently associated with a leukemia of congenitally or experimentally infected domestic chickens, cats, or inbred mice, has never been

observed in the bovine or human system. Accordingly bovine and human leukemia viruses could be isolated from certain leukemic cells only after cultivation *in vitro* away from the suppressive immune system of the host (71, 72). In regions of endemic bovine leukemia virus infection 60 to 100% of all animals in a herd were found to contain antiviral antibody (73, 74). However, the incidence of leukemia was reported to range only from 0.01 to 0.4% (16, 73). Experimental infections with cell-free virus have not provided conclusive evidence for viral leukemogenesis. As yet only 1 of 25 animals infected with bovine leukemia virus has developed a leukemia 7 years after inoculation (73). Additional inoculations of 20 newborn calves did not cause a single leukemia within 5 years, although all animals developed antiviral antibody.[5] However, 50% of newborn sheep inoculated with bovine leukemia virus developed leukemia about 4 years later (75). These sheep were probably more susceptible to the bovine virus than cattle, because they would lack maternal antibody to the virus. Indeed they could have been transiently viremic, because antibody was detected only 4 months after inoculation (75).

HTLV-I or ATLV was originally isolated from a human cell line derived from a patient with T-cell leukemia (71). It replicates in T-cells (27) and also in endothelial cells (76) or fibroblasts (77). The virus was subsequently shown, using antiviral antibody for detection, to be endemic as latent, asymptomatic infections in Japan and the Caribbean (27). Since virus expression is undetectably low not only in healthy but also in leukemic virus carriers, infections must be diagnosed indirectly by antiviral antibody or biochemically by searching for latent proviral DNA (Section D). Due to the complete and consistent latency, the virus can be isolated from infected cells only after activation *in vitro* when it is no longer controlled by the host's antiviral immunity and suppressors. Therefore the virus is not naturally transmitted as a cell-free agent like other pathogenic viruses, but only congenitally, sexually, or by blood transfusion, that is, by contacts that involve exchange of infected cells (13, 27).

It is often pointed out that functional evidence for the virus cancer hypothesis is difficult to obtain in humans because experimental infection is not possible and thus Koch's third postulate cannot be tested.

5. J.M. Miller and M.S. Van der Maaten, personal communication.

However, this argument does not apply here since naturally and chronically infected, asymptomatic human carriers are abundant. Yet most infections never lead to leukemias and none have been observed to cause viremias. Moreover, not a single adult T-cell leukemia was observed in recipients of blood transfusions from virus-positive donors (13, 78, 79), although recipients developed antiviral antibody (81).

The incidence of adult T-cell leukemia among Japanese with antiviral immunity is estimated to be only 0.06% based on 339 cases of T-cell leukemia among 600,000 antibody-positive subjects (78). Other studies have detected antiviral antibody in healthy Swedish blood donors (268) and in 3.4% of 1.2×10^6 healthy Japanese blood donors (79). Further, it was reported that 0.9% of the people of Taiwan are antibody positive, but the incidence of the leukemia was not mentioned (80).

In conclusion, the tumor risk of the statistically most relevant group of retrovirus infections, namely the latent natural infections with antiviral immunity, is very low. It averages less than 0.1% in different species, as it is less than 1% in domestic chickens, undetectably low in wild mice, 0.04% in domestic cats on an annual basis, 0.01 to 0.4% in cattle, and 0.06% in humans. Thus the virus is not sufficient to cause cancer.

Moreover, since the viruses associated with all human tumors and most natural tumors of animals are latent and frequently defective (Section D), it is difficult to justify the claims that these viruses play any causative role in tumorigenesis. Indeed nearly all healthy chickens, mice, cats, cattle, and humans carry endogenous and exogenous retroviruses that are latent and hence neither pathogenic nor oncogenic (12, 16–18, 78, 82). Latent infections by cytocidal viruses, such as herpes viruses, are likewise all asymptomatic (83).

Nevertheless it may be argued that only a small percentage of retroviral infections are expected to be oncogenic because only a small percentage of all other viral or microbial infections are pathogenic. However, the low percentage of symptomatic infections with other viruses and microbes reflects the low percentage of acute infections that have overwhelmed host defense mechanisms, but not a low percentage of latent infections that cause disease. Thus there is no orthodox explanation for the claims that some murine and avian, most feline, and all bovine and human leukemias (Section D) are the work of latent viruses.

Even the view that retroviruses cause leukemia or carcinoma directly in productive infections is debatable, because indeed highly productive infections are frequently asymptomatic. For example, despite chronic acute viremias certain chickens, mice, or cats, inoculated experimentally or by contact as immunotolerant newborns, do not develop leukemia (see above and Section C). Further, no malignant transformation has ever been observed in cultured cells that are actively producing retroviruses, and the probability that an infected cell of an animal will become transformed is only 10^{-11} (Section F). This low probability that a productively infected cell will become transformed is a uniquely retrovirus-specific reason for asymptomatic infections. It is for this reason that retroviruses without *onc* gene can be asymptomatic for cancer even in acute, productive infections of animals (30, 31, 36, 42, 66, 70), although they may then cause other diseases (Section B).

Thus retrovirus infections are not only asymptomatic due to latency and low levels of virus infiltration, like all other viruses, but are also asymptomatic due to a particular discrepancy between acute and productive infection and oncogenesis. To answer the question of why some viremic animals do and others do not develop leukemia and why tumors appear so late after infection (Section B), both tumor resistance genes (Section C) and the mechanism of transformation must be considered (Section H).

B. Discrepancies between the Short Latent Period of Replication and the Long Latent Periods of Oncogenesis: Further Proof That Virus Is Not Sufficient for Cancer

Here we compare the kinetics of virus replication and direct pathogenic and immunogenic effects with the kinetics of virus-induced transformation. If retroviral genes were sufficient to induce cancer, the kinetics of carcinogenesis would closely follow the kinetics of virus replication.

Kinetics of Replication and of Early Pathogenic and Immunogenic Effects. The eclipse period of retrovirus replication has been determined to be 1 to 3 days in tissue culture (Table 1) using either transforming *onc* genes as markers or the appearance of reverse transcriptase or interference with other viruses or plaque formation for viruses without *onc* genes (13, 16) (see below). The incubation period following which retroviruses without *onc* genes induce viremia in animals is

1 to several weeks (see below). The retroviruses with *onc* genes cause cancer essentially with the same kinetics namely within 1 to several weeks (9, 13, 14, 16) (Table 1). In immunocompetent animals antiviral immunity follows infections with a lag of 2 to 8 weeks.

In animals, retroviruses without *onc* genes can be directly pathogenic if they are expressed at high titers. For instance, avian retroviruses may cause in newborn chickens diseases of polyclonal proliferative nature like osteopetrosis, angiosarcoma, hyperthyroidism (84–87), or hyperplastic follicles of B-cells in the bursa of Fabricius (36, 37) after latencies of 2 to 8 weeks. The same viruses may also cause diseases of debilitative nature such as stunting, obesity, anemia, or immunodeficiency after lag periods of 2 to 8 weeks (88, 89). Infections of newborn mice that cause viremia also cause polyclonal lymphocyte hyperplasias, splenomegaly, and immunosuppression several weeks after infection (47) (Section A). The early appearance of hyperplastic nodules in mammary tumor virus-infected animals prior to malignant transformation has also been proposed to be a virus-induced, hyperplastic effect (56, 57). Infection of newborn kittens with feline leukemia virus causes early runting effects and depletion of lymphocytes within 8 to 12 weeks (64, 67, 68) followed by persistent viremia in up to 80% of the animals (90). In experimentally infected adult animals mostly transient (85%) and only a few persistent (15%) viremias are observed (64, 68, 90). Likewise primate retroviruses such as Mason-Pfizer virus (91) or simian AIDS virus (92) or STLV-III virus (93) may cause runting, immunodepression, and mortality several weeks after inoculation if the animals do not develop antiviral immunity. These early and direct pathogenic effects of retroviruses without *onc* genes depend entirely on acute infections at high virus titers and occur only in the absence of or prior to antiviral immunity.

Retroviruses have also been observed to be directly pathogenic by mutagenesis via provirus integration of cellular genes (13, 16, 94, 95). Given about 10^6 kilobases for the eukaryotic genome and assuming random integration, a given cellular gene would be mutated in 1 of 10^6 infected cells (see Sections E and F). Therefore this mechanism of pathogenesis would play a role *in vivo* only if mutagenesis were to occur at a single or few cell stage of development (94) or if such a mutation would induce clonal proliferation, as is speculated in Section E.

Table 1. Distinction between retroviruses

	With transforming (*onc*) genes	Without *onc* genes (leukemia viruses)
Epidemiology	Only in animals with tumors.	Widespread as latent infections in healthy animals and humans. Less than 0.1% develop leukemia or other tumors.
Latent periods of		
(a) Replication	1 to 3 days in animals or humans.	1 to 3 days in animals or humans.
(b) Virus-induced polyclonal hyperplasia and pathogenicity	Not known because of *(d)*.	Several weeks.
(c) Immunity	A few weeks or *(d)*.	A few wk in immunocompetent animals or humans.
(d) Oncogenic effect	Days to a few weeks.	From 6 mo to 10 years in animals and humans. No malignant transformation in cell culture.
Tumor resistance genes	None are known that suppress viral *onc* genes.	Tumor resistance genes of avian and murine model systems can completely suppress viral, but also nonviral tumors. Evidence for cellular tumor antigens (Part I, Section C).
Viral gene expression in tumors	All transformed cells express a viral *onc* gene.	The same viral genes are expressed in transformed and normal cells. However, some transformed cells do not express viral genes, although they contain complete proviruses, and others cannot because they contain only defective proviruses. No evidence for a transformation-specific function.
Clonality of tumors	Tumors are polyclonal with regard to provirus integration site.	Tumors are monoclonal with regard to provirus integration site, but integration sites are different in each different tumor.

	With transforming (*onc*) genes	Without *onc* genes (leukemia viruses)
Probability that infected cell will become transformed	Transformation is inevitable consequence of infection in susceptible cells ($P = 1$).	Approximately 10^{-11} (Part I, Section F): the product of (*a*) the ratio of symptomatic to asymptomatic carriers. This is 10^{-3} for infections with antiviral immunity and up to 1 for viremic animals without tumor resistance genes; (*b*) 10^{-8} to 10^{-9} for the progenitor of the clonal tumor, which emerges from about 10^{8} normal or at least 10^{9} hyperplastic cells; (*c*) 10^{-1} to 10^{-2} for the generations of infected cells during the latent period.
Chromosome abnormalities of viral tumors	Initially none. Late passages develop abnormalities.	All tumors studied show clonal chromosome abnormalities which are the only transformation-specific markers of viral tumor cells (Part I, Section G). Some are shared by virus-positive and virus-free murine and by human T-cell leukemias (Part 1, Section H).
Conclusions	Virus directly initiates and maintains cancer.	Virus is not sufficient to induce and not necessary to maintain cancer. Virus induces hyperplasia of prospective tumor cells. Less than one of 10^{11} infected cells becomes transformed. Since all virus-positive and even virus-free tumors of the same lineage share chromosome abnormalities and susceptibility to tumor resistance genes, transformation is proposed to be a virus-independent event (Part 1, Section H).

Certain direct, cytopathic effects of retroviruses without *onc* genes are also detectable *in vitro* within days or weeks after infection, although malignant transformation has never been observed in cell culture. For example, the avian reticuloendotheliosis viruses fuse and kill a fraction of infected cells during the initial phase of infection (96, 97). Certain strains of avian retroviruses form plaques of dead primary chicken embryo cells in culture within 7 to 12 days post infection. This effect is probably based on cell fusion and has been used as a reliable virus assay (45, 98). The plaque assays of murine leukemia viruses on XC rat cells (99) and on mink cells (100) or of feline, bovine, and simian viruses on appropriate cells (101–104) also reflect fast cytopathic effects involving fusions of infected cells (45). Cell fusion of human lymphocytes *in vitro* is also typical of HTLV-I (105, 106) and of AIDS virus (27) (see Part II). Cells are thought to be fused *in vitro* by cross-linking through multivalent bonds between viral envelope antigens and cellular receptors, a process that requires high local concentration of virus particles (13, 16, 27, 45, 105). The fusion effect is not observed in chronic acute or latent infections of animals or humans or in chronically infected cell lines cultured *in vitro.* Therefore it appears to be predominantly a cell culture artifact, possibly resulting from interaction between virus receptors of uninfected cells with viruses budding from the surface of adjacent cells. This has been directly demonstrated by inhibition of HTLV-I-mediated fusion with antiserum from infected individuals (105). Thus as direct pathogens the retroviruses are not "slow" viruses, as they are frequently termed with regard to their presumed role in carcinogenesis. The "lentiviruses" that are considered models of slow viral pathogenesis (13), but not carcinogenesis, are no exception. Recently an ovine lentivirus known as visna or maedi virus was shown to cause rapid lymphoid interstitial pneumonia in newborn sheep, several weeks after infection (269). This study pointed out that the virus, if expressed at high titer, is directly and rapidly pathogenic. Slow disease may reflect persistent virus expression at restricted sites.

Late Oncogenesis. Since retroviruses without *onc* genes do not transform cells in culture, all measurements of the latent period of viral oncogenesis are based on studies of infected animals or humans (Table 1). Typically, the latent periods are dated from the time of virus infection

and thus are somewhat presumptuous, in that the assumption is made that tumors, if they appear, were initiated by the virus.

The latent period between experimental or congenital infection and lymphomatosis in chickens ranges from 6 months to several years (13, 16, 30, 32, 36, 107). In mice congenitally or experimentally infected with murine leukemia viruses, leukemia takes 6 to 24 months to appear (9, 39, 42, 108). The latent period of mammary carcinomagenesis in mice infected by milk-transmitted MMTV ranges from 6 to 18 months and typically requires several pregnancies of the mouse (16, 54). Longer latent periods of up to 24 months are observed in mice that do not express virus in their milk (55, 109).

The latent period between experimental infection and leukemia is 8 and 12 months in most cats, but only 2 to 3 months in some (62, 66, 90). (The early tumors may have been hyperplasias or tumors induced by feline sarcoma viruses.) The latent period estimated between natural virus infection and leukemia is estimated to be 2 to 3 years in cats that express virus and about 2 to 6 years in cats that do not express virus (63, 66, 110). By contrast, induction of antiviral immunity occurs within several weeks after infection (64, 67).

Bovine leukemia virus-associated leukemias are never seen in animals less than 2 years old and appear at a mean age of 6 years (16). The only experimental bovine lymphosarcoma on record appeared 7 years (73) and some experimental ovine leukemias appeared 4 years (75) after virus inoculation. By contrast, antibody to viral core and envelope proteins appears 4 and 9 weeks after infection (73). Experimental infection of gibbon apes generated leukemia after a latent period of 1 year compared to only 2 weeks for the appearance of antiviral immunity (16, 70).

The latent period for the development of human T-cell leukemia in HTLV-I positive cancers has been estimated at 5 to 10 years based on the lag between the onset of leukemia and the first appearance of antiviral antibodies of proviral DNA (13, 111, 112). More recently, the latent period of HTLV-I has been raised to record heights of 30 (270) and 40 years (271). By contrast, the latent period of infection and subsequent antiviral immunity was determined to be only 50 days based on seroconversion of the recipients of HTLV-I-positive blood transfusions (81).

The 5- to 40-year latencies claimed for leukemogenesis by HTLV-I

are perhaps the most bizarre efforts in linking a virus with a disease. If correct this means either that an infected T-cell becomes leukemic by the time it is 5 to 40 years old or that one of its offspring becomes leukemic in the 50th to 500th generation, assuming an average generation time of a month (176). Clearly the role of the virus in such a process, if any, must be highly indirect. Since all viral genes are essential for replication (13, 204), there is nothing new that the virus could contribute after one round of infection or 24 to 48 hours. This is specifically relevant for HTLV-I and bovine leukemia viruses which are biochemically inactive not only during the long latent period but also during the lethal period of the disease (Sections A and D).

The monumental discrepancies between the long latent periods from 6 months to 10 years for leukemogenesis compared to the short latent periods of several weeks for virus replication or direct pathogenic and immunogenic effects are unambiguous signals that the viruses are not sufficient to initiate leukemia and other tumors (Fig. 1). The viruses are fast and efficient immunogens or pathogens but are either not or are highly indirect carcinogens.

Transformation *in Vitro* by HTLV-I in 30 to 60 days? Immortalization of primary human lymphocytes infected by HTLV-I or ATLV or simian retroviruses *in vitro* has been suggested to be equivalent to leukemogenic transformation *in vivo* (13, 27, 113, 114). If correct, this would be the only example of a retrovirus without *onc* genes capable of malignant transformation *in vitro*. The assay infects about 5×10^6 primary human lymphocytes with HTLV-I. However, less than one of these cells survives the incubation period of 30 to 60 days, termed "crisis" because the resulting immortal cells are monoclonal with regard to the proviral integration site and because only 4 of 23 such experiments generate immortal cells (115). Since no virus expression is observed during the critical selection period of the immortal cell and since some immortalized cells contain only defective proviruses (115), immortalization is not a viral gene function. Further it is unlikely that the integration site of the provirus (Sections E, G, and H) is relevant to the process of immortalization, since different lines have different integration sites (115). Indeed, spontaneous transformation or immortalization of primary human lymphocytes has been reported applying this assay to simian

viruses (113). It follows that immortalization in culture of cells infected by HTLV-I is an extremely rare, perhaps spontaneous event.

There are several indications that *in vitro* immortalization and leukemic transformation are different events and that both do not depend on HTLV-I: (*a*) the latent period for immortalization is 30 to 60 days, while that of leukemogenesis is estimated to be 5 to 10 years; (*b*) *in vitro* immortalized cells are diploid (116), while all leukemic cells have chromosome abnormalities (Section G); (*c*) leukemic cells do not express virus (Section D) while immortalized cells do (115); (*d*) cells that are clonal with regard to viral integration sites are not necessarily leukemic, because normal T-lymphocytes monoclonal with regard to HTLV-I integration were observed in 13 nonleukemic Japanese carriers (112); (*e*) finally immortalized cell lines with defective viruses (115) or no viruses (113) indicate that immortalization is a virus-independent, spontaneous event. The evidence that cat, rat, and rabbit cells are immortalized, although they are presumably insusceptible to the human virus (13), endorses this view. It would appear that HTLV-I is directly involved neither in immortalization nor in transformation (Sections A, B, G, and H). Instead the assay appears to be a direct measure of cell death of human lymphocytes, due in part to HTLV-I-mediated fusion *in vitro* (105, 106), and of rare spontaneous immortalization.

C. Tumor Resistance Genes That Inhibit Tumorigenesis but not Virus Replication

If the virus were a direct and specific cause of tumorigenesis, one would expect that all individuals who are permissive for infection would also be permissive for viral tumors. However, this does not appear to be so. For example certain inbred lines of chicken like line 7 (117, 118) or line SC (35, 107) are highly susceptible to induction of lymphomatosis by avian retroviruses, whereas line 151 (32, 119, 120) is highly susceptible to induction of erythroblastosis by the same avian retroviruses. By contrast other lines like line 6 (118, 121), line FP (107), or line K28 (122) are either completely or highly resistant to these leukemias but are just as susceptible to virus infection and replication as the tumor-susceptible lines (32, 117, 118, 122, 123). Indeed, both the lymphoma-susceptible SC chickens and the resistant FP chickens develop early viremias

and hyperplastic B-cell follicles, but only 50% of the SC chickens develop lymphomas (35, 36). Lymphoma resistance is dominant, indicating that tumor suppressors are encoded (120, 124). The same genes also appear to impart resistance to Rous sarcoma (124). By contrast resistance to erythroblastosis is recessive (Section E).

Analogous tumor resistance genes have been observed in mouse strains. For instance, resistance of C57BL mice to radiation leukemia virus-induced leukemia (125) or of AKR x BALB/c mice to AKR virus-induced leukemia (40) is controlled by the *H-2D* gene, which is dominant for resistance. Inoculation of the virus into adult C57BL mice caused polyclonal B- and T-cell hyperplasia from which most animals died after 4 to 5 months. However, no leukemia was observed (47). Clearly the tumor resistance genes of the C57BL mice do not suppress virus replication but apparently proliferation of transformed cells. Likewise the *Si* and the *Fv-2* genes of mice inhibit leukemogenesis but not replication of Friend leukemia virus (13, 16, 126). The fates of DBA/2 and ST/b mice inoculated neonatally with AKR virus are another example. After expressing virus for at least 8 months (41), only ST/b mice show a high incidence (about 80%) of leukemia between 8 and 12 months of age, whereas DBA/2 mice show a lower incidence (about 30%) but only at 2 to 3 years of age.[6]

Futhermore, not a single lymphoma developed during a period of 1 year in chronically viremic CBA/N mice, inoculated as newborns with Moloney leukemia virus, signalling an absolute resistance to leukemogenesis (42, 46). By contrast, about 90% of viremic AKR mice develop leukemia (40, 48). The wide range of susceptibilities to virus-induced leukemia among different mouse strains inoculated with AKR virus, as originally observed by Gross (9), probably also reflects postinfection tumor resistance genes in addition to genes conferring resistance to virus infection and expression (16).

The over 100-fold variation (from less than 1% to 90%) in the incidence of mammary carcinomas among mice that are susceptible to the mammary tumor virus and also contain endogenous MMTVs also reflects host genetic factors that govern resistance to tumorigenesis (16,

6. F. Lilly, personal communication.

54, 55, 58, 127–129). One set of resistance genes governs virus expression, as for example the sex of the host, because almost only females secrete virus and develop tumors (13, 16). Another set governs resistance to carcinogenesis because virus-induced hyperplasia does not necessarily lead to mammary tumors (56, 57).

Resistance to tumorigenesis in animals which are permissive for virus replication indicates that tumors contain nonviral, cellular determinants or tumor antigens. Moreover defects of tumor resistance genes rather than viral genes determine tumor specificity since the nature of the tumor induced by a given virus depends on the host and not on the virus. This lends new support to the conclusion that viruses are not direct causes of tumorigenesis.

D. Tumors without Virus Expression, without Complete Viruses, or without Viruses: Proof That Virus Is Not Necessary to Maintain Transformation

If the retroviruses encode transformation-specific functions, one would expect that viral genes are continuously expressed in viral tumors. However, only 50% of virus-induced avian lymphomas express viral RNA (130). In many clonal lymphomatoses of chickens only incomplete or truncated proviruses are found. These defective proviruses lack the 5' half of the genome and hence are unable to express any viral gene (36, 50, 131, 132).

Moreover neither exogenous nor active endogenous retroviruses can be detected in some lymphomas. One rare study that investigated lymphomatosis in lymphomatosis virus-free chickens found that 10 of about 2000 (0.5%) chickens of line 7 died from lymphomas that were indistinguishable from viral lymphomas at the ages of 6 to 18 months (49, 121). Thus the incidence of lymphoma in virus-free chickens is very similar if not the same as that of chickens infected by lymphomatosis virus with antiviral immunity (less than 1%) (Section A). Since almost all chickens contain multiple endogenous retroviruses (16, 133), it may be argued that these viruses were responsible for the leukemias in animals free of exogenous virus. However, the evidence that endogenous viruses were latent in leukemic as in nonleukemic birds indicated that the endogeous retroviruses were not involved in these spontaneous lym-

phomas (121). The existence of endogenous viruses in the lymphoma-resistant chickens of line 6 supports this view (121, 133). In fact, it has been argued that endogenous viruses protect by interference against infection by exogenous variants (13, 16, 134).

A few cases of mouse T-cell lymphomas with defective leukemia viruses have also been observed (135–137). These findings indicate that murine leukemia can also be maintained without expression of retroviral genes.

Expression of mammary tumor virus appears also not necessary to maintain tumors, because no viral antigens (138) and no virus expression are detectable in many virus-positive mammary tumors (9, 52, 139) and because defective proviruses are observed in some tumors (140). Moreover, in mice which lack mammary tumor virus altogether, mammary tumors were observed that cannot be distinguished from virus-positive tumors, indicating that the virus is not necessary to initiate mouse mammary tumors (141). However, in the absence of virus expression, mammary carcinomas develop at lower incidence and after longer latent periods (9, 16, 52, 139–142).

Among virus-positive feline leukemias, some contain only defective proviruses, as in the avian system (143–145). However, about 25 to 35% of all feline leukemias are free of virus, viral antigens (67, 68, 110), and proviral DNA (143–145). This is significantly higher than the percentage of virus-free avian lymphomas. In some virus-free leukemias, the presumably lymphotropic virus is believed to be in other cells of the cat (65).

In provirus-positive natural bovine and experimental ovine leukemias expression neither of virus nor of viral RNA have been detected (75, 146). This result is at odds with the proposal, based on *in vitro* evidence, that the virus encodes a protein that activates virus transcription and expression of latent cellular transforming genes (147). In addition, the 5' half of bovine leukemia provirus is absent from 25% of bovine leukemias (146, 148). This entirely prevents expression of all viral genes. Other investigators have described that 30% of bovine leukemias are virus free (72).

The proviruses of HTLV-I associated with human T-cell leukemias are also consistently latent. For instance, no expression of viral antigens (149) and no transcription of viral RNA are observed in freshly

isolated leukemic T-cells from (5 of 6) HTLV-I positive patients with human T-cell leukemia (150, 151). Again this is incompatible with the *in vitro* evidence for a viral transcriptional activator that was proposed to activate virus expression and expression of latent cellular transforming genes (152, 153) (Section H). Moreover, about 10% of the ATLV- or HTLV-I-positive adult T-cell leukemias from Japan contain only defective viruses (77, 151,154). Since the 5' half of the viral genome was reported to be missing no viral gene expression is possible (77, 151, 155). Further, a minority of Japanese ATL patients appears to be free of ATLV, based on the serological assays that are used to detect the virus (156, 157). A recent analysis found 5 virus-free cases among 69 Japanese ATL patients, who lacked both HTLV-I provirus and antiviral immunity (158). Comparisons among T-cell leukemias in Italy found only 2 of 68 (159) or 3 of 16 (160) otherwise identical cases to be HTLV-I positive. A survey from Hungary found 2 of 326 leukemias antibody positive (161). Other studies from the United States and Italy describe HTLV-I-free T-cell leukemias that share chromosome abnormalities with viral leukemias (Section H). Thus, the ratio of nonviral to viral T-cell leukemias in humans outside Japan appears to be even higher than that of nonviral to viral feline and bovine leukemias.

Since retrovirus expression is not observed in many virus-positive leukemias and since only defective viruses are associated with some leukemias it follows that viral gene products are not necessary to maintain these leukemias. These tumors must be maintained by cellular genes (Section H). The occurrence of "viral" leukemias of chicken, mice, cats, cattle, and humans despite antiviral immunity (Section A) supports this conclusion. This conclusion is also consistent with the evidence that about 30% of the natural feline and bovine leukemias as well as many human and some avian leukemias and murine mammary carcinomas are virus free, yet these tumors cannot be distinguished from viral tumors by any criteria other than the virus (Section H).

E. Transformation Not Dependent on Specific Proviral Integration Sites

Since retroviruses without *onc* genes are not sufficient to cause tumors and do not encode transformation-specific functions (Sections A-C) but

may nevertheless induce experimental tumors (Section A), several hypothetical mechanisms of viral carcinogenesis have been proposed that each require a specific interaction with the host cell (Section H). One of these postulates that retroviruses without *onc* genes activate latent cellular cancer genes, termed proto-*onc* genes, by site-specific proviral integration (13, 16, 130, 162). The proposal is based on structural analogy with retroviral *onc* genes, which are hybrids of sequences derived from retroviruses and proto-*onc* genes (5, 19, 20). It is termed downstream promotion hypothesis (130) because the promoter of the 3' long terminal repeat from the provirus is thought to promote transcription of a proto-*onc* gene downstream.

It is consistent with this hypothesis that leukemias and other tumors from retrovirus-infected animals and humans are typically all monoclonal with regard to the integration sites of the provirus in the host chromosome. However, if one compares different monoclonal tumors of the same cell lineage, different integration sites are found in each individual tumor. This has been documented for retroviral lymphomas of chickens (37, 131, 132), mice (13, 163, 164), cats (143–145), cattle (146, 148), and humans (13, 151, 154, 155, 165) and also for mammary tumors of mice (13). It is unlikely that the mutant genes generated by provirus integrations are transforming genes, because they are not specific and not known to have transforming function upon transfection. Instead the clonal proviral integration sites of individual tumors appear to be the consequence of clonal proliferation of a single transformed cell from which the clonal tumor originated (Section G).

Relevance of Preferred Integration Regions. Although the search for specific proviral integration sites in viral tumors has met with no success, preferred integration regions were observed in three systems, namely in erythroblastoses and lymphomas of chicken strains predisposed to these tumors and in mammary tumors of mice bred for susceptibility to this tumor (13, 16). For instance, in erythroblastosis-prone 15I chickens that suffer 80% erythroblastosis upon infection (120), integration upstream of proto-*erb* was observed in 90% (119) and 45% (120, 122) of erythroblastoses. Proto-*erb* is a proto-*onc* gene because it is the cellular progenitor of the transforming gene of avian erythroblastosis virus (13, 19). This region-specific integration appears to activate proto-*erb* transcription compared to certain normal controls (119). However,

there are as yet no data on activation of proto-*erb* translation in leukemic cells. Unexpectedly 45% of the erythroblastoses observed in 15I chickens contained viruses with transduced proto-*erb* (122). The outstanding yield of proto-*erb* transductions in this line of chicken compared to others (5, 19) (Section H) suggests an altered proto-*erb* gene, perhaps already flanked by defective proviral elements which would permit transduction via homologous recombination. It is consistent with this view that in 15I chickens susceptibility to erythroblastosis is dominant (120), while typically resistance to tumors is dominant in chickens and mice (Section C).

Further in about 85% of the viral lymphomas of lymphomaprone chicken lines (Section C) transcription of the proto-*myc* gene is activated compared to certain controls (130). Proto-*myc* is a proto-*onc* gene because it is the cellular progenitor of the transforming genes of four avian carcinomas viruses, MC29, MH2, CMII, and OK10 (5, 13, 19). Transcriptional *myc* activation ranges from 300- to 500-fold in some lymphoma lines (RP) to 30- to 100-fold in most primary lymphomas (85%) down to undetectable levels in a few (6%) primary lymphomas (130). However, the activation of proto-*myc* translation, compared to normal fibroblasts, was estimated as only 7-fold in one RP lymphoma line and even lower in three other lines (166). Assuming that the same ratios of transcriptional to translational activation apply to all lymphomas, activation of *myc* translation would be only 1- to 2-fold in most lymphomas, hardly enough to explain carcinogenesis. In 5 to 15% of the lymphomas there is no detectable transcriptional activation of proto-*myc* and the retroviruses appear to be integrated outside of and in random orientation relative to the proto-*myc* genes (50, 105, 130, 132, 167, 168, 169).

Thus, in lymphomas, proto-*myc* transcription is frequently but not always activated whereas proto-*myc* translation appears to be barely, if at all activated. It is not known whether translation of proto-*erb* is activated in viral erythroblastoses. By contrast viral *myc* and *erb* genes are efficiently translated in all virus-transformed cells (5, 13, 16, 19, 20). Moreover in contrast to the hypothetical lymphoma specificity of activated proto-*myc,* viral *myc* genes typically cause carcinomas and viral *erb* genes cause sarcomas in addition to erythroblastosis (5, 13).

Integration of mostly intact murine leukemia viruses into or upstream of proto-*myc* is also observed in mouse and rat lymphomas. But since

it occurs only in 10 (170, 171) to 65% (172) of the cases analyzed, it is not necessary for lymphomagenesis. Moreover provirus integration near murine proto-*myc* is also not sufficient for leukemogenesis. Virus integrated near proto-*myc* was found in 15% of the hyperplastic thymus colonies of AKR mice that appeared 35 days after infection with MCF virus. These colonies were not tumorigenic (172). However, more malignant lymphomas develop from cells with provirus integrated near *myc* than from other cells, because in 65% of the lymphomas virus was integrated in proto-*myc*.

There are also preferred regions of provirus integration for MMTV in carcinomas of mice, termed *int*-1 in C3H mice and *int*-2 in BR6 mice (13, 16). The *int* loci or genes are considered to be proto-*onc* genes only because they are preferred MMTV integration sites. They have not been progenitors of viral *onc* genes and there is no direct evidence that they can be activated to cellular cancer genes. Moreover transcriptional activation of *int* is observed only in some tumors (173) and there is no evidence for viral-*int* hybrid mRNAs (140). It is also not known whether the *int* loci are coding. The two *int* loci are totally unrelated to each other and map on different chromosomes (174). Integration within the *int* regions is neither site nor orientation specific with regard to the *int* loci (13). Integration at *int* loci is also not necessary for carcinogenesis, because integration in *int*-1 is found in only a fraction (20 of 26) of C3H tumors (173) and in *int*-2 only in a fraction (22 of 45) of BR6 tumors (140). Further integration in *int*-1 was found in benign hyperplastic nodules that did not become malignant, proving that it is also not sufficient for carcinogenesis (56, 57).

The hypothesis that region-specific integration generates hybrid transforming genes that are equivalent to viral *onc* genes is inadequate on several counts. (*a*) Region-specific integration is not necessary for transformation, because in most systems (human, bovine, feline) it is not observed and in all others it is not obligatory. (*b*) It is also not sufficient for carcinogenesis based on the particular cases of clonal murine leukemia virus integration into proto-*myc* that did not cause leukemia (172), clonal MMTV integration into *int*-1 that did not cause mammary carcinomas (56, 57), and monoclonal HTLV-I infections that did not cause T-cell leukemia (112). The nonleukemic proto-*myc* integration is incompatible with the model purporting that activated proto-*myc* is like

the inevitably transforming viral *myc* genes (5). (c) The prediction that native proviral-cell DNA hybrids have transforming function, like the related retroviral *onc* gene models, is unconfirmed. Attempts to demonstrate transforming function of proviral-proto-*myc* hybrids from chicken lymphomas were negative but led to a DNA with transforming function termed B-lym (13, 175). A plausible reason is that the *myc* RNAs initiated from upstream viral promoters are poor mRNAs because they start with intron sequences that are not part of normal mRNA and cannot be spliced out, since there is no splice donor downstream of the 3' viral long terminal repeat (Section H). (*d*) The prediction that the probability of all infected cells to become transformed should be the same as that of region-specific integration is also unconfirmed on the basis of the following calculations (5). The proto-*myc, -erb,* or *int* regions that are preferential proviral landing sites in viral tumors measure about 2 and 40 kilobases, respectively (13). Since the chicken chromosome contains about 1×10^6 kilobases and the mouse chromosome contains about 3×10^6 kilobases, and since provirus integration is random (13, 16), about 2 in 10^6 or 1 in 10^5 infections should generate a tumor cell, if region-specific integration were the mechanism of carcinogenesis. Yet the probability that an infected cell will initiate a monoclonal tumor is only about 10^{-11} (Section F). In addition, the latent period of tumorigenesis would be expected to be short because there are at least 10^8 target cells of the respective lineages and many more viruses to infect them (Section F). Moreover, given the long latent periods of carcinogenesis, polyclonal rather than monoclonal tumors would be expected from integrational carcinogenesis. It may be argued that this discrepancy reflects the work of tumor resistance genes. However, post infection resistance genes that suppress tumor formation by the viral derivatives of proto-*myc* or *erb,* like MC29 or avian erythroblastosis virus, have never been observed *in vivo* or *in vitro.* Clearly, since tumor resistance genes do not function *in vitro* it would be expected that at least 2 of 10^6 cells infected *in vitro* would be transformed by activation of proto-*myc* and 2 by activation of proto-*erb.* However, no transformation by leukemia viruses has ever been observed *in vitro* (Section B).

In view of this, it is more likely that region-specific integration may provide proliferative advantages to hyperplastic cells or may initiate hyperplasia by activating or inactivating growth control genes rather

than being the cause of malignancy. This proposal predicts that integration into proto-*myc* and proto-*erb* precedes tumorigenesis (Fig. 1).

It is consistent with this proposal that murine leukemia virus integration into proto-*myc* (172) and MMTV integration into *int*-1 (56, 57) occur prior to carcinogenesis and thus are not sufficient for carcinogenesis. This proposal predicts also that the chicken lines that are susceptible to lymphoma or erythroblastosis lack genes that check hyperplasia of lymphocytes or erythroblasts. It is consistent with this view that the same retroviruses cause either lymphomatosis or erythroblastosis or no tumors in different chicken lines. The exclusive (but not absolute) usage of only one of two different *int* loci by MMTV, namely *int*-1 in carcinomas of C3H mice and *int*-2 in BR6 mice, is also more likely to reflect strain-specific activation or inactivation of proliferative controls than two entirely different transforming genes that would nevertheless generate indistinguishable carcinomas.

F. The Probability that a Virus-Infected Cell Will Become Transformed is Only 10^{-11}

To calculate the probability that a retrovirus-infected cell will become transformed, we must consider the ratio of symptomatic to asymptomatic carriers, the clonality of the viral tumors, and the long latent periods of oncogenesis. (*a*) The ratio of symptomatic to asymptomatic carriers with latent infections and antiviral immunity averages less than 10^{-3} (Section A), but that of viremic animals susceptible to transformation may reach 0.9 (Section C). (*b*) Since monoclonal tumors emerge from at least 10^8 B- or T-cells (176), the probability of an infected cell in an animal to become the progenitor of a clonal leukemia is only about 10^{-8}. This calculation assumes that all of these cells are infected. This is certainly true for the mice that carry AKR virus, radiation leukemia virus (82), or inducible mammary tumor virus (75, 142) in their germ line, and is probably the case in congenitally infected viremic chickens, cats, gibbons, and mice (12, 16, 31, 39, 63, 66, 70). In fact in viremic animals, the hyperplastic effect of the virus would have enhanced the number of prospective tumor cells to at least 10^9 (Sections A and B). Even if only a fraction of susceptible cells are infected in animals or humans with latent infections and antiviral immunity, the number of

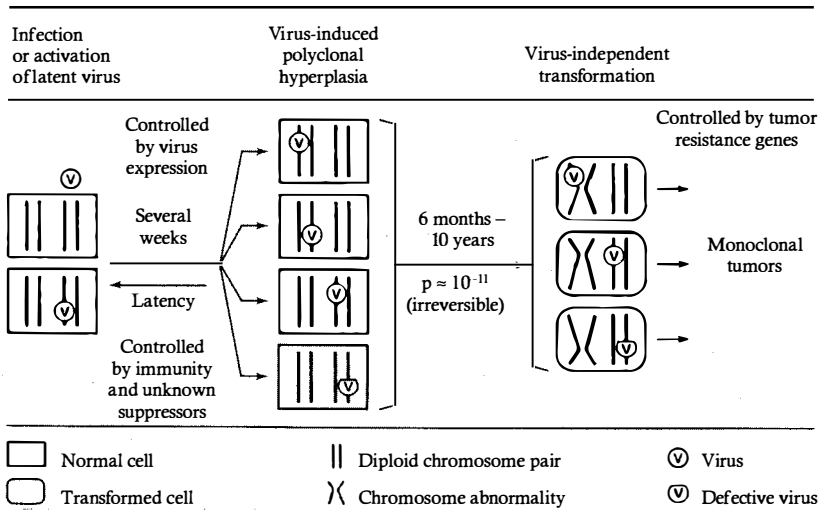

Figure 1 Retrovirus-independent transformation in virus-induced carcinogenesis. The diagram depicts the role of the virus in carcinogenesis. At high titers, known from experimental or congenital infections of domestic or laboratory animals, viruses induce polyclonal hyperplasia (Part I, Sections A and H). After latent periods of over 6 months, an animal with a virus-induced hyperplasia may develop a clonal tumor defined either by a clonal proviral integration site or by a clonal chromosome abnormality. Transformation of a virus-infected cell from which a tumor arises is proposed to be a virus-independent event. The following reasons support this proposal. (*a*) Viruses are not sufficient to induce tumors, because neither productively nor latently infected cells ever become transformed *in vitro* (Part I, Sections A and B) and less than 1 in 10^{11} infected cells become transformed in animals (Part I, Section F), because viruses do not encode a gene for late transformation, and because the latent period for transformation is much longer (6 months to 10 years) than the eclipse of a few days for virus replication (Part I, Section B), (*b*) Viruses are not necessary to maintain transformation, because in many animal and all known human tumors they are neither expressed nor biochemically active and frequently they are defective (Part I, Section D). (*c*) Since tumors have clonal chromosome abnormalities which are the only transformation-specific markers of "viral" tumor cells (Part I, Section G), these or associated events must initiate transformation. It is consistent with this view that chromosome abnormalities are typical of viral and nonviral tumors and are not found in normal, virus-infected cells. These chromosome abnormalities are not specific for a given type of tumor but they are also not random (Part I, Section G). The clonal proviral integration sites of viral tumors are proposed to be a direct consequence of clonal proliferation of a virus-infected cell that became transformed by a virus-independent mechanism (Part I, Section G). Therefore proviral integration sites are different in each tumor (Part I, Section E). (*d*) Tumorigenesis in retrovirus-infected animals, even in the presence of hyperplasia, is controlled by tumor resistance genes (Part I, Sections C and H). Moreover defects in tumor resistance genes rather than viral genes determine the nature of the tumor that develops in an infected animal. This indicates that tumors are defined by cellular transforming genes. (*e*) It is also consistent with cellular transforming genes that the pathogenesis and pathology of different viral and even nonviral tumors of the same cell lineage are highly uniform (Part I, Section H). By contrast hypothetical transforming genes generated by recombination between proviruses and cellular genes predict diploid tumors with great diversity, because viral integration sites are different in each tumor. Such tumors have never been described (Part I, Sections E and H). According to the above proposal, the role of the virus in carcinogenesis is limited to the induction of hyperplasia. Since it is known from experimental infections that retroviruses must be expressed at high titer to induce hyperplasia, it follows that the latent viruses associated with natural infections and certain leukemias of humans and animals (Part I, Sections D and H) are neither direct nor indirect carcinogens.

infected cells per host is estimated to be at least 10^6 to account for the immune response (Section B, and Refs. 13, 16, 27, 31, and 63) or the proviruses that are used to diagnose latent virus infection (Section D). Proviruses cannot be detected biochemically unless they are present in at least 1 of 100 cells. (*c*) Finally, the probability of an infected cell to become transformed in an animal is a function of the number of generations of infected cells that occur during the latent period of the disease. Given latent periods of 6 to 120 months (Section B) and assuming an average life span of 1 month for a susceptible B- or T-cell (176), about 10 to 100 generations of infected cells are required to generate the one transformed cell from which a clonal tumor emerges. The corresponding probability that a generation of cells will develop a clonal tumor would be 10^{-1} to 10^{-2}. Considering the proliferative effect of the virus on hemopoietic target cells in viremic animals, this may again be a conservative estimate. Indeed, a mitotic rate of 1 day has been assumed for B-cells of lymphomatosis virus-infected chickens (177).

Thus the probability that a virus-infected, hemopoietic cell will become transformed in an individual with a latent infection and antiviral immunity is about $10^{-3} \times 10^{-6} \times 10^{-2} = 10^{-11}$, and that in a viremic individual without tumor resistance genes is about the same, namely $0.9 \times 10^{-9} \times 10^{-2} = 10^{-11}$. Therefore the increased risk of viremic animals to develop leukemia must be a direct consequence of the hyperplasia of prospective tumor cells (Section A) (Fig. 1). In tumor-resistant animals the probability that the infected cell will become transformed may be the same, but the resistance genes would prevent proliferation of the transformed cells (Section C and H). The apparent probability that virus-infected, nonhemopoietic cells will become transformed must be lower in both susceptible and resistant animals, because the incidence of solid tumors is much lower than that of leukemia (9, 32).

G. Clonal Chromosome Abnormalities Are the Only Transformation-Specific Markers of Retrovirus-Infected Tumor Cells: Causes of Transformation?

The evidence that viral tumors are monoclonal (Section E) and that leukemogenesis by retroviruses (without *onc* genes) is highly dependent on tumor resistance genes, which are different from genes that deter-

mine susceptibility to the virus, suggest virus-independent steps in carcinogenesis (Section C). Indeed clonal chromosome abnormalities of virus-positive mammalian tumors provide direct evidence for cellular events that may be necessary for carcinogenesis. (Avian cells have not been studied because of their complex chromosome structure.)

For example, trisomies of chromosomes 15 have been observed frequently in viral T-cell leukemias of mice (16). In addition translocations between chromosomes 15, 17, and others have been recorded (108, 178–180, 272). In mammary carcinomas of mice, a chromosome 13 trisomy was observed in 15 of 15 cases including inbred GR and C3H mice (which contain MMTV) and outbred Swiss mice (which probably also contain the virus) (181). Clonal chromosome abnormalities have also been observed in 30 of 34 bovine leukemias examined (16, 182) as well as in ovine leukemias induced by bovine leukemia virus (75).

A recent cytogenetic analysis of human adult T-cell leukemias (ATL) from Japan showed that 10 of 11 cases had an inversion or translocation of chromosome 14 (183). Rearrangements of other chromosomes have been detected in 6 of 6 (184), 12 of 13 (116), and 8 of 9 cases of HTLV-I-positive leukemias (185). Thus over 90% of virus-positive T-cell leukemias have chromosome abnormalities. A survey of all viral T-cell leukemias analyzed shows rearrangements of chromosome 14 in 26% and of chromosome 6 in 29% (186, 187).

The chromosome abnormalities of these viral leukemias and carcinomas are as yet the only known determinants that set apart transformed from normal virus-infected cells. Since the chromosome abnormalities are clonal, the origin of the tumor must have coincided with the origin of the chromosome abnormality. Therefore chromosome abnormalities or closely associated events must be directly relevant to initiation of tumorigenesis. They could either be, or coincide with, a single step mechanism of transformation or with one of several steps in transformation, as postulated in the case of the Philadelphia chromosome (188). It is consistent with this view that chromosome abnormalities are found in all virus-infected tumors analyzed.

However, heterogeneity among the karyotypes of individual human or murine leukemias of the same lineage (16, 179, 182, 189, 190, 272) and thus heterogeneity of mutation support the view that chromosome

abnormalities are coincidental with rather than causal for transformation. Yet this view does not take into consideration that together with the microscopic alterations, other submicroscopic mutations may have occurred that could have initiated the disease (108). It is consistent with this view that tumor cells contain in addition to microscopic karyotype changes submicroscopic deletions, detectable as restriction enzyme site polymorphisms (191). Some of these mutations may be functionally equivalent to the truncation-recombination mechanism that activates the docile proto-*onc* genes of normal cells to the *onc* genes of directly oncogenic retroviruses (5, 192). Thus specific karyotypic changes may only be the tip of the iceberg of multiple chromosomal mutations, referred to as "genequake,"[7] which must have occurred in the same cell. One or several of these could have initiated the tumor. Chromosome recombination sites are also postulated to be cellular transforming genes of virus-negative tumors, as for example in Burkitt's lymphoma (5) or in human leukemia with the Philadelphia chromosome (193).

If chromosomal abnormalities are necessary for transformation of cells infected by retroviruses without *onc* genes, chromosomal abnormalities would not be expected in tumors caused by retroviruses with directly transforming *onc* genes. This has indeed been confirmed for tumors caused in mice by Rous sarcoma virus (194) or by Abelson leukemia virus (195) which have normal karyotypes (Table 1).

The clonality of retrovirus-positive tumors is then defined in two different ways: by a retroviral integration site (see Section E), and by a chromosome abnormality (see Fig. 1). Each of these two clonal chromosome alterations could then mark the origin of the tumor, while the other must have preexisted. Since the tumors originate late after infection and probably from a virus-infected, normal cell, the clonal retroviral integration site would appear to be a direct consequence of clonal proliferation of a cell transformed by a chromosome alteration. Indeed chromosome abnormalities are typical of tumor cells but not of virus-infected normal cells. This view is consistent with the evidence that retrovirus integration does not cause transformation and that transformation is not dependent on specific integration sites. It is also highly improbable that

7. G. Matioli, personal communication.

chromosome abnormalities are caused by the virus, because they are not found in virus-infected normal cells and because they are also characteristic of virus-negative tumors (Section H). The clonal retroviral integration sites in viral tumors the chromosomes of which have not been analyzed, as for example avian, feline, and simian leukemias, may indeed signal as yet undetected clonal chromosome abnormalities.

H. Virus-Independent Transformation in Virus-Positive and -Negative Tumors

Several hypotheses postulate that retroviruses play a direct role in carcinogenesis. One reason is that viruses, seemingly consistent with Koch's first postulate, are associated with tumors although frequently in a latent or defective form. In addition it appears consistent with Koch's third postulate that experimental infections with retroviruses may induce leukemia under certain conditions (see Sections B and C). However, none of these hypotheses provides an adequate explanation for the fact that retroviruses are not sufficient to initiate (Sections A to C) and not necessary to maintain (Sections D and E) transformation and do not encode a transformation-specific function. Moreover none of these hypotheses can explain why transformation is initiated with a clonal chromosome abnormality (Section G) and why tumor specificity is determined by the host rather than the virus (Sections C and E). The shortcomings of three of these hypotheses are briefly reviewed here.

1. **The Oncogene Hypothesis.** Huebner (8) and others (9, 82) have postulated that retroviruses (without *onc* genes) are direct carcinogens that include oncogenes, hence the term "oncogene hypothesis" (8). The hypothesis was based on abundant positive correlations between retrovirus expression and cancer incidence in laboratory mice and domestic chickens, which indeed suggested direct viral etiology in apparent accord with Koch's third postulate. The hypothesis generalized that either import of retroviruses from without, or activation of latent viruses from within, is the direct cause of spontaneous, chemically induced, or physically induced tumors (8, 9, 82). However, the hypothesis failed to account for the long latent periods of oncogenesis and for complete tumor resistance by certain animals that are highly susceptible to the virus and for host genes that would determine tumor specificity (Sec-

tion C). Above all the hypothesis failed to account for the monoclonality and the chromosome abnormalities of the resulting tumors.

2. **The Hypothesis That Latent Cellular Cancer Genes Are Activated by Provirus Integration.** This hypothesis has been introduced in Section E. It holds that retroviruses act as direct, albeit inefficient carcinogens by generating hybrid transforming genes from proviruses joint with cellular proto-*onc* genes. Excepting the specific cases described in Section E, this mechanism makes four clear predictions, namely: (*a*) that different transforming genes exist in each tumor, because each has a different proviral integration site (Section E); (*b*) that therefore a large number of tumor resistance genes exist in tumor-resistant animals (Section C); (*c*) that provirus-cell hybrid genes are expressed to maintain transformation; and (*d*) that virus-transformed cells exist without chromosome abnormalities, analogous to cells transformed by retroviruses with *onc* genes (Section G).

None of these predictions is confirmed, (*a*) Contrary to the expectation for many different transforming genes, all virus-positive tumors of a given lineage are phenotypically highly uniform (Section A). Even virus-free tumors are distinguishable from virus-positive tumors of the same lineage only by the presence of viruses. Examples are the identical pathologies and pathogeneses of viral and nonviral murine leukemias (196--198), chicken B-cell lymphomas (121), human T-cell leukemias (158, 161, 186), and mouse mammary tumors (11, 139, 141, 142) (Section D). (*b*) Contrary to expectation only a small set of cellular resistance genes controls the development of viral tumors in chicken or mice (13, 16) (Section C). Moreover apparently the same resistance genes of chickens of line 6 suppress viral and nonviral lymphomas, and even lymphomas induced by Marek's virus (124). By contrast chickens of line 7 that lack these genes are equally susceptible to both (121) (Section D). Mice provide parallel examples such as in the CBA strain, which is resistant to spontaneous (9) as well as to viral (46) leukemia (Section C). (*c*) Contrary to expectation for virus-cell hybrid transforming genes, proviruses are latent or defective and biochemically inactive in many animal and all bovine and human leukemias (Section D). (*d*) Contrary to expectation for viral carcinogenesis all virus-positive murine, bovine, and human tumors analyzed have chromosome abnor-

malities. Further, similar chromosome abnormalities in viral and nonviral tumors again suggest common cellular transforming genes. For instance, the same chromosome 15 trisomy is observed in murine leukemias induced by viruses, chemicals, or radiation (180, 190, 199–201,272). In addition virus-positive and virus-free human T-cell leukemias have common abnormalities in chromosomes 14 and 16 (160, 183, 186, 187, 189, 202, 203). Since all human T-cell leukemias and all bovine leukemias have chromosome abnormalities but not all are infected by viruses (Sections D and G), it would appear more likely that the viruses are coincidental passengers rather than causes of the disease.

3. **The Hypothesis that Latent Cellular Cancer Genes Are Transactivated by Viral Proteins.** This hypothesis postulates that certain retroviruses directly activate latent cellular transforming genes with a specific viral protein. This has been proposed for bovine leukemia virus and human HTLV-I based on *in vitro* models (147, 152, 153) (see Section D). However, the hypothesis is unlikely for the following reasons. Since the putative transactivation protein of HTLV-I is essential for replication (204), all cells in which the virus replicates would be expected to be transformed. This is clearly not the case. Further this gene cannot be relevant for transformation since bovine and human leukemias in particular do not express viral RNA or protein or cannot express RNA or protein because of defective proviruses (Section D). In addition this hypothesis also fails to account for the chromosome abnormalities found in all viral bovine and human leukemias (Section G). Finally both the proviral insertion and the transactivation hypotheses fail to explain the inevitably long latent periods of viral tumorigenesis (Section B).

Therefore it is proposed that transformation is a virus-independent event that must be due to cellular genes (Fig. 1). These genes would be generated by chromosomal mutations for which chromosome abnormalities are a macroscopic indicator. This explains the clonal chromosome abnormalities that could not be predicted by any of the virus-cancer hypotheses. In a given lineage of cells the number of cellular genes convertible to transforming genes must be limited since they cause highly uniform tumors which can be suppressed by a small set of resistance genes.

Retrovirus-independent transformation resolves the apparent paradox that tumors occur very seldom in typical natural infections of wild

animals and humans, and then only long after infection, and despite viral latency and antiviral immunity. It is also consistent with virus-independent transformation that the probability that an individual virus-infected cell will become transformed is only 10^{-11} and that this probability is the same in a viremic chicken with a virus-induced hyperplasia, as in a normal chicken with a latent infection and antiviral immunity (Section F). The low probability of virus-independent transformation also explains directly why cells infected by retroviruses are not transformed in culture, namely because not enough cells can be maintained for a long enough time to observe spontaneous transformation. Virus-independent transformation is also compatible with tumor resistance genes that do not inhibit viral replication or growth of normal virus-infected cells. In addition it is consistent with the notion that defects of cellular resistance genes rather than viral genes determine tumor specificity (Section C).

The role of the virus in tumorigenesis is then limited to the induction of hyperplasia by activating cellular proliferative functions either from within or from without via viral antigens or virus-induced growth factors (13, 16, 46). For this purpose the virus must be expressed at a high titer or it must have infected a large number of cells, if insertional mutagenesis of proliferative genes were involved (Section E). This may be similar to the mechanism whereby DNA viruses induce transformation, as for example Epstein-Barr virus which is thought to induce Burkitt's lymphoma. Exactly like their retroviral counterparts, all Burkitt's lymphomas have chromosome abnormalities but not all contain the virus (5). Thus the role of the retrovirus in carcinogenesis is as indirect as that of chemical or physical carcinogens.

Alternatively a latent retrovirus may itself be subject to activation by physical, chemical, or spontaneous events that can induce hyperplasias and cancer (8, 12, 82) (Fig. 1). The physically activated radiation leukemia virus (82) or the chemically activated endogenous retroviruses of mice or chickens (12, 16) are examples. It is uncertain whether under these conditions the retrovirus is just an indicator or an intermediate of proliferative activations that may lead to carcinogenesis because comparable studies with virus-free strains of animals are not available. The physically or chemically inducible phages or herpes

viruses may in turn be models for this (11, 83).

Little is known about the nature of the hyperplastic cell. The existence of viral hyperplasias in tumor-resistant animals indicates that the hyperplastic cell is not neoplastic (Section C). Most hyperplastic cells are polyclonal with regard to proviral integration sites (118) and are likely to have a normal karyotype, as has been shown in some cases (47) (Section C). Hyperplastic cells with normal karyotypes have also been observed as precursors of radiation leukemia in mice (205). Nevertheless the evidence for clonality with regard to a proviral integration site in T-cell hyperplasias (172) and mammary hyperplasias (56, 57) of mice and in T-cells of healthy humans (112) indicates clonal, possibly virus-induced alterations that are not sufficient for carcinogenesis. One could speculate then that hyperplastic cells fall into two classes, those which respond to viral antigens delivered from within or without (42) and those which respond to growth control genes altered by provirus integration (Section E).

Notable exceptions to virus-independent transformations are infections that generate retroviral transforming genes. However, the probability of generating a retrovirus with an *onc* gene is clearly much lower than integration into a cellular gene (10^{-6}; Section E) and even significantly lower than virus-independent transformation (10^{-11}, Section F) (273). Only about 50 such viral isolates have been recorded in history (5, 13, 19). [The frequent *erb* transductions from the chicken 15I line are an exception to this rule (Section E).] The generation of these viruses requires two rare illegitimate recombinations to transduce a transformation-specific sequence from a cell into a retrovirus vector (5, 19, 20, 273). However, one illegitimate recombination that unites the 5' promoter, translational start sequence, and splice donor of a retrovirus with a transformation-specific sequence from a cellular proto-*onc* gene would be enough to generate a functional virus-cell recombinant *onc* gene that cannot be replicated. Tumors caused by such genes are presently unknown. They will be harder to diagnose but are probably more frequent than the rare, natural tumors containing complete retroviruses with *onc* genes (273).

This raises the question of why orthodox integration of a provirus within a proto-*onc* gene, like proto-*myc,* is not observed to transform

infected cells *in vivo* or *in vitro* with the predicted probability. Based on the calculations described in Section E, this probability should be about 1 in 10^4 considering that about 20 proto-*onc* genes are known from 20 viral *onc* genes (5, 13, 19). A possible answer is that proviruses abutting proto-*onc* genes from the proviral ends rather than from within, as in viral *onc* genes (273), provide neither new downstream translational starts nor splice donors for those coding regions of the proto-*onc* genes that are separated from their native start signals by the inserted provirus. Nevertheless they can provide efficient downstream promoters (130) of RNAs that may not be translatable.

I. Are Retroviruses a Basis for Cancer Prediction, Prevention, or Therapy?

In assessing the tumor risk of a retrovirus-infected animal or human, latent infections must be clearly separated from chronic, acute, or viremic infections. The control of virus expression in a given host is a product of three factors: the virus; the host cell; and the animal. The viral factor is defined by viral genes and promoters (13, 16, 206). The cellular factor is defined by genes that encode viral receptors and unknown suppressors (8, 9, 11–13, 16–18, 82). The animal factor is defined by antiviral immunity.

By far the most common natural retrovirus infections are latent, chronic infections that persist in animals and humans in the presence of antiviral immunity presumably only in a limited number of cells (38, 40, 90, 207).[4] The leukemia risk of this statistically most relevant group of natural infections averages about less than 0.1% in different animal species (Section A). It is possibly the same as, but certainly not much higher than, that of uninfected controls (Sections A and D). Thus latent viruses offer no targets for tumor prevention. The low probability that an immunocompetent individual will develop chronic viremia and hence leukemia also suggests that retroviruses carrying therapeutic genes are not a significant risk as leukemogens.

By contrast, the leukemia risk of a viremic animal that survives the early pathogenic effects of the infection (Section B) can be high, barring tumor-resistance genes (Sections A and C). It ranges between 0 and 90% in different lines of chicken or strains of inbred mice and averages about 30% in domestic cats. However, outside the laboratory chronic

viremias are very rare and have never been recorded in humans. They result either from congenital infections in the absence of maternal antibody (Section A) or from rare, native immunodeficiency (66).

Thus a predictable tumor risk depends entirely on high virus expression and virus-induced hyperplasia. This risk can be reduced or prevented by limiting or blocking lymphoblast hyperplasia as for example by bursectomy or thymectomy (Section A). Alternatively, inoculation of newborn AKR mice with antiviral antibody was observed to suppress viremia and subsequent leukemia in 68% (208). It would appear more practical, however, to breed or select animals with genes that confer resistance either to the virus or to tumorigenesis or to both.

Above all, neither active nor latent viruses offer targets for tumor therapy, since tumors are not maintained and are not directly initiated by viral genes, and also occur despite active antiviral immunity.

Clearly the cell is the more complex variable in the as yet poorly defined interaction between retroviruses and cells that leads to hyperplasia and then to carcinogenesis. In view of the evidence for cellular, transforming genes in viral tumors and for cellular genes that determine resistance to hyperplasia and tumorigenesis, further progress in understanding and treating virus-induced cancer will depend on identifying cellular determinants of carcinogenesis and the function of hyperplasia and tumor resistance genes.

II. Retroviruses and AIDS

The isolation in 1983 of a retrovirus from a human patient with lymphadenopathy, a typical symptom of AIDS, led to the proposal that the virus, now termed lymphadenopathy-associated virus, is the cause of AIDS (26). Related viruses, termed HTLV-III, ARV, or HIV (209), have since been isolated from about one-half of the AIDS patients that have been sampled (210–214). In the United States about 26,000 AIDS cases and 15,000 AIDS fatalities have been reported between 1981, when the disease was first identified (215), and October 1986 (216). Women represent only 7% of the AIDS cases in the United States (216). The number of AIDS cases reported in the United States has increased from about 100 per 6-month period in 1981 to about 5,000 during the last three 6-month periods from January 1985 (216). At the same time the

case-fatality rate has declined from a high of 88% in 1981 to 32% in 1986 (216). In absolute numbers the known deaths have declined from a high of 2,600 in the first 6 months of 1985 to 1,800 in the first 6 months of 1986. This suggests either that the virulence of the disease is dropping or that other diseases were diagnosed as AIDS. Recently the virus was also suggested to cause disease of the brain and of the nervous system (230, 255, 268, 274) and lymphoid interstitial pneumonia (275).

Antibody to the virus is found in about 90% of AIDS patients and correlates with chronic latent infection by the virus (217–221). Because of the nearly complete correlation between AIDS and immunity against the virus, the virus is generally assumed to be the cause of AIDS (13, 27). Accordingly, detection of antiviral antibody, rather than virus, is now most frequently used to diagnose AIDS and those at risk for AIDS (27, 217–224). This is paradoxical, since serum antibody from AIDS patients neutralizes AIDS virus (225–227) and since antiviral immunity or vaccination typically protects against viral disease. It is even more paradoxical that a low antibody titer is equated with a low risk for AIDS (228, 229).

Unlike all other retroviruses, AIDS viruses are thought to be direct pathogens that kill their host cells, namely T-lymphocytes (13, 27), and possibly cells of the brain (230, 255). This view is compatible with the phenotype of AIDS, the hallmark of which is a defect in T-cells (13, 27, 215), and with experimental evidence that many but not all viral isolates induce cytopathic fusion of T-lymphocytes under certain conditions *in vitro* (Section D). Further it is compatible with neurological disease (231, 232, 255). However, cell killing is incompatible with the obligatory requirement of mitosis for retrovirus replication (16, 25) and with the complete absence of cytocidal effects in all asymptomatic infections *in vivo* (Section D).

A. Infections with No Risk and Low Risk for AIDS Indicate That the Virus Is Not Sufficient to Cause AIDS

Since their original discoveries in AIDS patients, the virus and more frequently antibody to the virus have also been demonstrated in a large group of asymptomatic persons (212, 214). The virus has been estimated to occur in about 1 to 2 x 10^6 or about 0.5 to 1% of all Americans (223, 224). In

the United States persons at high risk for infection include promiscuous homosexual and bisexual men, of whom 17 to 67% are antibody positive; intravenous drug users, of whom 50 to 87% are positive; and hemophiliacs, of whom 72 to 85% are positive according to some studies (13, 218, 223). On the basis of this particular epidemiology, it was concluded that the virus is not transmitted as a cell-free agent like pathogenic viruses but only by contacts that involve exchange of cells (13, 27).

In these virus-infected groups the annual incidence of AIDS was found to average 0.3% (224) and to reach peak values of 2 to 5% (218, 223, 233). However even in these groups there are many more asymptomatic than symptomatic virus carriers.

Other infected groups appear to be at no risk for AIDS. In Haiti and in certain countries in Africa antibody-positive individuals range from 4 to 20% of the population, whereas the incidence of AIDS is estimated at less than 0.01% (223, 229, 234). Several reports describe large samples of children from Africa who were 20 (228) to 60% (221) antibody positive and of female prostitutes who were 66 to 80% antibody positive (221,235), yet none of these had AIDS. Among male homosexuals and hemophiliacs of Hungary about 5% are AIDS virus positive, yet no symptoms of AIDS were recorded (161). Among native male and female Indians of Venezuela 3.3 to 13.3% have antiviral immunity, but none have symptoms of AIDS (236). Since these Indians are totally isolated from the rest of the country, in which only one hemophiliac was reported to be virus positive (236), the asymptomatic nature of their infections is not likely to be a consequence of a recent introduction of the virus into their population. Thus it is not probable that these infections will produce AIDS after the average latent period of 5 years (Section B).

Since the percentage of virus carriers with symptoms of AIDS is low and in particular since it varies between 0 and 5% depending on the AIDS risk group of the carrier, it is concluded that the virus is not sufficient to cause AIDS and that it does not encode an AIDS-specific function. The virus is also not sufficient to cause neurological disease, since it has been detected in the brains of persons without neurological disease and of healthy persons who had survived transient meningitis (230–232).

Thus the virus appears only rarely compatible with Koch's third

postulate as an etiological agent of AIDS. It may be argued that the asymptomatic infections reflect latent infections or infections of only a small percentage of susceptible cells, compared to presumably acute infections with symptoms of AIDS. However, it is shown in Section C that infections of neither symptomatic nor asymptomatic carriers are acute; instead both are equally latent and limited to a small percentage of susceptible cells.

Further, the observations that some virus carriers are at high and others at essentially no risk for AIDS directly argue for a cofactor (218, 237) or else for a different cause for AIDS. The strong bias against women, because only 2.5% (479 of 17,000 cases) of the sexually transmitted AIDS cases in the United States are women (216), is a case in point. The virus-positive but AIDS-negative children and prostitutes of Africa (221) or Indians from Venezuela (236) are other examples.

B. Long Latent Period of AIDS Incompatible with Short Latent Period of Virus Replication

The eclipse period of AIDS virus replication in cell culture is on the order of several days, very much like that of other retroviruses (238). In humans virus infection of a sufficient number of cells to elicit an antibody response appears to take less than 4 to 7 weeks. This estimate is based on an accidental needle-stick infection of a nurse, who developed antibody 7 weeks later (239), and on reports describing 12 (240) and 1 (232) cases of male homosexuals who developed antibody 1 to 8 weeks after infection. During this period a mononucleosis-like illness associated with transient lymphadenopathy was observed. In contrast to AIDS (see below), this illness appeared 1 to 8 weeks after infection and lasted only 1 to 2 weeks until antiviral immunity was established. The same early mononucleosis-like disease, associated with lymphocyte hyperplasia, was observed by others in primary AIDS virus infections (234). This is reminiscent of the direct, early pathogenic effects observed in animals infected with retroviruses prior to the onset of antiviral immunity (Part I, Section B).

By contrast the lag between infection and the appearance of AIDS is estimated from transfusion-associated AIDS to be 2 to 7 years in adults (220, 223, 241, 242) and 1 to 2 years in children from infected mothers

(220, 223). The most likely mean latent period was estimated to be 5 years in adults (220, 223). Unexpectedly, most of the AIDS virus-positive blood donors identified in transfusion-associated AIDS transmission did not have AIDS when they donated blood and were reported to be in good health 6 years after the donation (220). Likewise there is evidence that individuals shown to be antibody positive since 1972 have not developed AIDS (228). Further, 16 mothers of babies with AIDS did not have AIDS at the time of delivery but three of them developed AIDS years later (276). This indicates that the latent period may be longer than 5 years or that AIDS is not an obligatory consequence of infection.

In view of the claim that the virus directly kills T-cells and requires 5 years to cause disease, we are faced with two bizarre options: Either 5 year old T-cells die 5 years after infection or the offspring of originally infected T-cells die in their 50th generation, assuming a generation time of one month for an average T-cell (176). It may be argued that the virus is biochemically inactive during the first five years of infection and then activated by an unknown cause. However, AIDS virus is biochemically inactive even during the acute phase of the disease (Section C). Moreover it would be difficult for the retrovirus to become acute five years after it had induced chronic antiviral immunity.

Because of the 5 year latency between infection and AIDS, the virus has been likened to the lentiviruses (277), a group of animal retroviruses that is thought to cause debilitating diseases only after long latent periods (13) (Part I, Section B). However, recently an ovine lentivirus, the visna or maedi virus of sheep, was shown to cause lymphoid interstitial pneumonia in 2 to 4 weeks if expressed at high titer (269). [The same disease is believed to be caused by AIDS virus in humans (see below)]. Therefore lentiviruses are not models for retroviruses that are only pathogenic after long latency (Part I, Section B).

Based on the 5-year latent period of the disease and on the assumption that virus infection is sufficient to cause AIDS, one would expect the number of AIDS cases to increase to 1 to 2 x 10^6 in the United States in the next 5 years. The virus has reportedly reached its present endemic level of 1 to 2 x 10^6 in the United States (223, 224) since it was introduced there, presumably, less than 10 years ago (27). Yet the spread of AIDS from 1981 to 1986 has not followed the spread of virus with a

latent period of 5 years. Instead, recent statistics (see above) indicate no further increases in the number of AIDS cases and a significant decline in the number of AIDS fatalities in the United States (216, 244).

Clearly, the long lag between infection and AIDS and the large number of virus-positive cases in which as yet no AIDS is observed, even after long latent periods, lead to the conclusion that the virus is not sufficient to induce AIDS and does not encode an AIDS-specific function. Indeed, this conclusion is directly supported by genetic evidence against a viral AIDS gene. Deletion analysis has proved that all viral genes are essential for replication (28, 245), which requires not more than 1 or 2 days, yet AIDS follows infection only with an average lag of 5 years and even then only very rarely.

C. Levels of AIDS Virus Expression and Infiltration Appear Too Low to Account for AIDS or Other Diseases

If AIDS viruses were pathogenic by killing susceptible lymphocytes, one would expect AIDS to correlate with high levels of virus infiltration and expression, because uninfected cells would not be killed by viruses nor would unexpressed or latent viruses kill cells. As yet no report on virus titers of AIDS patients has appeared, despite the record interest in the epidemiology and nucleic acid structure of this virus (13, 27, 223). In view of the consistent antiviral immunity of AIDS patients and the difficulties in isolating virus from them (213), the virus titers are probably low. Titers have been said to range between only 0 and 10^2 per ml blood (213).[8]

Proviral DNA has been detected in only 15% (9 of 65) AIDS patients; in the remaining 85% the concentration of provirus, if present, was apparently too low for biochemical detection (246). Moreover, among positive samples less than 1 in 10^2 to 10^3 lymphocytes contained the provirus (246). Viral RNA was detected in 50 to 80% of AIDS blood samples. However, among the positive samples, RNA was found in only less than 1 of 10^4 to 10^5 presumably susceptible lymphocytes (247). The relatively high ratios of provirus-positive (10^{-2} to 10^{-3}) to viral RNA positive cells (10^{-4} to 10^{-5}) of AIDS patients indicate latent infections. Further there

8. J.A. Levy, personal communication.

is no evidence that the virus titer or the level of virus infiltration increases during the acute phase of the disease. It is probably for this reason that cells from AIDS patients must be propagated several weeks in culture, apart from the host's immune system, before either spontaneous (210–214) or chemically induced (248) virus expression may occur. Further, the AIDS virus is completely absent from the Kaposi sarcoma (27, 246), which is associated with 15% (216) to 30% (249) of AIDS cases and is one of the most characteristic symptoms of the disease.

Similar extremely low levels of virus infiltration and expression were also recorded in AIDS virus-associated brain disease (274). Likewise, in interstitial lymphoid pneumonia less that 0.1% of lung cells expressed viral RNA (275).

Indeed there is evidence that even latent virus may not be necessary for AIDS, since 85% of AIDS patients lack proviral DNA (246) and since over 10% of AIDS patients have been observed to lack antiviral immunity (214, 221, 222, 234). Further, in a study from Germany 3 of 91 AIDS patients were found to be virus free, based on repeated negative efforts to detect antibody or to rescue virus.[9]

It is concluded then that the AIDS virus infects less than 1%, and is expressed in less than 0.01%, of susceptible cells both in carriers with or without AIDS. This raises the question of how the virus could possibly be pathogenic and responsible for immunodeficiency or other diseases. For instance even if the virus were to claim its 10^{-4} or 10^{-5} share of T-cells that express viral RNA every 24 to 48 h, the known eclipse period of retroviruses, it would hardly ever match or beat the natural rate of T-cell regeneration (176).

All other viruses function as direct pathogens only if they are biochemically active and expressed at high levels. For instance, the titers that correlate with direct pathogenicity for avian retroviruses are 10^{5-12} (31, 35, 250)[4] and they are 10^{4-7} for murine retroviruses (12, 38, 40, 42, 251) (Section B). Hepatitis viruses reach titers of 10^{12-13} when they cause hepatitis (15), and latent infections are not pathogenic (83). Further, the very low levels of AIDS virus expression *in vivo* are difficult to reconcile with reports based on *in vitro* studies with synthetic indicator

9. H. Rübsamen-Waigmann, personal communication.

genes that the AIDS virus encodes a potent transcription-stimulating protein (28, 153, 245). Clearly such activators are not at work *in vivo.*

The extremely low virus titers of symptomatic and asymptomatic carriers also explain why infection by the virus in the United States is essentially limited to contacts that involve transmission of cells (244) rather than being transmitted as a cell-free, infectious agent like pathogenic viruses. For instance, among 1750 health care workers with exposure to AIDS, only 1 or 2 were found to be antibody positive (252). Another study failed to find a single antibody-positive person among 101 family contacts of 39 AIDS patients, all of whom had lived in the same household with an AIDS patient for at least 3 months (253).

D. AIDS Viruses Not Directly Cytocidal

The AIDS viruses are reported to display in culture a fast cytocidal effect on primary T-cells within 1 to 2 months after infection (13, 27, 254). The cytocidal effect was shown to involve cell fusion (27, 238, 254). The effect is thought to reflect the mechanism of how the virus generates AIDS after a latent period of 5 years (27, 254).

This is debatable on several grounds: (*a*) above all, the *in vitro* assay cannot account for the large discrepancy between the short latent period of cell death *in vitro* and the 5-year latent period of the disease; (*b*) T-cell fusion is not observed *in vivo* in chronic, asymptomatic virus carriers and not in prospective AIDS patients during the long latent period of the disease (255), although virus expression is not lower than during the acute phase of AIDS; (*c*) T-cell killing is also not observed in T-cell lines *in vitro* (27) and not in primary lymphocytes under appropriate conditions (238). Further primary lymphocytes infected by AIDS virus were shown to double every 5 days in cell culture for three weeks; at the same time the previously latent AIDS virus was activated to high levels of expression (278); (*d*) virus strains that do not cause cytopathic fusion *in vitro* have been isolated from 7 of 150 AIDS patients.[9] This demonstrates that the fusion-inducing function of the virus can be dissociated from a putative AIDS function.

Thus T-cell killing by fusion is apparently a cell culture artifact that depends on the virus strain and the cell used, as has been shown for

many other retroviruses including HTLV-I (Part I, Section B), and not an obligatory feature of virus infection. As with other retroviruses, fusion involves binding of viral envelope antigens on the surface of infected cells with receptors of uninfected cells. Accordingly, fusion is inhibited by AIDS virus-neutralizing antibody (256). It apparently depends on high local virus titers that in particular in the case of AIDS are not observed *in vivo*. This view of the cell-killing effect also resolves the apparent contradiction between the postulated cytocidal effects of AIDS viruses and the obligatory requirement of all retroviruses for mitosis in order to replicate (16, 25). Indeed AIDS viruses have been reported to replicate without cytocidal effects not only in T-cells but also in human monocytes and macrophages (257, 278), which share the same virus-specific receptors (258), and in B-cell lines (259), in fibroblasts (261) in human brain and the lung (213, 230, 232, 257, 261).

E. No Simian Models for AIDS

Since retroviruses have been isolated from monkeys in captivity with immunodeficiencies and since experimental viremia can depress immune functions in monkeys, such systems are considered to be animal models of human AIDS. For example, 42 of 68 newborn monkeys died with a broad spectrum of diseases that included runting and lymphadenopathy 4 to 6 weeks after inoculation with Mason-Pfizer monkey virus (91). However, this virus has since been found in healthy macaques (262). More recently a retrovirus termed simian AIDS or SAIDS virus was isolated from monkeys with immunodeficiency (92, 262). Inoculation of three juvenile rhesus monkeys by one isolate was reported to cause splenomegaly and lymphadenopathy within 2 to 5 weeks. One animal became moribund and two others were alive with simian AIDS at the time of publication (92). However, in another study only transient lymphadenopathy but no lasting AIDS-like disease was observed in macaques inoculated with this virus (263). Another simian virus that is serologically related to AIDS virus, termed STLV-III, was isolated from immunodeficient macaques and from one macaque with a lymphoma. Macaques inoculated with blood or tissue samples of the viral lymphoma died 50 to 60 days later with various diseases (93).

However, asymptomatic infections by the same virus have since been identified in no less than 50% of wild green monkeys that did not show any symptoms of a disease (264).

Eight chimpanzees infected with human AIDS virus had not developed symptoms of AIDS 1.5 years past inoculation (265). However, each animal developed antiviral immunity about 1 month after infection, followed by persistent latent infection, as in the human cases (265). A follow-up of champanzees inoculated with sera from AIDS patients in 1983 reports no evidence for AIDS in 1986 although the animals had developed antibodies to the virus (243).

Several reasons suggest that these experimental infections of monkeys are not suitable models for human AIDS. Above all, the human virus is not pathogenic in animals. The diseases induced in monkeys by experimental infections with simian viruses all occur fast compared to the 5-year latency for AIDS. Moreover the simian viruses are never associated with a disease in wild animals. Therefore these diseases appear to be exactly analogous to the direct, early pathogenic effects caused by other retroviruses in animals prior to antiviral immunity (see Part I, Section B), and thus are probably models for the early mononucleosis-like diseases which occur in humans infected with AIDS virus prior to antiviral immunity (232, 234, 240) (Section B). Indeed the persistent asymptomatic infections of wild monkeys with simian retroviruses appear to be models for the many asymptomatic infections of humans with AIDS virus or HTLV-I.

F. AIDS Virus As an Indicator of a Low Risk for AIDS

The only support for the hypothesis that the AIDS virus causes AIDS is that 90% of the AIDS patients have antibody to the virus. Thus it would appear that the virus, at least as an immunogen, meets the first of Koch's postulates for an etiological agent. This conclusion assumes that all AIDS patients from whom virus cannot be isolated (about 50%) (278) or in whom provirus cannot be demonstrated (85%) and the antibody-negative cases (about 10%) and the virus-free cases reported in one study (3%) (Section C) are false negatives. Indeed, the diagnosis of AIDS virus by antibody has recently been questioned on the basis of false positives (234).

At this time the hypothesis that the virus causes AIDS faces several

direct challenges. (*a*) First it fails to explain why active antiviral immunity, which includes neutralizing antibody (225–227) and which effectively prevents virus spread and expression, would not prevent the virus from causing a fatal disease. This is particularly paradoxical since antiviral immunity or "vaccination" typically protects against viral pathogenicity. It is also unexpected that AIDS patients are capable of mounting an apparently highly effective, antiviral immunity, although immunodeficiency is the hallmark of the disease. (*b*) The hypothesis is also challenged by direct evidence that the virus is not sufficient to cause AIDS. This includes (i) the low percentage of symptomatic infections, (ii) the fact that some infected groups are at a relatively high and others at no risk for AIDS, (iii) the long latent period of the disease (Section B), and (iv) the genetic evidence that the virus lacks a late AIDS function. Since all viral genes are essential for virus replication (28, 245), the virus should kill T-cells and hence cause AIDS at the time of infection rather than 5 years later. (*c*) The hypothesis also fails to resolve the contradiction that the AIDS virus, like all retroviruses, depends on mitosis for replication yet is postulated to be directly cytocidal (Section D). (*d*) The hypothesis offers no convincing explanation for the paradox that a fatal disease would be caused by a virus that is latent and biochemically inactive and that infects less than 1% and is expressed in less than 0.01% of susceptible lymphocytes (Section D). In addition the hypothesis cannot explain why the virus is not pathogenic in asymptomatic infections, since there is no evidence that the virus is more active or further spread in carriers with than in carriers without AIDS.

In view of this it seems likely that AIDS virus is just the most common among the occupational viral infections of AIDS patients and those at risk for AIDS, rather than the cause of AIDS. The disease would then be caused by an as yet unidentified agent which may not even be a virus, since cell-free contacts are not sufficient to transmit the disease.

Other viral infections of AIDS patients and those at risk for AIDS include Epstein-Barr and cytomegalovirus in 80 to 90% (222, 268), and herpes virus in 75 to 100%.[10]

10. D. Purtilo, personal communication.

In addition hepatitis B virus is found in 90% of drug addicts positive for antibody to AIDS virus (267). Among these different viruses, retroviruses are the most likely to be detectable long after infection and hence are the most probable passenger viruses of those exposed to multiple infectious agents. This is because retroviruses are not cytocidal and are unsurpassed in establishing persistent, nonpathogenic infections even in the face of antiviral immunity. Therefore AIDS virus is a useful indicator of contaminated sera that may cause AIDS (13, 27) and that may contain other cell-free and cell-associated infectious agents. It is also for these reasons that latent retroviruses are the most common nonpathogenic passenger viruses of healthy animals and humans. For the same reasons, they are also frequently passenger viruses of slow diseases other than AIDS like the feline, bovine and human leukemias (see Part I) or multiple sclerosis (268) in which latent or defective "leukemia viruses" are occasionally found.

It is concluded that AIDS virus is not sufficient to cause AIDS and that there is no evidence, besides its presence in a latent form, that it is necessary for AIDS. However, the virus may be directly responsible for the early, mononucleosis-like disease observed in several infections prior to antiviral immunity (Section B). In a person who belongs to the high risk group for AIDS, antibody against the AIDS virus serves as an indicator of an annual risk for AIDS that averages 0.3% and may reach 5%, but in a person that does not belong to this group antibody to the virus signals no apparent risk for AIDS. Since nearly all virus carriers have antiviral immunity including neutralizing antibody (225–227), vaccination is not likely to benefit virus carriers with or without AIDS.

Acknowledgments

I am grateful to R. Cardiff (Davis, CA), K. Cichutek, M. Gardner (Davis, CA), D. Goodrich, E. Humphries (Dallas, TX), J.A. Levy (San Francisco, CA), F. Lilly (New York, NY), G.S. Martin, G. Matioli (Los Angeles, CA), E. Noah (Villingen, Germany), S. Pfaff, W. Phares, D. Purtilo (Omaha, NE), H. Rubin, B. Singer, G. Stent, and R.-P. Zhou for critical comments or review of this manuscript or both and R.C. Gallo (NIH, Bethesda MD) for discussions.

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Chapter Two

HIV Is Not the Cause of AIDS

Science, Vol. 241, pp. 514–517, July 29, 1988.

HIV Is Not the Cause of AIDS

Human immunodeficiency virus (HIV) is not the cause of AIDS because it fails to meet the postulates of Koch and Henle, as well as six cardinal rules of virology.

1) HIV is in violation of Koch's first postulate because it is not possible to detect free virus (1, 2), provirus (3–5), or viral RNA (4, 6, 7) in all cases of AIDS. Indeed, the Centers for Disease Control (CDC) has established guidelines to diagnose AIDS when all laboratory evidence for HIV is negative (8).

2) In violation of Koch's second postulate, HIV cannot be isolated from 20 to 50% of AIDS cases (1, 9–11). Moreover, "isolation" is very indirect. It depends on activating dormant provirus in millions of susceptible cells propagated in vitro away from the suppressive immune system of the host.

3) In violation of Koch's third postulate, pure HIV does not reproduce AIDS when inoculated into chimpanzees or accidentally into healthy humans (9, 12, 13).

4) In contrast to all pathogenic viruses that cause degenerative diseases, HIV is not biochemically active in the disease syndrome it is named for (14). It actively infects only 1 in 10^4 to > 10^5 T cells (4, 6, 7, 15). Under these conditions, HIV cannot account for the loss of T cells, the hallmark of AIDS, even if all infected cells died. This is because during the 2 days it takes HIV to replicate, the body regenerates about 5% of its T cells (16), more than enough to compensate for losses due to HIV.

5) It is paradoxical that HIV is said to cause AIDS only after the onset of antiviral immunity, detected by a positive "AIDS test," because all other viruses are most pathogenic before immunity. The immunity against HIV is so effective that free virus is undetectable (see point 1), which is why HIV is so hard to transmit (9, 12, 13). The virus would be a plausible cause of AIDS if it were reactivated after an asymptomatic latency, like herpes viruses. However, HIV remains inactive during AIDS. Thus the "AIDS test" identifies effective natural vaccination, the ultimate protection against viral disease.

6) The long and highly variable intervals between the onset of antiviral immunity and AIDS, averaging 8 years, are bizarre for a virus that replicates within 1 to 2 days in tissue culture and induces antiviral immunity within 1 to 2 months after an acute infection (9, 17). Since all genes of HIV are active during replication, AIDS should occur early when HIV is active, not later when it is dormant. Indeed, HIV can cause a mononucleosis-like disease during the acute infection, perhaps its only pathogenic potential (9, 17).

7) Retroviruses are typically not cytocidal. On the contrary, they often promote cell growth. Therefore, they were long considered the most plausible viral carcinogens (9). Yet HIV, a retrovirus, is said to behave like a cytocidal virus, causing degenerative disease killing billions of T cells (15, 18). This is said even though T cells grown in culture, which produce much more virus than has ever been observed in AIDS patients, continue to divide (9, 10, 18).

8) It is paradoxical for a virus to have a country-specific host range and a risk group-specific pathology. In the United States, 92% of AIDS patients are male (19), but in Africa AIDS is equally distributed between the sexes, although the virus is thought to have existed in Africa not much longer than in the United States (20). In the United States, the virus is said to cause Kaposi's sarcoma only in homosexuals, mostly *Pneumocystis* pneumonia in hemophiliacs, and frequently cytomegalovirus disease in children (21). In Africa the same virus is thought to cause slim disease, fever, and diarrhea almost exclusively (22, 23).

9) It is now claimed that at least two viruses, HIV-1 and HIV-2, are capable of causing AIDS, which allegedly first appeared on this planet

only a few years ago (20). HIV-1 and HIV-2 differ about 60% in their nucleic acid sequences (24). Since viruses are products of gradual evolution, the proposition that within a few years two viruses capable of causing AIDS could have evolved is highly improbable (25).

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Blattner and Colleagues Respond to Duesberg

Biology is an experimental science, and new biological phenomena are continually being discovered. For example, recently some RNA molecules were shown to act as enzymes, ribozymes, even though biochemistry text books state that all enzymes are proteins. Thus, one cannot conclude that HIV-1 does or does not cause AIDS from Duesberg's "cardinal rules" of virology. In fact, the Henle-Koch postulates of 1840 and 1890 were formulated before the discovery of viruses. They are a useful historical reference point, but were not regarded as rigid criteria by Koch himself and should not be so regarded today (1).

Duesberg's description of the properties of viruses is in error and provides no distinction between knowing the cause of a disease, that is, its etiology, and understanding the pathogenesis of this disease. Duesberg is noted for his discoveries about the viral oncogene *src*. There is no question that the expression of this gene in chicken fibroblasts results in sarcomas. However, no one can yet explain how the expression by the *src* oncogene of an altered tyrosine protein kinase results in a cell becoming neoplastic. Similarly, there are many unanswered questions about the pathogenesis of AIDS, but they are not relevant to the conclusion that HIV causes AIDS.

Duesberg presents six (or nine) cardinal rules for viruses. Most are not relevant to the question of etiology and are misleading or wrong about viruses in general and HIV in particular.

1–2) It was formerly true that evidence for the presence of HIV-1 could not be found in all AIDS patients. But the overwhelming seroepidemiologic evidence pointing toward HIV as the cause of AIDS spurred research to improve the sensitivity of the detection methods. Better methods of virus isolation now show that HIV infection is present in essentially all AIDS patients (2).

The CDC definition of AIDS has been revised several times as new knowledge has become available and will undoubtedly be revised again. The 1981 CDC definition of AIDS did not mention HIV, since no strain of HIV was known until 1983. Many cases of AIDS are diagnosed on

clinical grounds alone because of the lack of availability or expense of HIV-1 antibody testing or because HIV testing is discouraged in some communities. Thus, rates of confirmation of AIDS cases by HIV testing in the United States vary geographically as reflected in CDC surveillance statistics.

3) It is true that HIV does not cause AIDS in chimpanzees. Most viruses are species-specific in host range and in capacity to produce disease. For example, herpes B virus, yellow fever virus, and dengue virus cause serious diseases in humans, but produce no disease symptoms during infection in many species of monkeys (3). Moreover, a virus closely related to HIV, simian immunodeficiency disease virus or SIV, causes an AIDS-like disease in rhesus macaques, but seldom, if ever, causes immunodeficiency in African Green monkeys (4, 5).

HIV-1 does indeed cause AIDS when inoculated into humans with no underlying medical condition. Accidental needlestick injuries with HIV-contaminated needles have resulted in HIV seroconversion and then clinical AIDS (6).

4) It is true that HIV infects only a small fraction of T cells. However, about 15% of the macrophage and monocyte cells from AIDS patients are positive for a viral protein, p24 (7), and the high concentration of this protein in the blood of AIDS patients indicates virus activity (8). The exact mechanism of CD4 cell depletion in AIDS patients is not known, but several indirect mechanisms are known by which HIV can cause CD4 cell depletion in laboratory studies and could operate in vivo.

5–6) Many viruses are highly pathogenic after evidence of immunity appears. For example, reactivated herpes zoster virus causes shingles, and reactivated herpes simplex virus causes local lesions as well as lethal necrotizing encephalitis; moreover, hepatitis B virus causes chronic active hepatitis, equine infectious anemia virus causes anemia, and visna virus causes central nervous system degeneration after the appearance of specific neutralizing antibodies (3, 9). (The last two viruses are lentiretroviruses as is HIV.) These diseases also can have long and variable latent periods.

7) It is true that some retroviruses, in particular, the highly oncogenic retroviruses of the kind that Duesberg has worked with, are not

cytocidal and promote cell growth. Most retroviruses have no effect on cell growth (9, 10). However, Rous-associated virus-2, spleen necrosis virus, visna virus, and HIV kill infected cells in culture and can establish a chronic stage of infection in which surviving infected cells continue to divide (11).

8) It was apparently "paradoxical for a virus to have a country-specific host range and a risk group-specific pathology." The properties of HIV resolved this paradox because the distribution of AIDS was found to mirror the distribution of HIV. The nature of the spread of the virus and the type of the AIDS-related clinical syndrome depend on social and environmental factors. Sexually active gay men and parenteral drug abusers were the first conduit for spread of HIV in the United States, whereas in some developing countries of Africa, young heterosexually active men and women were the major focus of spread. It is common for life-style to be a major determinant for the spread of an infectious agent. For example, until a vaccine became available, hepatitis B virus was clustered among the same U.S. populations that are now infected by HIV.

The underlying pathology in AIDS is immune deficiency. The nature of the opportunistic agents that invade the susceptible host is a function of which agents are most prominent in a particular population. For example, in the United States *Pneumocystis* is most prominent in affluent gay men, while human mycobacterial infections and toxoplasmosis are more frequent in socially disadvantaged Caribbean immigrants. Other agents, such as *Cryptococcus,* are more prominent in developing countries.

9) It is true that there are two viruses that cause human AIDS, HIV-1 and HIV-2. The origin of these HIVs is an interesting scientific question that is not relevant to whether or not HIV causes AIDS. Since a primate lentiretrovirus also causes an AIDS-like disease in rhesus monkeys, just as a cat lentiretrovirus, feline immunodeficiency virus, causes an AIDS-like disease in cats (12), one can suggest either that there is strong selection among retroviruses for this kind of pathology (13) or that the virus ancestor to HIV already had this property. In favor of the first hypothesis is the existence of feline, murine, and primate AIDS caused by retroviruses in a different subfamily from the lentiretroviruses (14).

In summary, although many questions remain about HIV and AIDS, a huge and continuously growing body of scientific evidence shows that HIV causes AIDS.

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HIV Causes AIDS

W. Blattner, R. C. Gallo, H. M. Temin

AIDS, a new disease, was first recognized in 1981, clustered in male homosexuals, intravenous drug abusers, and hemophiliacs in the United States and among sexually active heterosexuals in some countries of equatorial Africa. Human immunodeficiency virus (HIV) was first discovered in 1983 and was definitively linked in 1984 to AIDS patients and to groups whose members were at high risk for developing AIDS. The serological test for antibodies to HIV was developed at this same time and showed that HIV infection in the United States was concentrated in those populations at highest risk for AIDS, namely, male homosexuals, intravenous drug abusers, and hemophiliacs (1).

The strongest evidence that HIV causes AIDS comes from prospective epidemiological studies that document the absolute requirement for HIV infection for the development of AIDS. It has been shown for every population group studied in the United States and elsewhere that, in the years following the introduction of HIV and subsequent seroconversion of members of that population, the features characteristic of progressive immunodeficiency emerge in a predictable sequence resulting in clinical AIDS (2–4). Furthermore, other epidemiological data show that AIDS and HIV infection are clustered in the same population groups and in specific geographic locations and in time. Numerous studies have shown that in countries with no persons with HIV antibodies there is no AIDS and in countries with many persons with HIV antibodies there is much AIDS (3). Additionally, the time of occurrence of AIDS in each country is correlated with the time of introduction of HIV into that country; first HIV is introduced, then AIDS appears.

It is also noteworthy that HIV infection, and not infection with any other infectious agent, is linked to blood transfusion-associated AIDS (5). Similarly, in HIV-infected pregnant women, mother-to-child peri-

natal transmission of HIV occurs approximately 50% of the time, and over 95% of HIV-infected infants develop AIDS by 6 years, while their uninfected siblings never develop AIDS (3, 6).

Support for the linkage of HIV infection and AIDS comes as well from the results of public health interventions where interruption of HIV infection almost completely prevented the further appearance of AIDS in blood transfusion recipients (4). After the introduction of the HIV antibody screening test in the United States, the transmission of HIV in the blood supply in the United States was reduced from as high as 1 in 1,000 infected units in some high risk areas to less than an estimated 1 in 40,000 units countrywide (7). (The recently recognized cases of virus transmission by blood transfusion are due to donors being missed by current antibody screening tests during the window of seroconversion. There is a period of about 4 to 8 weeks in which newly HIV-infected persons are capable of transmitting HIV, but have not yet developed antibodies.) As a result of the decrease in blood transfusion-associated transmission of HIV, the incidence of blood transfusion-associated AIDS among U.S. newborns showed a decline (4).

Thirteen of the cases of blood transfusion-associated seroconversion identified since the start of blood bank screening were recently investigated (7). In one of these cases, the recipient of one unit of blood was one of a pair of fraternal twins. This baby seroconverted and developed AIDS without any other risk factor. Her twin and her mother received no blood products, developed no HIV antibodies, and remained healthy. The blood donor became HIV seropositive and developed AIDS.

Scientists conclude that a virus causes a disease if the virus is consistently associated with the disease and if disruption of transmission of the virus prevents occurrence of the disease. HIV can be detected by culture in most AIDS patients and by culture or polymerase chain reaction in most HIV seropositive individuals (8, 9). Epidemiological data show that transmission of HIV results in AIDS and blocking HIV transmission prevents the occurrence of AIDS. Thus, we conclude that there is overwhelming evidence that HIV causes AIDS.

Knowledge of the cause of a disease (etiology) is important for control of that disease and gives a basis for understanding the pathology

of the disease. However, knowing the cause of a disease does not mean that there is complete understanding of its pathology. Discovering the pathogenetic mechanisms of HIV in AIDS is a major focus for research.

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Duesberg's Response to Blattner and Colleagues

Blattner, Gallo, and Temin defend the hypothesis that HIV causes AIDS only with epidemiology and anecdotal clinical cases in which AIDS is correlated with antibody to HIV, but not with active virus. I submit that this is insufficient because such evidence cannot distinguish between HIV and other causes, unless there is also evidence for biochemical activity of HIV in AIDS.

1) My opponents say that "following introduction of HIV in a population ... immunodeficiency emerges in a predictable sequence." Instead, epidemiological surveys show that the annual incidence of AIDS among persons with antibody to HIV varies from almost 0 to over 10%, depending on factors defined by lifestyle, health, gender, and country of residence (see point 8 of my preceding statement). Among antibody-positive Americans the avenge conversion rate is 1% [10,000 to 20,000 (1) of 1 to 2 million (2, 3)] but that of certain hemophiliacs (4) or male homosexuals (5) is 10% or higher. These discrepancies between the epidemiologies of HIV antibody and AIDS indicate that neither HIV nor antibody to it is sufficient to cause AIDS.

2) The argument that HIV, "not ... any other infectious agent," is linked to AIDS in blood transfusion recipients and in congenitally infected children is presumptuous for several reasons. Blood transfusion does not distinguish between HIV and "any other infectious agent" or blood-borne toxin. Further, it is presumed that the recipient had no risk factors other than HIV during the average of 8 years between HIV transfusion and AIDS symptoms. The transfusion evidence would be more convincing if AIDS appeared soon after a singular transfusion in generally healthy recipients. Transfusion AIDS cases, however, only occur very late after infection and mostly in persons with health risks, such as hemophilia, that are not representative of healthy individuals. Likewise, it is presumptuous to assume that HIV was the cause of AIDS in antibody-positive children, of whom 96% had other health risks, such as mothers who are prostitutes or addicted to intravenously administered drugs or blood transfusions for the treatment of hemo-

philia or other diseases (1, 6). The references to these cases would have been more convincing if antibody-negative controls had been included, having none of "the broad range of clinical diseases . . . and the diversity of signs and symptoms of patients infected with HIV" (6).

3) According to authoritative sources, the primary defect of AIDS is a T cell deficiency induced by HIV infection (3, 7, 8). Therefore, it comes as a surprise that the primary clinical symptom of the children with AIDS was a B cell, not a T cell, deficiency (6). In fact, one of these same sources reports that "to fit observations from children into definitions for adult patients is unwise" (3). I wonder whether there is truly any disease that, in the presence of antibody to HIV, would not be called AIDS.

4) They claim that "interruption of HIV infection almost completely prevented the further appearance of blood-transfusion-associated AIDS." However, according to the CDC, transfusion-associated AIDS cases in adults have doubled to 752 cases and pediatric cases tripled to 68 in the year ending May 1988 compared to the previous year (1). This happened 3 years after antibody-positive transfusions were reduced 40-fold with the AIDS test (9). The steep increase in transfusion AIDS cases despite the great reduction of HIV-contaminated transfusions argues directly against HIV as the cause of AIDS.

5) In addition to the correlation that "in countries with many persons with HIV antibodies there is much AIDS," it is necessary to demonstrate some HIV-specific biochemical activity at the onset of AIDS to prove that HIV causes AIDS. All other viruses and microbes are very active when they cause fatal, degenerative diseases similar to AIDS. There is also abundant generic evidence that this activity is necessary for pathogenicity. Antibodies are evidence for the absence of an active virus, not a prognosis for future disease or death. Prior claims for etiology without genetic or molecular evidence for activity proved to be some of the most spectacular misdiagnoses in virology: (i) Based on epidemiological evidence, "scientists concluded" that Epstein-Barr virus was the cause of Burkitt's lymphoma—until the first virus-free lymphomas were found (10). (ii) On epidemiological grounds, human and bovine retroviruses were believed to cause leukemia after bizarre latent periods of up to 40 years in humans (11)—but finding these viruses in

billions of normal cells of millions of asymptomatic carriers has cast doubt on this view (12). It is scarcely surprising that these leukemias arose from virus-infected cells. Consistent with this view, these "viral" leukemias are clonal and not contagious, behaving like virus-negative leukemias, and the associated "leukemia" viruses are not biochemically active (12). (iii) "Slow viruses" were accepted as causes of Alzheimer's, kuru, and Creutzfeldt-Jakob disease (13) on the basis of the same kind of epidemiology and transmission evidence used here for HIV—but these viruses have never materialized. These examples illustrate that correlations without evidence for biochemical activity are not sufficient to prove "etiology."

6) I fully support the view that "knowledge of the cause of a disease (etiology) is important for control." Since the cause of AIDS is debatable, the control of AIDS may not be achieved by controlling HIV. This is particularly true for the highly toxic "control" (preventive or therapeutic) of AIDS with azidothymidine (AZT)—AZT is designed to inhibit viral DNA synthesis in persons who have antibodies to a virus that is not synthesizing DNA (14).

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Chapter Three

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome: Correlation But Not Causation[1,2]

Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 755–764, February 1989
Contributed June 14, 1988; revision received October 21, 1988

Abstract

AIDS is an acquired immunodeficiency syndrome defined by a severe depletion of T cells and over 20 conventional degenerative and neoplastic diseases. In the U.S. and Europe, AIDS correlates to 95% with risk factors, such as about 8 years of promiscuous male homosexuality, intravenous drug use, or hemophilia. Since AIDS also correlates with antibody to a retrovirus, confirmed in about 40% of American cases, it has been hypothesized that this virus causes AIDS by killing T cells. Consequently, the virus was termed human immunodeficiency virus (HIV), and antibody to HIV became part of the definition of AIDS. The hypothesis that HIV causes AIDS is examined in terms of Koch's postulates and epidemiological, biochemical, genetic, and evolution-

1. This paper, which reflects the author's views on the causes of AIDS, will be followed in a future issue by a paper presenting a different view of the subject. (Note: According to the editor of the *Proceedings of the National Academy of the Sciences,* this "different view" was to be prepared by R. Gallo, but it has not appeared as of August 1995.)
2. Abbreviations: AIDS, acquired immunodeficiency syndrome; AZT, azidothymidine; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

ary conditions of viral pathology. HIV does not fulfill Koch's postulates: (*i*) free virus is not detectable in most cases of AIDS; (*ii*) virus can only be isolated by reactivating virus *in vitro* from a few latently infected lymphocytes among millions of uninfected ones; (*iii*) pure HIV does not cause AIDS upon experimental infection of chimpanzees or accidental infection of healthy humans. Further, HIV violates classical conditions of viral pathology. (*i*) Epidemiological surveys indicate that the annual incidence of AIDS among antibody-positive persons varies from nearly 0 to over 10%, depending critically on nonviral risk factors. (*ii*) HIV is expressed in ≤1 of every 10^4 T cells it supposedly kills in AIDS, whereas about 5% of all T cells are regenerated during the 2 days it takes the virus to infect a cell. (*iii*) If HIV were the cause of AIDS, it would be the first virus to cause a disease only after the onset of antiviral immunity, as detected by a positive "AIDS test." (*iv*) AIDS follows the onset of antiviral immunity only after long and unpredictable asymptomatic intervals averaging 8 years, although HIV replicates within 1 to 2 days and induces immunity within 1 to 2 months. (*v*) HIV supposedly causes AIDS by killing T cells, although retroviruses can only replicate in viable cells. In fact, infected T cells grown in culture continue to divide. (*vi*) HIV is isogenic with all other retroviruses and does not express a late, AIDS-specific gene. (*vii*) If HIV were to cause AIDS, it would have a paradoxical, country-specific pathology, causing over 90% *Pneumocystis* pneumonia and Kaposi sarcoma in the U.S. but over 90% slim disease, fever, and diarrhea in Africa. (*viii*) It is highly improbable that within the last few years two viruses (HIV-I and HIV-2) that are only 40% sequence-related would have evolved that could both cause the newly defined syndrome AIDS. Also, viruses are improbable that kill their only natural host with efficiencies of 50–100%, as is claimed for HIVs. It is concluded that HIV is not sufficient for AIDS and that it may not even be necessary for AIDS because its activity is just as low in symptomatic carriers as in asymptomatic carriers. The correlation between antibody to HIV and AIDS does not prove causation, because otherwise indistinguishable diseases are now set apart only on the basis of this antibody. I propose that AIDS is not a contagious syndrome caused by one conventional virus or microbe. No such virus or microbe would require almost a decade to cause primary dis-

ease, nor could it cause the diverse collection of AIDS diseases. Neither would its host range be as selective as that of AIDS, nor could it survive if it were as inefficiently transmitted as AIDS. Since AIDS is defined by new combinations of conventional diseases, it may be caused by new combinations of conventional pathogens, including acute viral or microbial infections and chronic drug use and malnutrition. The long and unpredictable intervals between infection with HIV and AIDS would then reflect the thresholds for these pathogenic factors to cause AIDS diseases, instead of an unlikely mechanism of HIV pathogenesis.

Introduction

> The important thing is to not stop questioning.
>
> —Albert Einstein

In 1981, acquired immunodeficiency was proposed to be the common denominator of a newly defined syndrome (AIDS) of diseases that were on the rise in promiscuous male homosexuals and intravenous drug users, referred to as "AIDS risk groups" (1, 2). Since then, about 70,000 persons have developed AIDS in the U.S., of whom over 90% are still from these same risk groups (3, 4). The hallmark of AIDS is a severe depletion of T cells (3, 5–7). By definition, this immunodeficiency manifests itself in over 20 previously known degenerative and neoplastic diseases, including Kaposi sarcoma, Burkitt and other lymphomas, *Pneumocystis* pneumonia, diarrhea, dementia, candidiasis, tuberculosis, lymphadenopathy, slim disease, fever, herpes, and many others (5, 7–11). The frequent reference to AIDS as a new disease (12–14), instead of a new syndrome composed of old diseases, has inspired a search for a single new pathogen (12). However, it is debatable whether a single pathogen can explain over 20 diseases, whether a clustering of old diseases in risk groups that only recently became visible signals a new pathogen, and whether an AIDS pathogen must be infectious. Indeed, compared to conventional infectious diseases, AIDS is very difficult to acquire and has a very selective host range, usually manifesting only in individuals who have taken AIDS risks for an average of 8 years (see below).

The Virus-AIDS Hypothesis. About 40% of the AIDS patients in the U.S. (5), and many of those who are at risk for AIDS, have been confirmed to have neutralizing antibodies to a retrovirus (3, 7) that was discovered in 1983 (15). These antibodies are detected by the "AIDS test" (3). Less than a year later, in 1984, this virus was adopted as the cause of AIDS by the U.S. Department of Health and Human Services and the AIDS test was registered as a patent, even before the first American study on the virus was published (16). The epidemiological correlation between these antibodies and AIDS is the primary basis for the hypothesis that AIDS is caused by this virus (3, 7, 12, 14, 17, 18). AIDS is also believed to be caused by this virus because AIDS diseases appear in a small percentage (see below) of recipients of blood transfusions that have antibodies to this virus (3, 12, 19–22). In view of this the virus has been named human immunodeficiency virus (HIV) by an international committee of retrovirologists (18) and antibody to HIV became part of the definition of AIDS (3, 5, 7). "... Patients are excluded as AIDS cases if they have a negative result(s) on testing for serum antibody to HIV, do not have a positive culture for HIV" (3). If confirmed, HIV would be the first clinically relevant retrovirus since the Virus-Cancer Program called for viral carcinogens in 1971 (23, 24).

The virus-AIDS hypothesis holds that the retrovirus HIV causes AIDS by killing T cells in the manner of a cytocidal virus (3, 6, 7, 12, 18) and is transmitted by sex and parenteral exposure (3, 7, 12, 19, 22). Early evidence for a T cell-specific HIV receptor lent support to this hypothesis (25). Recently, however, the presumed T cell specificity of HIV has lost ground, as HIV is only barely detectable in T cells and often is detectable only in monocytes (26–28) and other body cells (23, 29–32), displaying the same lack of virulence and broad host range toward differentiated cells as all other human and animal retroviruses (17, 23). In about 50% of those who habitually practice risk behavior or regularly receive transfusions, AIDS is estimated to occur after an average asymptomatic period of about 8 years from the onset of antiviral immunity, and in up to 100% after about 15 years (5–7, 20—22, 33–38). Therefore, HIV is called a "slow" virus, or lentivirus (40). It is on the basis of the relatively high conversion rates of these risk groups that every asymptomatic infection by HIV is now being called "HIV

disease" (7), and that some are subjected to chemotherapy (39). Nevertheless, individual asymptomatic periods are unpredictable, ranging from <1 to >15 years (22, 33–38). Once AIDS is diagnosed, the mean life expectancy is about 1 year (35).

The early adoption of the virus-AIDS hypothesis by the U.S. Department of Health and Human Services (16) and by retrovirologists (17, 18) is the probable reason that the hypothesis was generally accepted without scrutiny. For instance, the virus is typically referred to as deadly by the popular press (41, 42) and public enemy number 1 by the U.S. Department of Health and Human Services (43). In view of this, it is surprising that the virus has yet to cause the first AIDS case among hundreds of unvaccinated scientists who have propagated it for the past 5 years at titers that exceed those in AIDS patients by up to 6 orders of magnitude (see below) with no more containment than is required for marginally pathogenic animal viruses (44). It is also surprising that despite 2000 recorded (and probably many more unrecorded) parenteral exposures to HIV-infected materials, unvaccinated health care workers have exactly the same incidence of AIDS as the rest of the U.S. labor force (19, 22, 45, 186). Further, it is difficult to believe that a sexually transmitted virus (7, 12) would not have caused more than 1649 sex-linked AIDS cases among the 125 million American women in 8 years (4)—and this number is not even corrected for the antibody-negative women who might have developed such diseases over an 8-year period. Moreover, it is paradoxical for a supposedly new viral epidemic (12–14) that the estimates of infected persons in the U.S. have remained constant at 0.5 to 1.5 million (46, 47) or even declined to <1 million (7, 38) since the "AIDS test" became available in 1985.

About 2 years ago I proposed that HIV is not likely to be the cause of AIDS (23, 48–50, 180). This proposal has since been fiercely challenged or defended at meetings and in publications (14, 32, 51–65, 180). Here I respond to these challenges.

HIV Does Not Meet Koch's Postulates

HIV Cannot Account for the Loss of T Cells and the Clinical Course of AIDS. The causative agent of an infectious disease is classically

defined by the postulates of Robert Koch and Jacob Henle (66, 67). They were originally formulated *a priori* by Henle about 50 years before bacteria and viruses were discovered to be pathogens (67). However, their definitive text was formulated by Koch to distinguish causative from other bacteria at a time when bacteriologists applying newly developed tools in the search for pathogenic microbes found all sorts of bacteria in humans. This situation was quite similar to our current increasing proficiency in demonstrating viruses (68). The first of these postulates states that "the parasite must be present in every single case of the disease, under conditions that can account for the pathological lesions and the clinical course of the disease" (67). However, there is no free virus in most—and very little in some—persons with AIDS, or in asymptomatic carriers (69, 70). Virus titers range from 0 to 10 infectious units per milliliter of blood (69, 70). Viral RNA is found in a very low percentage (see below) of blood cells of 50–80% of antibody-positive persons (71–74, 187). Further, no provirus is detectable in blood cells of 70–100% of symptomatic or asymptomatic antibody-positive persons, if tested by direct hybridization of cellular DNA with cloned proviral DNA (73, 75, 187) at the limit of detection by this method (76). Antibody to HIV is confirmed in only about 40% of the U.S. cases and in only 7% of the AIDS cases from New York and San Francisco, which represent one-third of all U.S. cases (5). In some cases, even the antibody to HIV disappears, due to chronic dormancy or loss of the HIV provirus (77, 78)—analogous to the loss of antibody to other viruses long after infection. Indeed, the Centers for Disease Control publishes specific guidelines for AIDS cases in which laboratory evidence for HIV is totally negative (5). Thus, although viral elements can be traced in many AIDS patients, and antibody to HIV is, at least by definition, present in all of them, HIV violates Koch's first postulate in terms of a tangible presence, of being "under conditions that can account for" the loss of T cells, and of the "clinical course of the disease" that lags 8 years behind infection.

The absence of free virus in most AIDS cases and in antibody-positive asymptomatic carriers explains why HIV is not casually transmitted (19, 22, 23, 35). For example, the probability of transmission of

the virus from an antibody-positive to an antibody-negative person by heterosexual intercourse is estimated to be 1 in 500 (79, 80).

Due to Extremely Low Titers, HIV Can Be Isolated Only with Great Difficulty from AIDS Patients. Koch further postulated that it must be possible to isolate and propagate the etiological agent from all cases of the disease. However, virus isolation, although possible in up to 80% of AIDS cases, is technically very difficult and is perhaps best described as maieutic (23, 69, 70, 81–84). It depends on reactivation of dormant proviruses from one or a few latently infected lymphocytes among millions of uninfected lymphocytes from AIDS patients. This is only possible by culturing these cells for several weeks *in vitro,* away from the suppressive, virus-neutralizing immune system of the host (23, 48–50). Even then success sometimes comes only after 15 (!) trials (85). These difficulties and the often over 20% failure rate (84) in isolation of HIV from AIDS patients are consistent with the extremely low titers of HIV in such patients. Thus, HIV does not meet Koch's second postulate.

In vitro reactivation of latent HIV from antibody-positive persons is exactly analogous to the *in vitro* reactivation of latent Epstein-Barr virus (EBV) from healthy persons with antibody to EBV (86). As in the case of HIV (see below), acute EBV infections occasionally cause mononucleosis (86–88). Subsequent antiviral immunity restricts EBV to chronic latency (86). Since latent EBV, again like latent HIV, is present in only 1 of 10^7 lymphocytes, millions of these cells must be cultivated *in vitro* to reactivate the virus (86).

HIV Does Not Reproduce AIDS When Inoculated into Animals or Humans. *Animal infections.* Koch's third postulate calls for inducing the disease by experimental infection of a suitable host with pure pathogen. Chimpanzees infected with pure HIV develop antibodies, indicating that they are susceptible to HIV. However, all attempts to cause AIDS in chimpanzees have been unsuccessful, even after they have been antibody-positive for 4 to 5 years (23). Thus, Koch's third postulate has not been fulfilled in animals.

Accidental human infections. Due to the extremely low titers of HIV

in all antibody-positive materials, very few infections have occurred. Four women who received infected donor semen in 1984 developed antibody to HIV. Yet none of them developed AIDS or transmitted the virus to their husbands, although insufficient time has elapsed for the average latent period that the virus is thought to require to cause AIDS (see below). Moreover, three of these women subsequently became pregnant and gave birth to healthy infants (89). Further, 15 to 20 accidental infections of health care workers and scientists propagating HIV were identified during the last 4 years on the basis of antiviral antibodies, and none of these people have developed AIDS (19, 22, 23, 45, 85, 90, 186).

Recently, a single conversion to AIDS of such an antibody-positive health care worker was reported anonymously without data on gender, latent period, or AIDS symptoms (45). This case was claimed to prove Koch's third postulate (14). However, 2586 health care workers got AIDS without occupational infection. About 95% of these fall into the conventional risk groups and 5% are without verifiable AIDS risks (4, 45)—which are notoriously difficult to verify (91, 92). From the 135 (5% of 2586) health care workers who developed AIDS without verifiable risks, the one who contracted an occupational infection was selected to prove that such infections, rather than other risks, caused AIDS. It is arbitrary to base a hypothesis on 1 case when 134 cases do not support the hypothesis. To prove the hypothesis, it is necessary to show that the percentage of health care workers with AIDS who do not belong to the known risk groups exceeds that of the rest of the population and reflects their sexual distribution. However, the incidence and even the sexual distribution of AIDS cases among health care workers are exactly the same as that of AIDS in the general population (4), namely 92% males, although 75% of the health care workers are female (45). Moreover, a subsequent study (186) that included this case described only transient, mononucleosis-like symptoms but not one AIDS case among occupationally infected health care workers.

Blood transfusions are another source of iatrogenic infections. The best-documented cases are the 10,000 to 14,000 U.S. hemophiliacs with antibody to HIV (19, 38, 47, 93, 94), of whom only 646 developed symp-

toms of AIDS between 1981 and August 1988 (4). During the year that ended in August 1988, 290 developed AIDS, whereas 178 developed AIDS in the previous year (4). This corresponds to annual conversion rates of about 1–3%. Higher rates, of up to 25%, have been observed in certain groups of hemophiliacs (20, 21, 35, 36, 38). However, the view that AIDS in recipients of transfusions is due to HIV transmission is presumptive on several grounds. (*i*) Blood transfusion does not distinguish between HIV and other undetected viruses, microbes, and blood-borne toxins. This is particularly true since HIV-positive blood was never knowingly transfused. (*ii*) It is presumed that the recipients had no AIDS risks other than HIV during the average of 8 years between HIV infection and AIDS symptoms (20, 21). The transfusion evidence would be more convincing if AIDS appeared in step with virus replication (see below) soon after a singular transfusion. (*iii*) Transfusion-related AIDS cases occur primarily in persons with other health risks, such as hemophilia, that are not representative of healthy individuals. (*iv*) Above all, the transfusion cases are all anecdotal (95, 96). There are no controlled studies to show that recipients of transfusions with antibody to HIV have more of the diseases now called AIDS than those without antibody to HIV.

The assertion that HIV causes AIDS is also contained in the erroneous claims that new cases of transfusion AIDS have virtually ceased appearing since the AIDS test became available in 1985 (12, 14), due to a factor-of-40 reduction of transfusions with antibody-positive blood (95). In fact, adult transfusion AIDS cases have doubled and pediatric cases have tripled in the year ending August 8, compared to the previous year (4, 49). The increase in adult cases could be expected if one were to accept the assumptions that HIV requires 8 years to cause AIDS (see below) and that there was a rapid increase in unconfirmed HIV transfusions 8 years ago, which stopped 3 years ago. However, the increase in pediatric cases in the face of a 40-fold reduction of antibody-positive transfusions argues directly against HIV as the cause of AIDS, because the average latent period in children is only 2 years (21, 36).

HIV Does Not Meet Established Epidemiological, Biochemical, Genetic, and Evolutionary Criteria of a Viral Pathogen

Epidemiologies of AIDS and HIV Are Not Consistent. Epidemiology has been proposed as adequate to identify causative agents, particularly in human diseases where Koch's postulates are difficult to meet (67), as in the case of HIV (12, 14, 32). Nevertheless, even a consistent correlation with virus—not with antibody—would fulfill only the first postulate. However, the epidemiologies of AIDS and HIV are not consistent in different risk groups and countries.

About 10% of the 30 million people in Zaire have been reported since 1985 to be antibody-positive (46, 98, 184). However, only 335 AIDS cases have been reported in Zaire as of 1988 (97, 99). This corresponds to an annual conversion rate of 0.004%. Also, since 1985, 6% of the 6 million Haitians have been reported to be antibody-positive (46,100), but only 912 had developed AIDS by 1988 (97). This corresponds to an annual conversion rate of 0.1%. of 0.5 to 1.5 million antibody-positive Americans, about 29,000 [including 9000 who meet only the 1987 definition for AIDS (5)] developed AIDS in the year ending August 1988, and, according to earlier definitions, 16,000 to 17,000 developed AIDS in each of the previous 2 years (4). This corresponds to an annual conversion rate of about 1.5% for the average antibody-positive American. Thus, the AIDS risk of an antibody-positive person varies with the country of residence. These calculations all assume that the pools of short- and long-term HIV carriers in each of these countries are comparable. This assumption is based on the claims that HIV was newly introduced into all countries with AIDS about 10 to 20 years ago (3, 7, 12–14).

Moreover, the AIDS risk of an antibody-positive American varies a great deal with his or her risk group. For example, 3–25% of antibody-positive Americans who habitually practice risk behavior or are hemophiliacs develop AIDS annually (7, 21, 22, 33–38). Thus, the 1.5% annual conversion rate of antibody-positive Americans is an average of

minorities with high conversion rates of 3–25% and a majority with a conversion rate close to 0%.

Since the incidence of AIDS among antibody-positive persons varies from 0 to over 10% depending on factors defined by lifestyle, health, and country of residence (35), it follows that HIV is not sufficient to cause AIDS.

AIDS Occurs Despite Minimal Viral Activity. During replication, viruses are biochemically very active in the host cell. If they replicate in more cells than the host can spare or regenerate, they typically cause a disease (48, 86).

Paradoxically, HIV is very inactive even when it is said to cause fatal immunodeficiency. Viral RNA synthesis is detectable in only 1 of 10^4 to 10^6 mononuclear lymphocytes, including T cells (71–74). Frequently, virus can only be found in monocytes, and not in T cells (26–28). Virus expression recorded in monocyte-macrophages is at the same low levels as in other lymphocytes (72). Thus, there is as yet no experimental proof for the suggestion, based on experiments in cell culture, that monocyte-macrophages may be the reservoirs of the virus *in vivo* (6, 12, 28). Also, very few lung and brain cells ever express HIV (101, 102, 187). At this level of infiltration HIV cannot account by any known mechanism for the loss of T cells that is the hallmark of AIDS (3, 5, 6, 12), even if all actively infected T cells died. During the 2 days it takes for a retrovirus to replicate, the body regenerates about 5% of T cells (23, 103), more than enough to compensate for presumptive losses due to the virus. Hence, HIV cannot be sufficient to cause AIDS.

Although there is virtually no free virus, and HIV RNA synthesis is extremely low, both in AIDS patients and in asymptomatic carriers (71–74), it has been argued that the viral core protein p24 is produced at higher levels in AIDS patients than in asymptomatic carriers (83, 84, 104–108, 183). However, all studies on p24 report AIDS cases that occur without p24 antigenemia, indicating that p24 is not necessary for AIDS (83, 84, 104–108, 183). They also report antigenemia without AIDS, indicating that p24 is not sufficient for AIDS (72, 84, 104–108, 183). Moreover, antigenemic carriers are not viremic because they always

maintain an excess of virus-neutralizing antibodies directed against the viral envelope, a positive AIDS test (72, 83, 84, 104–108, 183). In addition, the colorimetric antibody test used to measure p24 protein raises unresolved questions. Reportedly, the assay's detection limit is 50 pg/ml, and up to 100 times more p24 than that is found in some HIV carriers (83, 84, 104–109). Five hundred picograms of p24 is the protein equivalent of 10^6 HIV particles, given 10^{-3} pg per retrovirus, half of which is core protein (110). Yet such high concentrations of p24 cannot be reconciled with the extremely low numbers of cells in AIDS patients that are engaged in viral RNA synthesis (6, 71–74, 101, 102), nor can the failure to isolate virus from 20–50% of p24-antigenemic patients (83, 84). Based on my 24-year experience with retroviruses, only large numbers of infected cells growing in the absence of antiviral immunity *in vivo* or *in vitro* produce such high titers of virus or viral protein. Thus, the assertions that HIV becomes activated during AIDS or that p24 antigenemia is necessary for the syndrome (6, 7, 12, 31, 35) are without experimental support.

AIDS Occurs Despite Antiviral Immunity. Viruses typically cause disease before virus-neutralizing antibodies and cellular immunity appear. Antiviral antibodies signal a successful rejection of the virus and a lasting protection (vaccination) against diseases by the same or related viruses. Immunity is the only weapon against viral disease.

Paradoxically, HIV is said to cause AIDS, by definition, only years after inducing very active antiviral immunity (3, 5). If this assertion were correct, HIV would be the first virus to cause a disease only after antiviral immunity. Yet the effectiveness of this immunity is the reason that provirus remains dormant and that free HIV cannot be found in AIDS patients (69). In view of this, vaccination of antibody-positive persons would appear to be completely superfluous, even if HIV were the cause of AIDS (3, 7, 12, 111–113). The claims of some scientists that antiviral antibodies fail to neutralize HIV (3, 32, 55, 56, 59, 113–115) are incompatible with the efficient immunity *in vivo* and with experimental evidence for virus-neutralizing activity *in vitro* (23, 115–119).

Although most viruses are eliminated by immunity, some, such as the retroviruses and the herpes viruses, may persist—severely restricted

by antiviral immunity—as latent infections (23, 86, 87). Such viruses can again become pathogenic, but only when they are reactivated. For example, upon reactivation, the herpes viruses cause fever blisters or zoster even in the presence of serum antibody (120). Reactivation may follow a decline of cellular immunity in response to other parasitic infections, radiation, or immunosuppressive therapy (23, 86). Further, it has been claimed that 8 years after primary infection and immunity, latent measles virus may cause subacute sclerosing panencephalitis (121) in about 1 case per million (86) and that another latent paramyxovirus may cause multiple sclerosis (121). However, these viruses could be isolated from each system in only 2 of 8 cases after cultivating millions of patient cells *in vitro* (121). Moreover, multiple sclerosis has since been suggested to be caused by a latent retrovirus closely related to HIV (122) and subacute encephalitis by HIV (28, 187). Thus, there is no proven precedent for the hypothesis that HIV causes AIDS only years after the onset of antiviral immunity and yet remains as inactive as it is in asymptomatic infections.

It has been proposed that pathogenic HIV mutants arise during the long intervals between infection and AIDS and that these mutants might escape antiviral immunity by losing specific epitopes (28, 31, 82, 90, 112, 113, 123, 124) or even by changing their host range from T cells to macrophages (44). However, there is no report of a mutant HIV present at high titer in AIDS. Further, it is very unlikely that a mutant could escape an existing immunity, because it would share most variable and, of necessity, all constant determinants with the parent virus. Even though all retroviruses, including HIV (125–128), mutate at a frequency of 1 in 10^4 nucleotides per replicative cycle, they have never been observed to escape an existing antiviral immunity. It has also been proposed that HIV escapes immunity by spreading via cell-to-cell transmission (28, 32, 115, 117, 129). However, consistent with the syncytium-blocking function of natural antibodies (23, 115, 119), there is no spread of HIV *in vivo*.

Intervals of 2 to 15 Years Between Infection and AIDS Are Incompatible with HIV Replication. If cytocidal viruses or retroviruses cause disease, they do so within 1 to 2 months of infection (23, 86). By that time, the host's immune system either eliminates the virus or restricts

it to latency, or the virus overcomes the immune system and kills the host. Indeed, clinicians have reported that, in rare cases, HIV causes a disease like mononucleosis prior to immunity, presumably due to an acute infection (23, 69, 130, 186). Since this disease correlates with viral activity (69) and disappears within weeks as the body develops antiviral immunity, it may reflect the true pathogenic potential of HIV.

Considering that HIV replicates within 2 days in tissue culture and induces antiviral immunity within 1 to 2 months (19, 23, 69, 130), the inevitably long and seemingly unpredictable intervals, ranging from 1 to 15 years (20, 35, 37), between the onset of antiviral immunity and AIDS are bizarre. The average latent period is reported to be 8 years in adults (21, 33–38) and 2 years in children (21, 36). Indeed, at least 2 years of immunity is required before AIDS appears in adults (7, 38). If one accepts that 50–100% of antibody-positive Americans eventually develop AIDS (7, 20–22, 33–37), the average 1.5% annual conversion corresponds to grotesque viral latent periods of 30 to 65 years. These intervals between HIV infection and AIDS clearly indicate that HIV by itself is not sufficient to initiate AIDS. Because all genes of HIV are expressed during the early immunogenic phase of the infection, AIDS should occur at that time, rather than years later when it is latent (23).

In an effort to rationalize the long intervals between infection and AIDS, HIV has been classified as a slow virus, or lentivirus (40), a type of retrovirus that is thought to cause disease only after long incubation periods (129). Yet there are no "slow" viruses. Since viral nucleic acids and proteins are synthesized by the cell, viruses must replicate as fast or faster than cells (i.e., within hours or days) to survive (86, 87).

Nevertheless, as pathogens, viruses may be (*i*) fast in acute infections that involve many actively infected cells, (*ii*) slow in subacute infections that involve moderate numbers of actively infected cells, or (*iii*) asymptomatic and latent. Retroviruses provide examples of each different pathogenic role. Acute infections with the "slow" Visna/Maedi retrovirus of sheep, a lentivirus, rapidly cause pneumonia (131), and those with equine anemia lentivirus cause fever and anemia within days or weeks of infection (132). Such infections typically generate titers of 10^4 to 10^5 infectious units per milliliter or gram of tissue (132, 133). The caprine arthritis-encephalitis lentivirus is also pathogenic within 2

months of inoculation (134). Acute infections with other retroviruses also rapidly cause debilitating diseases or cancers (23). This includes retrovirus infections that are now considered to be animal models of AIDS, termed simian or feline AIDS (12, 23, 30, 111, 135). Unlike HIV in AIDS, these viruses are all very active when they cause diseases, and the respective diseases appear shortly after infection (23). In rare cases, when antiviral immunity fails to restrict Visna/Maedi or other retroviruses, they persist as subacute symptomatic infections (3, 86, 129, 133). Under these conditions, Visna/Maedi virus causes a slow, progressive pulmonary disease (129, 133, 136) by chronically infecting a moderate number of cells that produce moderate titers of 10^2 to 10^5 virus particles per gram of tissue (136). However, in over 99% of all Visna/Maedi or caprine arthritis-encephalitis virus infections, and in most equine anemia virus infections, the retrovirus is either eliminated or restricted to latency by immunity, and hence asymptomatic, exactly like almost all other retroviruses in mice, chickens, cats, and other animals (23). For instance, 30–50% of all healthy sheep in the U.S., Holland, and Germany have asymptomatic Visna/Maedi virus infections (129, 137, 138), and 80% of healthy goats in the U.S. have asymptomatic caprine arthritis-encephalitis virus infections (133) in the presence of antiviral immunity.

Thus, the progressive diseases induced by active retroviruses depend on relative tolerance to the virus due to rare native or acquired immunodeficiency or congenital infection prior to immune competence. Since tolerance to HIV that would result in active chronic infection has never been observed and is certainly not to be expected for 50–100% of infections [the percentage of infections said to develop into AIDS (ref. 7 and above)], the rare retrovirus infections of animals that cause slow, progressive diseases are not models for how HIV might cause AIDS. Indeed, not one acute retrovirus infection has ever been described in humans (23).

The Paradox of How HIV, a Noncytocidal Retrovirus, Is to Cause the Degenerative Disease AIDS. Unlike cytocidal viruses, which replicate by killing cells, retroviruses need viable cells for replication (139). During retroviral infection, proviral DNA becomes a cellular gene as

it is integrated into the DNA of the cell. Such a mechanism is superfluous for a cytocidal virus. Virus reproduction from then on is essentially gene expression in viable cells, often stimulating hyperplastic growth (17, 23). Alternatively, retroviruses survive as latent proviruses, like latent cellular genes. The very distinction of not killing the host cell is the reason that scientists have for so long considered retroviruses to be the most plausible viral carcinogens (17, 23, 140).

Yet HIV, a retrovirus, is said to behave like a cytocidal virus, causing AIDS by killing billions of T cells (3, 5, 6, 12, 31). This is said even though some infected T-cell lines remain immortal (12, 23), and primary umbilical-cord blood cells may continue to divide in culture while propagating up to 10^6 infectious units per milliliter (82), much more than in AIDS patients. Also, there are no cytopathic changes or cell death in cultures of HIV-infected monocytes and macrophages (28, 141–146) and B cells (17, 23, 147). As is typical of retroviruses, HIV does not kill its host cells.

The cytocidal effects that are occasionally observed in HIV-infected cultures (but as yet, never in humans) soon after infection do not break this rule (23). These early effects result from fusions of HIV-infected and uninfected cells that depend on virus isolates and cell culture conditions (23, 82, 146, 147), and are completely inhibited by antiviral antibody (23, 115, 119). They are not HIV-specific, because many animal and human retroviruses show conditional, but never absolute, cytocidal effects in cell culture (23). Thus, the fusion effect in culture might be relevant for the mononucleosis observed in some patients soon after infection, when free virus (but no fusion-inhibitory antibody) is present. However, the effect cannot be relevant to AIDS because there is plenty of fusion-inhibitory antibody and because the virus isolates from some patients fuse, and those from others don't (23, 82, 146, 147). Thus, HIV is not sufficient to kill even the few T cells it infects in AIDS.

HIV Is a Conventional Retrovirus, Without an AIDS Gene. The virus-AIDS hypothesis proposes that HIV is an unorthodox retrovirus (6, 12, 14, 31, 32) containing specific suppressor and activator genes that control the 2- to 15-year intervals between infection and AIDS (12, 37,188). However, the two known HIVs (see below) are profoundly con-

ventional retroviruses. They have the same genetic complexity of about 9150 nucleotides, the same genetic structure, including the three major essential retrovirus genes linked in the order *gag-pol-env,* the same mechanism of replication, and the same mutation frequency (3, 7, 17, 90, 125, 126, 148) as all other retroviruses (17, 127, 128, 149, 150). Humans carry between 50 and 100 such retroviruses in their germ line, mostly as latent proviruses (151). The presumably specific genes of the HIVs (12, 188) are alternative reading frames of essential genes shared by all retroviruses (3, 7, 12, 23, 90, 148). Their apparent novelty is more likely to reflect new techniques of gene analysis than to represent HIV-specific retroviral functions. Indeed, analogous genes have recently been found in other retroviruses, including one bovine and at least three other human retroviruses that do not cause AIDS (23, 152, 188). Because HIV and all other retroviruses are isogenic, the newly discovered genes cannot be AIDS-specific. Moreover, it is unlikely that these genes even control virus replication. *In vivo,* HIV lies chronically dormant, although the presumed suppressor genes are not expressed. *In vitro,* HIV is propagated at titers of about 10^6 per ml in the same human cells in which it is dormant *in vivo,* although the presumed suppressor genes are highly expressed (23, 188). Therefore, I propose that antiviral immunity rather than viral genes suppress HIV *in vivo,* as is the case with essentially all retroviruses in wild animals (23). Further, I propose that the multiplicity of AIDS diseases are caused by a multiplicity of risk factors (see below), rather than by one or a few viral activator genes, since viral gene expression in AIDS is just as low as in asymptomatic carriers. Also, the extremely low genetic complexity of HIV can hardly be sufficient to control the inevitably long times between infection and AIDS, and the great diversity of AIDS diseases. Thus, there is neither biochemical nor genetic evidence that HIV genes initiate or maintain AIDS.

The Paradoxes of an AIDS Virus with Country- and Risk-Specific Pathologies and Host Ranges. It is yet another paradox of the virus-AIDS hypothesis that HIV is said to cause very different diseases in different risk groups and countries. For example, in the U.S. over 90% of AIDS patients have *Pneumocystis* pneumonia or Kaposi sarcoma. However, Kaposi sarcoma is found almost exclusively in homosexuals (8,

191). By contrast, in Africa over 90% of the AIDS cases are manifested by slim disease, fever, and diarrhea (9, 10, 64). Moreover, it is paradoxical that the prevalence of Kaposi sarcoma among U.S. AIDS cases has shifted down from 35% in 1983 (156) to 6% in 1988 (4) (see below and refs. 190 and 191), and *Pneumocystis* pneumonia has shifted up from 42% to 64% (8), while the alleged cause, HIV, has remained the same.

One explanation of these facts is that HIV is not sufficient to cause AIDS but depends critically on country- and risk-specific cofactors. However, the simplest explanation proposes that HIV is a harmless, idle retrovirus that is not the cause of AIDS.

In view of the claims that AIDS is a sexually transmitted viral syndrome (3, 7, 12), it is surprising (47, 64, 65, 91, 92, 154, 155) that, in the U.S., about 90% of all HIV carriers and AIDS patients are male (4, 7, 22, 38, 47). Even if one assumes that the virus was originally introduced into the U.S. through homosexual men (7), this epidemiology is hard to reconcile with the spread of a sexually transmitted virus 8 years later. In order to survive, a virus must infect new hosts, which it does most readily when it is at the highest titer (153). In the case of HIV, this would be before antiviral immunity, or 1 to 2 months after infection (69). Thus, the 8 years of AIDS in the U.S. represent about 50 to 100 human passages of HIV, enough time for the virus to equilibrate between the sexes. By contrast, the uniform sexual distribution of HIV in Africa appears consistent with a sexually transmissible virus, underscoring the paradox of the U.S. epidemiology, particularly since the viruses (12) and the epidemics (12–14, 90, 113) of both countries are thought to be equally new.

A solution of the paradox is that HIV is not new but is endemic in Africa and, like most retroviruses (23), is transmitted perinatally rather than sexually. Accordingly, 10% of healthy Zairians are antibody-positive (46, 98,184), and not more than 30% of the Kaposi sarcoma patients in Africa are infected with HIV (157, 158). Indeed, perinatal transmission between mother and child occurs with an efficiency of 30–50% (7, 22, 39), while sexual transmission is extremely inefficient (65, 79, 80, 154, 155). Since the virus is not endemic in the U.S., it is transmitted more often by parenteral exposures associated with risk behavior (see below) than perinatally.

Evolutionary Arguments Against AIDS Viruses. It is now claimed that there are at least two new retroviruses capable of causing AIDS, HIV-1 and HIV-2 (3, 7, 12–14), which differ about 60% in their nucleic acid sequences (148). Both allegedly evolved only 20 to <100 years ago (12). Since viruses, like cells, are the products of gradual evolution, the proposition that, within a very short evolutionary time, two different viruses capable of causing AIDS would have evolved or crossed over from another species is highly improbable (56, 64, 159). It is also improbable that viruses evolved that kill their only natural host with efficiencies of 50–100% as is claimed for the HIVs (7, 33–38).

Conclusions and Perspectives

It is concluded that HIV is not sufficient to cause AIDS because HIV meets neither Koch's postulates nor established epidemiological, biochemical, genetic, and evolutionary criteria of a viral pathogen. Further, it is concluded that HIV may not even be necessary for AIDS because there is neither biochemical nor genetic evidence that it initiates or maintains AIDS. HIV infiltration and activity are just as low in symptomatic carriers as in asymptomatic carriers, and HIV lacks an AIDS gene. The association between AIDS and antibody to HIV—now part of the definition of AIDS—does not prove causation because otherwise indistinguishable diseases are now set apart only on the basis of this antibody. According to this view, HIV is an ordinary harmless retrovirus that, in rare acute infections, may cause a mononucleosis-like disease before immunity.

Antibody to HIV Is a Surrogate Marker for Risk of AIDS. Although HIV does not appear to cause AIDS, it may serve in the U.S. and Europe as a surrogate marker for the risk of AIDS for the following reasons. (*i*) In these countries, HIV is not widespread but is one of the most specific occupational infections of persons at risk for AIDS (3, 7, 38, 47, 61, 94, 160). (*ii*) Since HIV is extremely difficult to transmit, like all latent viruses, it would specifically identify those who habitually receive transfusions or intravenous drugs or are promiscuous. Indeed, the probability of being antibody-positive correlates directly with the frequency

of drug use (38, 47, 160), transfusions (94, 161), and male homosexual activity (38, 160). (*iii*) Since HIV is not cytocidal, it persists as a minimally active virus in a small number of cells, which will chronically boost antiviral immunity to produce a positive AIDS test. Latent EBV, cytomegalovirus, or other herpes virus infections will likewise maintain a chronic immunity (86, 120), although less specific for AIDS risk. By contrast, antibodies against viruses and microbes, which cannot persist at subclinical levels, tend to disappear after primary infection.

Epidemiology Is Not Sufficient to Prove Etiology. It has been argued that Koch's postulates can be abandoned as proof for etiology in favor of epidemiological correlations (67, 68, 162), most recently in the case of HIV (14, 32). However, adherence to this epidemiological concept (68, 162) as a substitute for biochemical and genetic proof of etiology has resulted in some of the most spectacular misdiagnoses in virology. (*a*) Based on epidemiological correlations, EBV was thought to be the cause of Burkitt lymphoma—until Burkitt lymphomas free of the virus were discovered (163). [It is ironic that HIV is currently a proposed cause of Burkitt lymphoma (5).] (*b*) Also on the basis of seroepidemiological evidence, retroviruses were thought to cause human and bovine leukemias after bizarre latent periods of up to 40 years in humans (164), until the discovery of these viruses in billions of normal cells of millions of asymptomatic carriers cast doubt on this hypothesis (23). It is scarcely surprising that the particular T cell from which a rare clonal leukemia originated was also infected. It is consistent with this view that these tumors are clonal and not contagious, like virus-negative leukemias, and that the presumably causative viruses are biochemically inactive in the human and bovine leukemias (23). Instead of viruses, the only specific markers of such tumors are clonal chromosomal abnormalities (23). (*c*) Likewise, slow viruses have gained acceptance as causes for such diseases as kuru, Creutzfeld-Jacob disease, and Alzheimer disease on the basis of epidemiological evidence (165), although these viruses have never been detected.

Proof of Etiology Depends on Evidence for Activity. Regrettably, the hasty acceptance of the virus as the cause of AIDS (16), signaled by

naming it HIV (18), has created an orthodoxy whose adherents prefer to discuss "how" rather than "whether" HIV causes AIDS. They argue that it is not necessary to understand HIV pathology, or how a latent virus kills, in order to claim etiology (7, 14, 32, 51). Therefore, many different mechanisms, including ones in which HIV is said to depend on cofactors to cause AIDS, have been discussed (6, 12, 31, 32, 35, 61, 91) to explain how the virus supposedly kills at least 10^4 times more T cells than it actively infects (26–28, 71–74). Yet all speculations that HIV causes AIDS through cofactors cast doubt on HIV as a cause of AIDS, until such factors are proven to depend on HIV.

In contrast to what is claimed for HIV, there is unambiguous genetic evidence that biochemical activity in or on more cells than the body can spare or regenerate is absolutely necessary for viral or microbial pathogenicity. Examples are transformation-defective mutants of Rous sarcoma virus (166) and replication-defective mutants of cytocidal viruses (87). If latent viruses or microbes were pathogenic at the level of activity of HIV, most of us would have *Pneumocystis* pneumonia (80–100%) (167), cytomegalovirus disease (50%) (88), mononucleosis from EBV (50–100%) (see above; ref. 88), and herpes (25–50%) (88) all at once, and 5–10% also would have tuberculosis (168), because the respective pathogens are latent, immunosuppressed passengers in the U.S. population at the percentages indicated. Since we can now, through molecularly cloned radioactive probes, detect latent viruses or microbes at concentrations that are far below those required for clinical detectability and relevance, it is necessary to reexamine the claims that HIV is the cause of AIDS.

In response to this, it has been argued that a biochemically inactive HIV may cause AIDS indirectly by a mechanism(s) involving new biological phenomena (12, 14, 31, 32). This is argued even though HIV is like numerous other retroviruses studied under the Virus-Cancer Program during the last 20 years (17, 140), which are only pathogenic when they are biochemically active (23). Nevertheless, some retroviruses (23) and DNA viruses [e.g., hepatitis virus in hepatomas (169)] are thought to cause tumors indirectly by converting, by means of site-specific integration, a specific gene of a rare infected cell to a cancer gene. Such a cell would then grow autonomously to form a monoclonal tumor, in

which the virus may be inactive and often defective (17, 23, 140, 169). However, such highly specific, and hence rare, virus-cell interactions cannot explain the loss of billions of cells during a degenerative disease like AIDS. It is also hard to accept that HIV could cause AIDS through a T cell autoimmunity (12, 31, 32, 170), because it reaches far too few cells to function as a direct immunogen and because it is unlikely to function as an indirect immunogen since it is not homologous with human cells (73, 75, 77). Further, it is extremely unlikely that any virus could induce autoimmunity, which is a rare consequence of viral infection, as efficiently as HIV is thought to cause AIDS, namely in 50–100% of all infections.

Not All AIDS Diseases Can Be Explained by Immunodeficiency. Clearly, immunodeficiency is a plausible explanation for the microbial and viral AIDS diseases (5) and *Pneumocystis* pneumonia. However, the effective immunity against HIV, which defines AIDS, together with those against cytomegalovirus, herpes simplex virus, hepatitis virus, and other viruses (3, 23, 61, 94), is hard to reconcile with acquired immunodeficiency. One would have to argue that T cell depletion in AIDS is highly selective in order to allow *Pneumocystis* but not HIV or other viruses to become active. If HIV were able to induce T cell immunodeficiency against itself, its titer during AIDS should be as high as it is in cultures of infected human monocytes—namely, up to 10^6 infectious units per milliliter (see above), just as high as the titers of all other retroviruses when they are pathogenic in animals (23).

Moreover, immunodeficiency does not explain AIDS neoplasias such as lymphomas or Kaposi sarcoma, which may be a hyperplasia (175, 178). The hypothesis that cancers reflect a defective immune system, the immune-surveillance hypothesis (176), has been disproven through athymic (nude) mice, which develop no more cancers than other laboratory mice (177). In fact, no immunodeficiency was observed in HIV-infected African patients who had Kaposi sarcomas (157, 158). In addition, Kaposi sarcoma tissue does not contain any HIV (23, 178, 179). Immunodeficiency also cannot explain dementia; nor can dementia be explained by HIV infection of neurons, because retroviruses are dependent on mitosis for infection (17, 23, 139, 140) and neurons do

not divide (169). HIV would indeed be a mysterious virus (31) to kill T cells and neurons that are not infected and, at the same time, to induce hyperplastic or neoplastic growth of other cells that are also not infected.

HIV Is Not a Rational Basis for AIDS Therapy. Since there is no proven mechanism of HIV pathogenesis, HIV is not a rational basis for the control of AIDS. Thus the treatment of symptomatic and even asymptomatic HIV carriers with azidothymidine (AZT) (7, 39) cannot be justified in terms of its original design, which is to inhibit HIV DNA synthesis by chain termination (171). Even if HIV were to cause AIDS, it would hardly be a legitimate target for AZT therapy, because in 70–100% of antibody-positive persons proviral DNA is not detectable (73, 75, 187) without amplification (77), and its biosynthesis has never been observed.

Nevertheless, AZT has been claimed to have beneficial effects for AIDS patients on the basis of a 16- to 24-week double-blind trial (194). However, AZT, originally developed for chemotherapy by terminating cellular DNA synthesis, efficiently kills dividing blood cells and other cells (39, 84, 172–174, 189, 193, 195) and is thus directly immunosuppressive. Moreover, the immediate toxicity of AZT (174, 189, 193, 195) suggests that this trial could hardly have been double-blind and hence unbiased.

What Are the Causes of AIDS? I propose that AIDS is not a contagious syndrome caused by one conventional virus or microbe, because no such virus or microbe would average 8 years to cause a primary disease, or would selectively affect only those who habitually practice risk behavior, or would be able to cause the diverse collection of over 20 degenerative and neoplastic AIDS diseases. Neither could a conventional virus or microbe survive if it were as inefficiently transmitted as AIDS, and killed its host in the process. Conventional viruses either are highly pathogenic and easy to transmit or are nonpathogenic and latent and hence very difficult to transmit (153). Conventional viruses or microbes also exist that cause secondary—or even primary—diseases long after infection, but only when they are activated from dormancy by rare acquired deficiencies of the immune system (86). Such opportunistic infections are the consequence rather than the cause of immunodeficiency.

Since AIDS is defined by new combinations of conventional diseases, it may be caused by new combinations of conventional pathogenic factors. The habitual administration of factor VIII or blood transfusions (94, 161) or of drugs (47, 64, 160, 190–192), chronic promiscuous male homosexual activity that is associated with drugs (64, 160, 191), numerous acute parasitic infections, and chronic malnutrition (159, 160)—each for an average of 8 years—are factors that appear to provide biochemically more tangible and plausible bases for AIDS than an idle retrovirus. Indeed, the correlation between AIDS and such factors is 95% (4, 5). Among these factors, EBV, cytomegalovirus, herpes simplex virus, and administration of blood components and factor VIII have all been identified as causes of immunodeficiency not only in HIV-positive, but also in HIV-negative, hemophiliacs (11, 61, 94, 161). In fact, the dose of factor VIII received was found to be directly proportional to subsequent immunodeficiencies (94, 161). The habitual admission of narcotic toxins appears to play a major immunosuppressive role in the U.S. and Europe (11, 64). About 30% of the American AIDS patients are confirmed users of injected drugs (4, 47). Because of the difficulties in assessing drug data (47, 91, 92), it is probable that the percentage who use injected and/or noninjected drugs is even higher (64, 155, 185, 190–192). For example, nine different drugs were used in combination by a cohort of antibody-positive homosexuals in San Francisco (160). Again there are quantitative drug-AIDS correlations. For example, the decreased use of nitrite inhalants was shown to correlate with the decreased incidence of Kaposi sarcoma in homosexuals (190, 191). Moreover, that the Kaposi sarcoma cases decreased exactly with the use of nitrites, rather than lagging behind it by 8 years as would be expected from the presumed 8-year latent period of HIV, argues directly against a role of HIV in Kaposi sarcoma. Further, it has been documented that protein malnutrition and parasitic infections are the most common causes of T cell immunodeficiency worldwide, particularly in developing countries (181). Unlike HIV, the specifics of these risk factors provide a plausible explanation for the risk specificity of AIDS diseases. The long and unpredictable intervals between the appearance of antibody to HIV and the onset of AIDS would then reflect the thresholds for these factors to cause AIDS diseases, rather than an unlikely

mechanism of HIV pathogenesis.

In response to this view it is often pointed out that AIDS risks have existed for a long time (55, 59), whereas AIDS is said to be a new syndrome (3, 7, 12–14). However, this argument fails to consider that the major risk groups—male homosexuals and intravenous drug users—have only become visible and acceptable in the U.S. and in Europe during the last 10 to 15 years, about the same time that AIDS became visible. Acceptability facilitated and probably enhanced risk behavior, and thus the incidence of the many diseases now called AIDS. Increased consumption of drugs was reported to have increased the number of drug-related deaths, although unconfirmed HIV infections were the prefered interpretation (190, 192). Moreover, the particular permissiveness toward these risk groups in metropolitan centers encouraged the clustering of cases that was necessary to detect AIDS. Further, it has been pointed out that slim disease, fever, and diarrhea in Africa are not a new epidemic, but old diseases under a new name, caused by previously known infectious agents and malnutrition (11, 64, 98, 182).

This analysis offers several benefits. It ends the fear of infection by HIV, and particularly of immunity to HIV, because it proves that HIV alone is not sufficient to cause AIDS. To determine whether HIV is necessary for AIDS, controlled, randomized analyses (196) either of risk takers who differ only by the presence of antibody to HIV or of antibody-positive individuals who differ only in taking AIDS risks must be carried out. Moreover, assessment of a pathogenic potential of HIV would depend on evidence that the life-span of antibody-positive risk takers is shorter than that of antibody-free controls. In addition, it should be determined whether, prior to 1981, AIDS-risk takers ever developed what are now called AIDS diseases. This analysis also suggests studies on how the nature, frequency, and duration of AIDS risks generate risk-specific diseases. Such studies should include persons treated with AZT before or after AIDS symptoms to assess the AIDS risks of AZT. To this end, diseases should be reported by their original names (8–10), rather than as AIDS (4) because of their association with antibody to HIV. Finally, this analysis suggests that AIDS prevention efforts be concentrated on AIDS risks rather than on transmission of HIV (43).

Acknowledgments

This article is dedicated to the memory of Charlotte Friend. I am very grateful to Klaus Cichutek, Dawn Davidson, Thelma Dunnebacke-Dixon, David Goodrich, Steve Martin, Seth Roberts, Harry Rubin, Russell Schoch, Gunther Stent, and Ren-Ping Zhou (Berkeley); Jad Adams and Mike Verney-Elliott (London); Ruediger Hehlmann (Munich); George Miller (New Haven); Nicholas Regush (Montreal); and Harvey Bialy, Celia Farber, John Lauritsen, Nathaniel Lehrman, Katie Leishman, Anthony Liversidge, Craig Schoonmaker, and Joseph Sonnabend (New York) for encouragement, critical information, discussions, or reviews of this manuscript and, above all, for common sense. Further, the Chairman of the *Proceedings* Editorial Board is acknowledged for providing critical reviews and comments. P.H.D. is supported by Outstanding Investigator Grant 5-R35-CA39915-03 from the National Cancer Institute and Grant 1547AR1 from the Council for Tobacco Research.

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Chapter Four

AIDS Epidemiology: Inconsistencies with Human Immunodeficiency Virus and with Infectious Disease

Proc. Natl. Acad. Sci. USA, Vol. 88, pp. 1575–1579, February 1991
Contributed by Peter H. Duesberg, October 11, 1990.

Abstract

The newly defined syndrome AIDS includes 25 unrelated parasitic, neoplastic, and noninfectious indicator diseases. Based on epidemiological correlations, the syndrome is thought to be due to a new, sexually or parenterally transmitted retrovirus termed human immunodeficiency virus (HIV). The following epidemiological data conflict with this hypothesis. (i) Noncorrelations exist between HIV and AIDS; for example, the AIDS risks of infected subjects vary >10-fold with their gender or country. Abnormal health risks that are never controlled as independent AIDS causes by AIDS statistics, such as drug addiction and hemophilia, correlate directly with an abnormal incidence of AIDS diseases. Above all, the AIDS diseases occur in all risk groups in the absence of HIV. (ii) American AIDS is incompatible with infectious disease, because it is almost exclusively restricted to males (91%), because if it occurs, then only on average 10 years after transfusion of HIV, because specific AIDS diseases are not transmissible among different risk groups, and because unlike a new infectious disease, AIDS has not spread exponentially since the AIDS test was established and AIDS received its current definition in 1987. (iii) Epidemiological evidence indicates that HIV is a long-established, perinatally transmitted retrovirus. HIV acts

as a marker for American AIDS risks, because it is rare and not transmissible by horizontal contacts other than frequent transfusions, intravenous drugs, and repeated or promiscuous sex. It is concluded that American AIDS is not infectious, and suggested that unidentified, mostly noninfectious pathogens cause AIDS.

Introduction

> Epidemiology is like a bikini: what is revealed is interesting; what is concealed is crucial.

AIDS is a newly defined syndrome of 25 old parasitic, neoplastic, and noninfectious diseases, including in the United States 53% pneumonia, 19% wasting disease, candidiasis, 11% Kaposi sarcoma, 6% dementia, 3% lymphoma, and 2% tuberculosis (1). These unrelated diseases are grouped together because they are all thought to be indicators of an acquired immunodeficiency (2). In America AIDS is almost completely restricted (91%) to males (1). About 90% of all AIDS patients are 20- to 40-year-olds, 30% are intravenous drug users and their children, 60% are male homosexuals and some heterosexuals who frequently use oral psychoactive drugs (3–7), and 7% are hemophiliacs and other recipients of transfusions (1).

As of 1982, the Centers for Disease Control (CDC) considered AIDS infectious because it appeared to be transmitted among intravenous drug users and homosexuals by sexual contact or by contaminated blood (8). Among infectious agents, cytomegalovirus and various bacteria were proposed as causes of AIDS (6, 8, 10). In 1983 Montagnier and coworkers (11) suggested lymphadenopathy-associated virus [now termed human immunodeficiency virus (HIV)] and Gallo et al. (12) human T-cell leukemia virus (HTLV) as causes of AIDS. However, psychoactive drugs, like aphrodisiac nitrite inhalants ("poppers"), were also proposed as causes for Kaposi sarcoma and pneumonia in homosexuals (3–7, 9).

In April 1984 the Secretary of Health and Human Services announced that HIV was the cause of AIDS, and an antibody test for HIV, termed the AIDS test, was registered as a patent by Gallo and col-

laborators (13–15). This happened before even one American study on HIV had been published (13). According to this view HIV is a lymphotropic retrovirus that is sexually transmitted (16–20). On average 10–11 years after infection and appearance of neutralizing antibodies, HIV is postulated to cause immunodeficiency by killing billions of T cells (16–21). Only then, indicator diseases are said to develop from which patients die on average within 1 year (21–26). Thus HIV became the first virus for which a positive antibody test is interpreted as an indicator for primary diseases that have yet to come. Antibodies against conventional viruses typically signal protection against disease and those against some persistent viruses also signal a small risk of secondary disease upon virus reactivation (27, 28). Although no retrovirus has ever been shown to be pathogenic in humans (29), HIV is thought to be 50–100% fatal, more than any other human virus (16–21). The novelty of AIDS is postulated to reflect the novelty of HIV. The large variety of indicator diseases are postulated to reflect underlying immunodeficiency, and the almost exclusive concentration of AIDS in 20- to 40-year-olds (1) is postulated to reflect sexual or parenteral transmission of HIV (16–20).

This virus-AIDS hypothesis was accepted by most medical scientists, in particular virologists, by 1986 (16–18, 30). Accordingly, the virus was named HIV by an international committee of retrovirologists (30) and became the only basis for the definition of AIDS: "Regardless of the presence of other causes of immunodeficiency, in the presence of laboratory evidence for HIV, any disease listed ... indicates a diagnosis of AIDS" (2). AIDS is now diagnosed whenever antibody to HIV is detectable along with any of the 25 indicator diseases, even if no immunodeficiency or opportunistic infections are detected, as in cases of Kaposi sarcoma, lymphoma, dementia, and wasting syndrome (2, 18, 23–26, 31). Moreover, infection in the absence of any clinical symptoms is now termed, and often treated as, "HIV disease" (18). However, all efforts directed by the virus-AIDS hypothesis, for over 2 billion dollars annually, have failed to contain or cure AIDS (32, 33).

Since 1987 I have challenged the virus-AIDS hypothesis because HIV is latent and is present in only 1 out of 500 T cells during AIDS, because retroviruses typically do not kill cells, and because AIDS appears

on average 10 years after the virus has been neutralized by antibodies (7, 29, 34). In response to this challenge it was agreed that the hypothesis cannot be defended in terms of orthodox virology, based on known genetic and biochemical properties of HIV (35–47). However, it was claimed that epidemiological evidence supports the virus-AIDS hypothesis (35, 36, 38–41, 44–47) and that Gallo (48), Montagnier (editorial comment in ref. 7, p. 5), and possibly others (editorial footnote in ref. 34, p. 755) would prove it. Here this epidemiological evidence is called into question.

Noncorrelations Between AIDS and HIV

AIDS Risks of HIV-Infected Persons Differ 10- to 65-Fold Depending on Their Country. If AIDS is caused by HIV, the ratio of infected to diseased carriers should be similar in different countries. However, in the United States about 10% (or 100,000) (1) of 1 million HIV-positives (16, 18, 49, 50) have developed AIDS since 1985, but in Uganda only 0.8% (or 8000) of 1 million (51), and in Zaire only 0.15% (4636) (52) of 3 million HIV-positives (34). Although AIDS surveillance by some African countries has been questioned, surveillance by Uganda is reported as "highly successful," providing "the highest number ... of cases ... in Africa" (51). Since the HIV epidemics of both the United States and Africa are said to be new and to have an African origin (17, 20, 36, 45), but the AIDS risks of infected Americans are 10- to 65-fold higher than those of Africans, country-specific pathogens are necessary for AIDS. Moreover, if AIDS equaled opportunistic infections resulting from immunodeficiency, more, instead of less, AIDS per HIV carrier would be expected in Africa than in the United States.

AIDS Risks Among HIV-Infected Americans Differ About 10-Fold Based on Gender. Since 1985 the U.S. Army has tested 1.15×10^6 male and female 17- to 19-year-old recruits for antibodies to HIV. Every year 0.03% of the males and females in this age group were found to be HIV-positive (53). Although HIV has been distributed equally between the sexes among 17- to 24-year-old Americans for the last 5 years, about 10

times more AIDS cases have occurred in males (1, 53). Ninety-five percent of these were either intravenous drug users or homosexuals (1, 53).

Abnormal Health Risks Correlate Directly with the Incidence of AIDS Diseases. Since 97% of the American AIDS patients come from behavioral or clinical health-risk groups and since the incidence of AIDS indicator diseases in risk-matched, HIV-free control groups is never reported (1), it may be argued that pathogens associated with abnormal lifestyles are causing AIDS (3–7, 32, 34, 54)—particularly because the diseases are risk-specific (see below).

In response to this, it has been pointed out that AIDS occurs outside the major risk groups in Americans and Africans. However, to date only 3900, or about 3%, of all American AIDS cases have come from groups without health risk (1). These represent 25 conventional diseases that occurred in a country of 250 million inhabitants over the last 9 years (1). To determine whether these diseases are due to HIV, their incidence must be compared with that in the normal, HIV-free population. However, this has not been done, because these diseases are only reportable and recorded by the CDC as AIDS if HIV is present (1). Thus there is no controlled epidemiological evidence that HIV is pathogenic in the normal United States population. The same is true for Africa. The cumulative incidence of AIDS from 1986 to 1989 in Uganda was only 8000 (0.8%) out of 1 million HIV-positives (51), or about 0.2% annually. (Most AIDS statistics are cumulative and thus always increasing.) Since >90% of these cases are common African diseases like slim disease, fever, diarrhea, and tuberculosis (34, 51) and their incidence in HIV-free controls is not reported, it is uncertain whether HIV is pathogenic in Africa.

Further, it has been argued based on anecdotal cases that AIDS did not exist prior to HIV in clinical health-risk groups such as *(i)* hemophiliacs, *(ii)* other recipients of transfusions, *(iii)* children of drug-addicted mothers, and *(iv)* drug addicts (1, 18, 35, 36, 38, 44, 45, 47). However, competing causes for AIDS diseases have not been excluded in any of these cases.

(i) Transfusions of blood and factor VIII and intrinsic deficiencies

associated with hemophilia, acting over the long time periods said to be latent periods of HIV, have all been identified as pathogenic factors for AIDS-like diseases in hemophiliacs (55–61). To determine whether HIV or clinical deficiencies and their treatment cause AIDS in hemophiliacs, either controlled epidemiological studies comparing matched hemophiliacs, with and without HIV, or epidemiological evidence that the mortality of hemophiliacs is increased by HIV would be necessary.

Surprisingly, in view of the many claims that HIV causes AIDS in hemophiliacs, there is not one controlled study that has found HIV to be a health risk. There is also no report from any country that the mortality rate of hemophiliacs has increased due to the infection of hemophiliacs with HIV (59). In fact, it appears to be lower than ever (56, 59). About 75% of the 20,000 severe hemophiliacs in the United States are reported to be HIV-positive at least since 1980 to 1982, owing to the administration of blood or factor VIII (16, 18, 59, 61, 62). Because the administration of plasma fractions prepared from large numbers of donors started in 1965, many hemophiliacs may have been HIV-positive for >10 years now (56, 59). Since 50–100% of HIV-infected persons are postulated to develop AIDS after an average latent period of 10 years (18, 21, 34), at least half of the 15,000 HIV-positive hemophiliacs should have died from AIDS. Yet <2% of the 15,000 HIV-positive hemophiliacs in the United States have died with a diagnosis of AIDS in 1988 and in 1989 (1).

The low annual incidence of AIDS-like diseases among hemophiliacs in the United States is likely to reflect hemophilia-related morbidity and mortality under a new name. Indeed, among American hemophiliacs infected for an average of at least 10 years with HIV, elapsed time as a hemophiliac stands out as the critical determinant for AIDS diseases. The median age of hemophiliac AIDS patients is 34 years, or 14 years higher (59) than that of their asymptomatic peers, which is 20–22 years (16, 59).

(ii) The thesis that HIV transfusions cause AIDS in other patients is also entirely uncontrolled (36). Indeed, a controlled study might be difficult because 50% of American patients (other than hemophiliacs) die within 1 year (58) and 60% within 3 years (63) after a transfusion—long before the average 10 years that HIV is said to require for patho-

genicity have elapsed. The pathogenic conditions that necessitated the transfusions are obviously deadlier than the hypothetical pathogen HIV.

(iii) About 95% of the children with AIDS in the United States were subject to pathogenic conditions other than the putative pathogen HIV, either drug addiction of the mother or deficiencies of their own that required blood transfusions (1). The remainder probably reflects normal morbidity of infants born to healthy mothers who are perinatally (see below) or iatrogenically infected by HIV.

(iv) A rare controlled study showed that among 297 asymptomatic, HIV-positive intravenous drug users the AIDS risk over 16 months was 3 times higher in those who persisted than in those who stopped injecting drugs (95).

Since the incidence of AIDS diseases in non-risk groups appears normal, and since the abnormal incidence of AIDS diseases in risk groups correlates directly with their abnormal health risks, there is no epidemiological evidence that HIV is pathogenic. Although longitudinal studies of selected risk groups claim, some even without published data or references (64), that HIV-positives have more AIDS, none of these studies have controlled the negatives for all health risks and selection biases (18, 47, 62, 65).

AIDS Indicator Diseases Occur Without HIV in All Risk Groups. Tsoukas et al. (61) observed severe immunodeficiency in 6 of 14 HIV-free and 9 of 15 HIV-positive hemophiliacs. Ludlam et al. (60) described a group of 15 hemophiliacs who had acquired immunodeficiency before they were infected by HIV. Others observed HIV in only 7 of 19 (55) or 10 of 19 (66) hemophiliacs who had very similar immunodeficiencies. However, direct correlations were observed between the degree of immunodeficiency and the amount of clotting factor consumed, in both HIV-negatives and HIV-positives (60, 66).

A prospective study from Canada identified immunodeficiency in 33 of 161 HIV-free homosexual men. Nine of these became subsequently infected by HIV (65). Further, a recent study identified initially 6 and now 12 HIV-free Kaposi sarcoma cases in male American homosexuals, some of which occurred in the absence of immunodeficiency (67,

68). Others recorded the occurrence of Kaposi sarcoma in AIDS risk groups long before AIDS (57). And recently, CDC workers have postulated a Kaposi agent other than HIV, because of the almost exclusive occurrence of Kaposi sarcoma in homosexuals among AIDS risk groups (69). Moreover, there is no trace of HIV even in the Kaposi sarcomas of patients in which antibody to HIV is confirmed (34). Thus HIV is necessary neither for immunodeficiency nor for Kaposi sarcoma in homosexuals, although their association is perceived as the hallmark of AIDS (68, 69).

Among intravenous drug users in New York representing a "spectrum of HIV-related diseases," HIV was not observed in 26 of 50 pneumonia deaths, 15 of 22 endocarditis deaths, and 5 of 16 tuberculosis deaths (70). Likewise, no HIV was observed in 24 of 54 prisoners with tuberculosis in New York State, of whom 47 were street-drug users (71). Similar neurological deficiencies were recently observed in 12 HIV-infected and 16 uninfected infants from drug-addicted mothers (72). In a group of 21 heroin addicts, of whom only 2 were infected by HIV, the ratio of helper to suppressor T cells was found to decline within 13 years from a normal of 2 to <1 (73), which is typical of AIDS (16).

Since all AIDS indicator diseases occur in AIDS risk groups in the absence of HIV, HIV is not a necessary cause for these diseases (except for their diagnosis as AIDS). Current AIDS statistics probably include additional HIV-free cases because HIV was confirmed up to 1989 in only about 73% of all American AIDS cases, and in only 39% of the AIDS cases from New York and 61% from California (74). Moreover, statistics are biased in favor of HIV-positive cases because AIDS is reportable whereas most HIV-free indicator diseases are not (57).

Inconsistencies Between AIDS and Infectious Disease

AIDS Diseases That Are Not Male-Specific Show a 10-Fold Preference for Males. The distribution of conventional sexually transmitted diseases is almost even between the sexes (75). By contrast American AIDS occurs almost exclusively (91%) in males, although none of the

25 AIDS diseases is male-specific (1). However, African AIDS appears largely compatible with infectious diseases that strike without preference for sex, risk, and age groups (17, 18, 51) and that hardly overlap with American AIDS (see below).

Latent Periods of 10 Years Are Not Compatible with Infectious Disease. Viruses, retroviruses, and HIV are immunogenic and biochemically most active within weeks or months after infection (27, 28, 34, 76, 77). There is no precedent for an infectious agent that causes primary diseases on average only years after it is neutralized by antibodies (27, 28, 38, 39). Yet HIV is claimed to cause AIDS on average 10 years after transfusion in adults and only after 2 years in children (18, 34, 62). The diversity of these latent periods is inconsistent with one infectious agent, and their magnitude is characteristic for diseases caused by chronic exposure to toxic substances.

Specific AIDS Diseases Are Not Transmissible Among Different Risk Groups. If AIDS diseases are caused directly by HIV or are due to HIV-induced immunodeficiencies and available parasites, all infected subjects should have the same risk of developing those AIDS diseases that are not associated with group- or region-specific parasites. However, 53% of American AIDS patients have *Pneumocystis* pneumonia and 13% have candidiasis (1), whereas 90% of the African AIDS patients have slim disease, fever, diarrhea, and tuberculosis but not pneumonia and candidiasis (34, 51), although *Pneumocystis carinii* and candida are ubiquitous in humans, including Africans (34, 78, 79). In addition, the AIDS diseases of American children are different from those of adults—namely, 50% pneumonia, 16% wasting disease, 12% dementia, and 20% bacterial infections, which are exclusively diagnosed in children (1). Further, in the United States, Kaposi sarcoma occurs 20 times more often in homosexuals than in hemophiliacs and intravenous drug users (69), often in the absence of immunodeficiency (23–26, 67). Thus, specific AIDS diseases are not transmissible among different risk groups, suggesting that distinct, nontransmissible pathogens must be primary causes.

Unlike New Infectious Diseases, AIDS Does Not Spread Exponentially. AIDS is said to be a new sexually transmitted disease (17, 18, 36, 45). The epidemiological hallmark of a new transmissible disease is that it spreads exponentially until it has saturated a susceptible pool of the population, a process described by Farr's law (80). Therefore AIDS would be expected to increase in the sexually active population at an exponential rate, provided there is at least some promiscuity. Yet since the AIDS test has been established and AIDS was given its current definition in 1987 (2), AIDS has spread very slowly, claiming among >100 million sexually active Americans only 20,000–30,000 cases annually (1).

Epidemiological Evidence That HIV Is Not Pathogenic

HIV Is Epidemiologically Not New. Since 1985, when HIV infection became detectable with the "AIDS test," the number of infected Americans has remained constant at about 1 million, or 0.4% of the population (16, 18, 49, 50). Likewise, the percentage of HIV-positive male and female U.S. Army recruits has remained constant at 0.03% for 5 years, although >70% of 17- to 19-year-olds are sexually active and about 50% are promiscuous (53, 62). The strikingly constant incidence of HIV indicates that it is epidemiologically not new in the United States and thus not a plausible cause for the new epidemic AIDS.

HIV Depends on Perinatal Transmission for Survival and Is Thus Not Likely to Be Fatally Pathogenic. Due to the absence of HIV in the semen of 24 of 25 HIV-positive men, with one provirus detected per 10^6 cells (81), and due to the chronic latency and presence of HIV provirus in only 1 of 500 susceptible lymphocytes (34, 82), HIV depends on an average of about 500 sexual contacts to be transmitted (83, 84). Perhaps even more contacts are necessary, because only about 15% of the wives of hemophiliacs are HIV-positive (20), although about 75% of severe hemophiliacs in the United States have been positive for 8–10 years. Therefore it is unlikely that HIV could survive by sexual transmission. Further, it is unlikely to be preferentially transmitted by homo-

sexual males, since about 10% of both males and females frequently practice anal intercourse (62).

Based on animal and human models, retroviruses depend almost exclusively on perinatal transmission for survival. They are very difficult to transmit horizontally by immune competent animals and humans, because they are chronically suppressed, first by maternal antibody and then by the baby's own (76, 77), and possibly also by cellular suppressors (34). Even retroviruses with sarcomagenic or leukemogenic oncogenes have never spread horizontally in breeding colonies (29, 85). Therefore, specific strains of mice, chickens, or humans from geographically distinct regions are often marked for generations by distinct strains of perinatally transmitted, latent retroviruses (85, 86). For example, HTLV is endemic in certain islands of Japan and marks specific ethnic groups among mixed populations in the Caribbean (86). Wild animals (29, 85, 86) or humans (42, 43, 86) with an acute retrovirus infection are virtually never observed. Acute retrovirus infections result from experimental infection or horizontal infections among mass-bred animals, typically prior to immune competence with virus strains not covered by maternal antibodies (76, 77, 85).

Since perinatal transmission of HIV is at least 50% efficient (18, 20, 34, 62), and sexual transmission is <0.2% efficient, it appears that HIV, like other retroviruses, depends on perinatal transmission for survival. Therefore, it cannot be fatally pathogenic in most infections within 2–10 years, as postulated by the virus-AIDS hypothesis. This provides the only plausible explanation for the random distribution of HIV in even as few as 0.03% of 17- to 19-year-old healthy Americans (53) and in about 10% of Africans of all ages (31, 34, 49, 51). This explains why no more than 2456 AIDS cases have been recorded among about 75 million Americans under the age of 19 in the last 9 years (1), although at least 0.03%, or 25,000, can be estimated to be perinatally infected (53). It appears that >90% of perinatally infected Americans are asymptomatic for at least 19 years.

Antibody to HIV Is a Marker for American AIDS Risks. American AIDS risk groups and patients are marked by antibodies not only to HIV but also to many other viruses and microbes, such as

cytomegalovirus, hepatitis virus, herpes simplex virus, HTLV, parvovirus, Epstein-Barr virus, genital papilloma virus, *Treponema, Neisseria,* amoebae, candida, and mycoplasma (1, 5, 6, 10, 12, 54, 57, 67, 75, 78, 87, 88). Among these, antibodies to HIV and HTLV are perhaps the most specific markers because their prevalence in AIDS patients is 73% (74) and 25% (87), respectively, but only 0.03% (53) and 0.025% (86) in the general United States population.

Because AIDS patients carry antibodies to many more viruses and microbes, in particular, rare ones such as HTLV, than the general population, it is arbitrary to delineate HIV as an etiologic agent of AIDS by the presence or titer of antibody alone. In addition, this hypothesis is inconsistent with the typical sequence of events in which antibodies follow rather than precede viral pathogenicity (27, 38, 39), incompatible with HIV-free indicator diseases, and implausible in the absence of HIV activity (34, 82). As tens of thousands of positive tests for antibody and hundreds of negative tests for free virus have shown (34), HIV remains typically dormant in "T-cell reservoirs" even during AIDS (82). The simultaneous occurrence of HIV viremia and antiviral antibodies was reported in some AIDS patients in 1989, but this observation has not been replicated by others (42, 43). More and more of the AIDS-associated parasites are now named as AIDS cofactors of HIV, most recently HTLV and mycoplasma (45, 88).

A consistent alternative explanation for the high prevalence of antibody to HIV (and other microbes) in AIDS risk groups and AIDS patients proposes that HIV is a marker for American AIDS risks (34). The probability of becoming HIV antibody-positive correlates directly with the frequency of injecting unsterile drugs (34, 62, 70, 89–91), with the frequency of transfusions (59–61), and with promiscuity (62, 65, 89, 92). However, in America, only promiscuity aided by aphrodisiac and psychoactive drugs, practiced mostly by 20 to 40-year-old male homosexuals and some heterosexuals, seems to correlate with AIDS diseases (3–7, 62, 67). HIV would thus be a marker for these drugs and also for the frequent infections by conventional venereal diseases such as gonorrhea and syphilis (5, 6) which are not part of the AIDS definition (2), and for the corresponding therapeutic and prophylactic medications. In fact, HIV was named as a marker for homosexual

promiscuity (92) and recently for an "unknown sexually transmitted agent" that is presumed to cause Kaposi sarcoma in male homosexuals (45, 67–69).

However, not all HIV antibody-positives above those expected from perinatal transmission (e.g., 0.03% in the United States) must reflect promiscuity and parenteral infection. Instead, perinatally infected persons may develop antibodies only with age, as latent proviruses become activated by transient immunosuppression or other stimuli. This predicts that the percentage of antibody-positives among provirus-positives increases with age. The lower incidence of antibody to HIV in 1- to 14-year-old Zairen children (1–2%) compared with adults (4–10%) (31) is a case in point. The incidence of antibody to HTLV also increases with age in countries where HTLV is endemic, although HTLV is just as difficult to transmit sexually as HIV (86).

An Alternative Hypothesis

Numerous correlations have linked American AIDS with the consumption of drugs. The CDC reports that 30% are intravenous drug users (1) but does not report that another 50–60% have used oral psychoactive drugs (3–7) and medical drugs, above all the DNA-chain terminator 3'-azido-3'deoxythymidine (AZT) (7, 34). AZT is currently prescribed to 125,000 sick and healthy HIV-positive persons worldwide, including about 80,000 Americans, based on annual sales of $284 million and a wholesale price of $2200 for a year of AZT at 500 mg/day (Burroughs Wellcome Annual Report 1990 and Office of Public Affairs, personal communication). Therefore it is proposed that either drug consumption (frequently associated with malnutrition) by recently established behavioral groups or conventional clinical deficiencies and their treatments are necessary and sufficient to cause indicator diseases of AIDS. This hypothesis resolves the many paradoxes of the virus-AIDS hypothesis. *(i)* American AIDS is new because of the recent dramatic increase in the consumption of psychoactive and medical drugs (4, 7, 70, 91). For instance, cocaine-related hospital emergencies increased 5-fold from 1984 to 1988 (93). *(ii)* American AIDS is prevalent in 20- to 40-year-old men, although not one AIDS disease is male-specific, and

this age group is the least likely to develop any diseases. The reason is that men of this age group consume 80% of hard psychoactive drugs (94). *(iii)* The vastly different AIDS diseases are caused by different pathogens, pathogenic conditions, and their treatments. This also explains "AIDS diseases" that do not depend on immunodeficiency and occur without it, including Kaposi sarcoma, lymphoma, dementia, and wasting disease (1, 2, 23–26, 34, 67). *(iv)* African AIDS would be old diseases caused by malnutrition and parasitic infections under a new name, the reason why it is equally distributed between the sexes (16, 51). *(v)* The long and unpredictable latent periods between infection by HIV and specific AIDS diseases are the product of functionally unrelated events: the pathogenic events necessary to reach an individual's threshold for AIDS diseases, and infection by the marker HIV.

Acknowledgments

I thank Walter Gilbert, Howard Green, Barbara McClintock, Sheldon Penman, Robert Root-Bernstein, and Harry Rubin for critical and constructive reviews of the manuscript and Robert Da Prato, Bryan Ellison, Harry Haverkos, Robert Hoffman, Marion Koerper, Anthony Liversidge, Charles Ortleb, Claus Pierach, Russell Schoch, John Scythes, Joan Shenton, Joseph Sonnabend, Charles Thomas, and Michael Verney-Elliott for comments and essential information. I am supported by Outstanding Investigator Grant 5-R35-CA39915-06 from the National Cancer Institute.

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Chapter Five

Latent Viruses and Mutated Oncogenes: No Evidence for Pathogenicity

Peter H. Duesberg and Jody R. Schwartz

Progress in Nucleic Acid Research and Molecular Biology 43:135–204, 1992

> "Circumstantial evidence is a very tricky thing," answered Holmes, thoughtfully. "It may seem to point very straight to one thing, but if you shift your point of view a little, you may find it pointing in an equally uncompromising manner to something entirely different.... There is nothing more deceptive than an obvious fact...."
>
> —Sir Arthur Conan Doyle, in *The Boscombe Valley Mystery,* 1928

The scientific community has been virtually unanimous in admiring its recent triumphs in biotechnology—above all, the detection and amplification of minute amounts of materials into workable and marketable products. However, in clinical diagnostic applications, the new detec-

tion methods have become a mixed blessing, which benefits medical scientists but not necessarily their clients. Since rare signals have become just as detectable as abundant ones, many latent viruses have been detected and have been assumed to be just as pathogenic as active prototypes (1–3). Likewise, cellular mutations have become detectable that do not, or just barely, affect the function and activity of genes. Yet when the affected genes are structurally related to retroviral oncogenes, they are assumed to be just as oncogenic as highly active retroviral oncogenes (1, 4–8). However, the evidence for these hypotheses is only circumstantial—based on structural similarities to classical pathogenic viruses and viral oncogenes. Thus, without direct proof, these hypotheses may open the doors to psychologically harmful prognoses and clinically harmful prevention programs, termed "molecular genetics at the bedside" by Bishop (9).

I. New Technology and Old Theories in the Search for the Causes of Disease

A. A New Generation of Virologists Presents Latent Viruses as Pathogens

Although viral epidemics have all but disappeared in the Western world since polio was eliminated with vaccines in the 1950s, the number of viruses currently discovered and studied by virologists has reached epidemic proportions. For example, zealous virus hunters have been able to detect by ultrasensitive biological and biotechnical methods latent viruses that are neutralized by antiviral immunity in diseases such as AIDS, leukemias, lymphomas, hepatomas, hepatitis, cervical cancers, encephalitis, and many others (1,3). Their proposals that latent viruses cause these diseases are widely accepted, because from the days when only the most pathogenic and abundant viruses were detectable, all viruses still have the reputation of being pathogens.

However, the diseases with which these newly discovered latent viruses are associated are not contagious—unless one makes bizarre assumptions. One assumption postulates that these viruses are "slow viruses" or "lentiviruses" causing diseases only up to 55 years after infection and only after they are neutralized by antibodies (see Sections

II and III). Yet all of these viruses replicate and are immunogenic within weeks, not years, after infection just like conventional viruses. Another assumption is that these viruses can shift from a nonpathogenic dormant state to a pathogenic state without increasing their biochemical activity or abundance.

A case in point is the assumption that AIDS is caused by a virus. There were over 160,000 AIDS patients in the U.S. in the last 10 years, and there is no antiviral vaccine or drug. Yet at the time of this writing there is not even one confirmed case of a health care worker who contracted AIDS from a patient, nor of a scientist who contracted AIDS from the "AIDS virus" that is propagated in hundreds of research laboratories! The AIDS virus is just as inactive in patients as it is in asymptomatic virus carriers (see Section II).

Such assumptions are not compatible with classical criteria of viral pathogenicity. Conventional viruses are very active, abundant and replicating in many cells that are killed or transformed when they cause diseases such as polio, flu, measles, mumps, hepatitis, herpes, Rous sarcoma, and many others (3, 10–12). Likewise, SV40 and adenoviruses inundate many cells with viral T-antigens when they cause tumors, even though the respective host animals are not permissive for viral replication (13). Pathogenicity by these classical viruses results from high biochemical activity in large numbers of cells. These viruses are not pathogenic when they are latent or infect only small numbers of cells. Indeed, even the most pathogenic viruses depend for their survival on asymptomatic infections in which they are highly active in small numbers of cells before they are stopped by antiviral immunity, the reason that such infections are asymptomatic (3).

Furthermore, all conventional viruses are maximally pathogenic within weeks or months after infection before they are neutralized by antiviral immunity, causing disease as soon as they reach pathogenic thresholds in the host (10–12). In rare cases, they may be reactivated to resume replication, and hence pathogenicity, long after they are neutralized by antiviral immunity (e.g., the herpes simplex virus). Reactivation typically follows a transient immunodeficiency acquired by another primary disease or other immunosuppressive conditions (12). Except for these instances of viral reactivation, there are no known

examples of viruses that cause diseases only after a long latent period and only after they have been neutralized by antibodies.

Thus, the evidence that latent viruses can be pathogenic is only circumstantial, based on structural similarities between latent viruses and active, pathogenic viral prototypes. Further, these hypotheses are based on the epidemiological evidence that latent viruses occur, or appear to occur, in diseases at a higher rate than would be expected from random infection (3, 14, 15) (see Section V).

B. From Retroviral to Cellular Oncogenes— The Oncogene Hypothesis

New technology detecting point-mutations, deletions, and truncations of cellular genes and latent or defective viruses put new life in the somatic mutation hypothesis of cancer (16). It was postulated in 1969 by Huebner and Todaro that latent viruses and covert cancer genes preexist in normal cells and are "activated" to cancer genes and cancer viruses by mutation (17). The proposal became known as the oncogene hypothesis. The discoveries in 1970 of retroviral oncogenes (18, 19) and in 1973 of cellular genes from which the coding regions of retroviral oncogenes are derived (20–22) put the oncogene hypothesis to its first test. It was proposed that mutation turns those genes from which the coding regions of retroviral oncogenes are derived into equivalents of viral oncogenes (6). These genes are now called either proto-*onc* genes or cellular oncogenes (1, 5–8, 23, 24) or even "enemies within" the cell (25). And mutated cellular oncogenes are euphemistically termed "activated" cellular oncogenes (1, 5–8).

Examples of "activated" oncogenes are point-mutated proto-*ras* genes that are thought to be bladder or colon cancer genes (23, 26–28), truncated proto-*myc* genes that are thought to be Burkitt's lymphoma genes (29, 30), proto-*myc* genes with retroviruses integrated upstream (31) and downstream (32) that are thought to be avian lymphoma genes, and rearranged proto-*abl* genes that are thought to be myelogenous leukemia genes (7, 8, 33). By analogy to proto-*onc* genes, even genes that are not related to retroviral *onc* genes are now thought to be "activated" oncogenes if mutated by provirus integration, like the *int* genes of mouse mammary tumors with retroviruses integrated within or nearby (5, 8, 34).

However, mutated proto-*onc* genes and *int* genes with integrated retroviruses are either just as active or only slightly more active than their normal counterparts (see Section IV). Moreover, the mutant genes from tumors do not transform cells upon transfection. By contrast, proviral DNA copies of retroviral oncogenes transform susceptible cells and are about 100 times more active than normal proto-*onc* genes (24, 35–38). During the last 5 years, the transforming function of retroviral oncogenes, including those of Rous sarcoma, Harvey sarcoma, and MC29 and MH2 carcinoma viruses, has been shown to depend absolutely on transcriptional activity, rather than on mutations in the coding region (39–44). This high transcriptional activity of retroviral oncogenes results from retroviral promoters.

The latest modification of the oncogene hypothesis, the antioncogene hypothesis, proposes that constitutively active, but as yet unnamed, oncogenes are "activated" by mutational inactivation of tumor suppressors or anti-oncogenes (8, 9, 45). Examples are the retinoblastoma and p53 anti-oncogenes that are thought to cause retinoblastoma (45) and colon cancer (46) if they are inactivated by point-mutation, truncation, or deletion. However, unmutated antioncogenes do not revert tumor cells to normal (see Section IV).

Thus, the evidence for these hypotheses is only circumstantial, based on structural similarities between mutated "cellular oncogenes" displaying a normal level of activity and about 100 times more active viral oncogenes. Further, these hypotheses are based on the epidemiological evidence that mutated genes occur, or appear to occur, in diseases at a much higher rate than would be expected from spontaneous mutation (4, 5, 7, 28, 47) (see Section V).

C. From Autonomous Pathogens to Multifactorial Causes of Disease

In view of the apparent non-equivalence between the postulated pathogens and their prototypes, the original hypotheses have been supplemented by *ad hoc* hypotheses. Typically, these *ad hoc* hypotheses postulate second- or even higher-order mechanisms of pathogenesis that include cofactors and helper genes, in contrast to the classical prototypes, which all follow first-order mechanisms of pathogenesis. More-

over, the putative helper genes, like the putative primary pathogens, are not disease-specific, because they are also found in asymptomatic subjects. Indeed, "cofactors" are euphemisms for new hypotheses, which grant face-saving roles to failing incumbents with large constituencies.

D. The Search for Alternative Hypotheses

In the following, we have reinvestigated the evidence for the claims that latent viruses and mutated genes are pathogenic. Since the available evidence for pathogenicity is insufficient, we conclude that the latent viruses and mutated genes must be considered innocent until proven guilty.

Since falsification creates a vacuum, we have attempted to present brief alternatives, drawing in most cases from published work. However, in the case of AIDS, we have documented an alternative to the virus-AIDS hypothesis more extensively, because there is hardly any mention of alternatives in the over 60,000 papers published on the AIDS virus and AIDS since 1983 (48). By challenging currently unproductive hypotheses and by providing falsifiable alternatives, we hope to contribute to the search for what really causes these diseases.

II. Inactive Viruses and Diseases Resulting from the Loss of Cells

A. Human Immunodeficiency Virus (HIV) and AIDS

AIDS is a new syndrome of 25 previously known diseases (49–52). In America, 61% are microbial diseases such as pneumonia, candidiasis, tuberculosis, cytomegalovirus, and herpes virus disease (50, 52) that result from immunodeficiency due to a severe depletion of T-cells (49, 51). The remaining 39% of AIDS diseases are dementia, wasting disease, Kaposi sarcoma, and lymphoma, which are not consistently associated with immunodeficiency and microbes (52–54). In the U.S., 32% of AIDS patients are intravenous drug users (52, 55), about 60% are male homosexuals (52) who frequently used drugs as aphrodisiacs (54, 56–64, 103), and most of the remainder have severe clinical or congenital deficiencies, including hemophilia (52, 54, 61). Over 80% of the American AIDS patients are 20- to 44-year olds, of which about 90%

are males (52). Different AIDS-risk groups have different AIDS diseases. For example, homosexuals have 20 times more Kaposi sarcoma than other AIDS patients (65), intravenous drug users have a proclivity for tuberculosis (66, 67), "crack" (cocaine) smokers for pneumonia (68), and users of the cytotoxic DNA-chain-terminator AZT, prescribed to inhibit HIV, for anemia, nausea, and lymphoma (69–71).

About 50% of all American AIDS patients are currently confirmed to have antibodies to a retrovirus, termed human immunodefieieney virus (HIV) (51, 54, 72). However, all AIDS diseases occur in all risk groups in the absence of HIV (see Section II,A,3) (54). In the U.S., HIV is fixed to an extremely constant reservoir of about 1 million carriers, ever since 1985, when it became possible to detect antibody against HIV (the "AIDS test") (54, 73). HIV is naturally transmitted from mother to child, like other retroviruses, at an efficiency of about 50% (54). This efficiency might be higher than serological tests indicate, because some proviruses of other perinatally transmitted human retroviruses only become immunogenic with advanced age (54) (see Section III). Sex is another natural mode of transmission. However, it is highly inefficient, depending on an average of about 1000 sexual contacts (54, 74), because there is no HIV provirus detectable, even with the polymerase chain reaction (PCR), in semen in 24 out of 25 HIVpositive men (75). Since 1987, when AIDS was given its current definition (50), about 30,000, or 3% of the 1 million Americans infected by HIV (53, 54, 73), develop AIDS annually (52).

1. The Virus-AIDS Hypothesis

Currently, most medical scientists believe that AIDS is caused by HIV (51). The hypothesis assumes: (i) that AIDS is new because HIV is thought to be new in all countries with AIDS (14, 51); (ii) that AIDS is acquired by sexual and parenteral transmission of HIV; (iii) that HIV causes immunodeficiency by killing infected T-cells; (iv) that 50–100% of HIV infections lead to fatal AIDS diseases; (v) that AIDS occurs on average only 10 years after antibodies to HIV appear (a positive "AIDS test"), to reconcile the low (3%) morbidity with the large number of asymptomatic HIV carriers; (vi) that antibodies to HIV do not neu-

tralize the virus (53, 76, 77), to reconcile AIDS with antibodies to HIV; and (vii) that all unrelated AIDS diseases are caused by the same HIV (49, 51, 54, 78).

In view of this hypothesis, AIDS has been defined exclusively by the association of the 25 indicator diseases with antibody to HIV (50, 51, 54). Further, "safe sex" (49, 51) and "clean injection equipment" for recreational drugs (55) are recommended as AIDS prophylaxis for uninfected persons, and the cytotoxic DNA-chain-terminator, 3'azidothymidine (AZT) is prescribed to infected healthy, as well as sick, persons to inhibit HIV (51, 71, 80a, 79, 80). The presence of antibody to HIV in a healthy person is interpreted as a prognosis for AIDS. Testing and counseling are provided routinely to applicants of the U.S. Job Corps (81). Several countries, including the U.S. and China, bar entry to HIV-positive persons. And a negative "AIDS test" for antibodies to HIV has become mandatory in the U.S. since 1985 for the approximately 12 million blood donations that are collected annually (82) by the American blood banks and the Red Cross (Irwin Memorial Blood Bank, San Francisco, personal communication, 1990) and for admission to the U.S. Army (73, 83).

Each of the seven assumptions of the virus-AIDS hypothesis can be challenged on epidemiological and virological grounds:

1. Since all new microbes spread exponentially in a population (11), the complete failure of HIV to spread from its 1985 level, when it became first detectable, indicates that the American "HIV epidemic" is old. This is particularly compelling if one considers that there is no antiviral vaccine and no antiviral drug. Thus, HIV is not new in the U.S.

2. Given that procreative sex is about 10% efficient (3 days per month) and sexual transmission of HIV only 0.1%, it follows that HIV depends on perinatal transmission for its survival (54). If HIV survives naturally via perinatal transmission, it cannot be pathogenic by itself, just like all other perinatally transmitted parasites (12)—except if one assumes latent periods that exceed the normal generation time of humans. Indeed, chimpanzees experimentally

inoculated and health care workers accidentally inoculated with HIV do not develop AIDS (51, 54). Thus, sexual transmission of HIV cannot be a sufficient cause for AIDS.

3. Since no more than 1 in 500 T-cells of AIDS patients ever contains a DNA provirus of HIV and over 99% of infected T-cells survive infection (84), and since about 1 in 25 T-cells is regenerated during the 2 days it takes a retrovirus to infect a cell, HIV infection cannot be responsible for the loss of T-cells in AIDS (53). Thus, HIV, like all other retroviruses, does not kill cells (53, 85, 86). Indeed, HIV is propagated commercially for the "AIDS test" in cultured lines of the same human T-cells that it is said to kill *in vivo* (87).

4. The assumption that HIV is 50–100% fatal within 10 years cannot be correct, because about 1 million Americans carry HIV since 1985 but only about 30,000 develop AIDS annually since 1987, when AIDS received its current definition (50). Instead, it would take 33 years for all U.S. HIV carriers to develop AIDS diseases based on the current data (3% per year). An average latent period of 10 years would predict that 100,000 Americans would develop AIDS in 1 year.

5. Since viruses, as self-replicating toxins, are all fast immunogens and thus potentially fast pathogens, but AIDS diseases are estimated to occur on average only 10 years after HIV is neutralized by antiviral antibodies, the assumption that HIV needs 10 years to cause AIDS is arbitrary. The long intervals between infection and AIDS probably indicate that HIV is not even necessary for AIDS, because there is no "late" HIV activity, and because antibodies continue to neutralize the virus during AIDS (53, 54).

6. The complete absence of free HIV in nearly all AIDS patients (53, 54, 88)—the reason that the isolation of HIV had escalated into an international scandal (89, 90)—invalidates the assumption that antibodies to HIV do not neutralize HIV. Indeed, antiviral immunity effectively restricts HIV in AIDS patients (91, 92)

to 1 provirus in about 500 T-cells, and viral activity to less than 1 in 10,000 T-cells (53, 54, 84).

7. Since all AIDS diseases occur in the absence of HIV in intravenous drug users, homosexuals, and hemophiliacs, HIV is not even necessary for AIDS diseases—except for their classification as AIDS (53, 54).

Because of the many virological and epidemiological inconsistencies of the virus-AIDS hypothesis, some, notably Montagnier (93) and recently Maddox (94–96), have proposed that HIV is not sufficient for AIDS. Accordingly, a number of "cofactors" such as mycoplasmas (85, 93) and other viruses (15, 76) have been postulated as helping HIV to cause AIDS. However, there is no consensus at this time about a specific cofactor that would be sufficient to cause AIDS in combination with HIV (76, 93). Moreover, there is not even one plausible hypothesis as to how a latent retrovirus such as HIV, which is present in no more than 1 in 500 T-cells, could possibly help another microbe to cause AIDS that, by itself, is not able to do so.

Indeed, there are at least six inconsistencies between AIDS and infectious disease:

1. Paradoxically, there is not even one case reported in the scientific literature of a health care worker who contracted AIDS from a patient, although there were over 200,000 AIDS patients in the U.S. in the last 10 years (52). Likewise, not even one scientist contracted AIDS from the "AIDS virus" or from other microbes from AIDS patients, which are propagated in hundreds of research laboratories and companies (53, 54, 87).

2. All new infectious diseases spread exponentially in susceptible populations (11). However, despite widespread alarm, AIDS claims since 1987 only about 30,000 or 0.03% per year from a reservoir of over 100 million susceptible, sexually active Americans. This is particularly paradoxical for a presumably infectious syndrome, because conventional venereal diseases are increasing in the U.S. (97) and because there is no anti-HIV vaccine and no anti-HIV drug.

3. The distribution of all infectious venereal diseases is almost even between the sexes (98). By contrast, 90% of American AIDS is restricted to males since 1981 (52). This is incompatible with infectious venereal disease.

4. Almost all (94%) of the Americans who develop AIDS have been subject to abnormal health risks (52). These risks include either long-term consumption of recreational, psychoactive, and aphrodisiac drugs and anti-HIV drugs such as the cytocidal DNA chain-terminator AZT (see below) or congenital or acquired deficiencies such as hemophilia (52, 54). This indicates that specific health risks are necessary for AIDS.

5. The observations that distinct AIDS-risk groups have distinct AIDS diseases—e.g., homosexuals having 20 times more Kaposi sarcoma than HIV carriers from other risk groups (65), intravenous drug users having a proclivity for tuberculosis (66, 67), "crack" (cocaine) smokers for pneumonia (68), and AZT users for anemia, nausea, and lymphoma (69–71)—are also difficult to reconcile with a single infectious cause.

6. All AIDS diseases occur in all AIDS-risk groups in the absence of HIV (54).

In view of these inconsistencies between AIDS and infectious disease and the total lack of a common active microbe in AIDS, several investigators, including us, have concluded that AIDS may not be infectious (54, 56–62, 99–102).

2. The Drug-AIDS Hypothesis

An alternative hypothesis proposes that American AIDS diseases, above their normal background, are the result of the long-term consumption of (*a*) intravenous and (*b*) oral recreational drugs, and (*c*) anti-HIV drugs (54, 60, 103). The following epidemiological and drug-toxicity data support this hypothesis.

a. Intravenous Recreational Drugs. Currently, 32% of the American AIDS patients come from groups that use intravenous drugs such as

heroin, cocaine, and others (52, 55). This group includes about 75% of the heterosexual AIDS cases, 71% of the females with AIDS, and over 10% of the male homosexuals and hemophiliacs with AIDS (52, 55). In addition, about 50% of American children with AIDS were born to mothers who are confirmed intravenous drug users and another 20% to mothers who had "sex with intravenous drug users" and are thus likely users themselves (52, 55). Likewise, 33% of European AIDS patients are intravenous drug users (104).

b. Oral Recreational Drugs. Approximately 60% of the American AIDS patients are 20- to 44-year-old male homosexuals (52). The following evidence indicates that they come from groups who use oral psychoactive and aphrodisiac drugs. A survey of 3916 self-identified American homosexual men, the largest of its kind, reported in 1990 that 83% had used one, and about 60% two or more, drugs with sex during the previous 6 months (105). These drugs include nitrite and ethylchloride inhalants, cocaine, amphetamines, methaqualone, lysergic acid, phenylcyclidine, and more (59, 61–63, 101,105–112). A study of 359 homosexual men from San Francisco reported in 1987 that 84% had used cocaine, 82% alkylnitrites, 64% amphetamines, 51% quaaludes, 41% barbiturates, and 20% injected drugs, and 13% shared needles (107). This group had been randomly selected from a list of homosexuals who had volunteered to be investigated for hepatitis B virus infection and to donate antisera to hepatitis B virus between 1978 and 1980.

Nitrite inhalants and possibly other drugs are preferred by male homosexuals as aphrodisiacs because they facilitate anal intercourse (105, 111, 113, 114). For example, an early CDC study that included 420 homosexual men found nitrite use far more frequent among homosexuals than among heterosexuals and correlating directly with the number of different homosexual partners (57). Surveys studying the use of nitrite inhalants in San Francisco found that among homosexual men 58% were users in 1984 and 27% in 1991 compared to less than 1% among heterosexuals and lesbians of the same age group (115).

The nitrites are directly toxic as oxidants of biological molecules such as hemoglobin, and are effective mutagens (101, 103). The National Institute on Drug Abuse reports correlations from 69% (116) to virtually 100% (101, 113) between nitrite inhalants and Kaposi sarcoma and

pneumonia, which are diagnosed as AIDS in the presence of antibody to HIV (50, 51, 54). In view of this, a causal link between nitrite inhalants and Kaposi sarcoma and pneumocystis pneumonia in homosexuals was first suggested in 1982 by the CDC (57) and other investigators (56, 58). As a consequence, the sale of nitrite inhalants was banned by the U.S. Congress in 1988 (Public Law 100–690) (117, 118). The direct and indirect toxicity associated with the long-term use of other recreational drugs has been described elsewhere (103).

c. Anti-HIV Drugs. About 80,000 Americans and 120,000 persons worldwide with and without AIDS currently take the cytocidal DNA chain-terminator AZT (54) and an unknown number take other DNA chain-terminators such as ddI and ddC (71). AZT has been prescribed since 1987 to symptomatic (51, 70, 79, 119), and since 1990 to asymptomatic, carriers of HIV, including babies and hemophiliacs (80, 120), in an effort to inhibit HIV DNA synthesis (121). Thus, an unknown, but possibly high, percentage of the 30,000 Americans that currently develop AIDS per year (52) have used AZT prior to or after the onset of AIDS. For instance, 249 out of 462 HIV-positive, AIDS-free homosexual men from Los Angeles, included in the above survey (105), are on AZT or ddI (122).

Although AZT is an inhibitor of HIV DNA synthesis, it is not a rational medication for persons with antibodies to HIV for the following reasons: (i) There is no proof that HIV causes AIDS. (ii) Since no detectable RNA-dependent viral-DNA synthesis occurs, and since the number of infected cells remains stable once the virus is neutralized by antibodies (53, 54) only cell DNA with and without proviruses of HIV is terminated by AZT treatment. Further, since AZT cannot distinguish infected from uninfected cells, and only 1 in 500 T-cells is infected in AIDS patients and asymptomatic carriers (54, 84), it kills 500 uninfected cells for every infected cell. Thus, AZT is inevitably toxic, killing 500 times more uninfected than infected cells. (iii) In view of the hypothesis that HIV causes AIDS by killing T-cells (49, 51), it is irrational to overkill infected cells with AZT.

As expected from an inhibitor of DNA synthesis, many studies report AZT-mediated toxicity. Anemia, neutropenia, and leukopenia occur in 20–50%, with about 30–50% requiring transfusions within several

weeks (70, 71, 123–125). Severe nausea from intestinal intoxication is observed in up to 45% (70, 71, 80) and severe muscle atrophy in 6–8% (70, 126–128). Acute hepatitis, insomnia, headaches, dementia, seizures, and vomiting are also reported effects of AZT (71). Lymphomas appear in about 9% within 1 year on AZT (69). AZT is also mutagenic and carcinogenic in mice (129, 130) and transforms cells *in vitro* as effectively as methylcholanthrene (131). AZT toxicity varies a great deal with the patient treated, due to differences in kinases involved in its uptake and in AZT metabolism (71, 121, 131, 132). All of these results explain Temin's profound observation that "... the drug generally becomes less effective after six months to a year. ..." (134).

Nevertheless, AZT is thought to have serendipitous therapeutic benefits based on the only placebo-controlled study of its effects on AIDS patients (70, 119). The study was sponsored by Burroughs Wellcome, the manufacturer of AZT (70, 119). In this study, T-cell counts were observed to increase from 4 to 8 weeks and then to decline to pretreatment levels. Above all, AZT was claimed to "decrease mortality" because only 1 out of 143 in the AZT-treated group died compared to 19 out of 135 in the placebo group.

However, 30 out of the 143 in the AZT group depended on multiple transfusions for survival from anemia, compared to only 5 out of the 135 in the placebo group. Since the number of subjects in the AZT group who would have died from anemia if untreated (30) was larger than the AIDS deaths and anemias of the control group combined (19 + 5), the claim of decreased mortality is not realistic (70, 119). Moreover, 66 in the AZT group suffered from severe nausea and 11 from muscle atrophy, compared to only 25 and 3 in the control group. The lymphocyte count decreased over 50% in 34% of the AZT group and in only 6% of the control. The study is further compromised by "concomitant medication" (70), the failure to consider the effects of recreational drug use and of patient-initiated randomizations of blinded AZT and placebo controls (135). The brief AZT-induced gain of T-cells may reflect compensatory hemopoiesis and random killing of pathogenic parasites (132) and the influence of concomitant medication (70).

In view of the inevitable toxicity of AZT, its popularity as an anti-HIV drug can only be explained by the widespread acceptance of the

virus-AIDS hypothesis and the failure to consider the enormous difference between the viral and cellular DNA targets. This may also be the reason that long-term studies of AZT in animals compatible with human applications have not been published (71).

3. The Drug- Versus the Virus-AIDS Hypothesis

To distinguish between HIV and drugs as causes of AIDS, it is necessary to determine whether HIV carriers develop AIDS only when they use drugs, and whether HIV-free drug users develop AIDS indicator diseases.

A. Drug Use Necessary for AIDS in Presumed or Confirmed Carriers of HIV. (i) Epidemiological correlations suggest that nitrites are necessary for Kaposi sarcoma. (a) A 27- to 58-fold higher consumption of nitrites (111, 115) correlates with a 20-fold higher incidence of Kaposi sarcoma in male homosexuals compared to all other AIDS patients of the same age group (65). (b) Among male homosexuals, those with Kaposi sarcoma have used nitrite inhalants twice as often as those with other AIDS diseases (101). (c) During the last 6–8 years, the use of nitrite inhalants among male homosexuals decreased (e.g., from 58% in 1984 to 27% in 1991 in San Francisco) (115). In parallel, the incidence of Kaposi sarcoma among American AIDS patients decreased from a high of 37% in 1983 (136) to a low of 10% in 1990 (52). In fact, nitrites may be sufficient causes for these diseases, because there is no evidence that HIV was even present in any of these studies.

(ii) Specific correlations indicate that nitrites are necessary for AIDS. The first five cases diagnosed as AIDS in 1981, before HIV was known, were male homosexuals who had all consumed nitrite inhalants and presented with pneumocystis pneumonia and cytomegalovirus infection (137). Early CDC data indicate that, in 1981 and 1982, 86% of male homosexuals with AIDS had used oral drugs at least once a week and 97% occasionally (57, 138), and that every one of 20 Kaposi sarcoma patients had used nitrites (56). The National Institute on Drug Abuse reports correlations from 69% (116) to virtually 100% (101,113) between nitrite inhalants and Kaposi sarcoma and pneumonia. Again, drugs may have sufficed to cause these diseases, because HIV was not diagnosed (50, 51, 54).

(iii) The incidence of AIDS diseases among 297 HIV-positive, asymptomatic intravenous drug users over 16 months was three times higher in those who persisted than in those who stopped injecting drugs (139).

(iv) The T-cell count of 65 HIV-infected drug users from New York dropped over 9 months in proportion with drug injection—on average, 35%—compared to controls who had stopped (140).

(v) A placebo-controlled study, investigating AZT as AIDS prophylaxis in HIV-positive, AIDS-free 25- to 45-year-old male homosexuals and intravenous drug users, indicates that AZT induces diseases from within and without the AIDS definition (80). During 1 year of taking 500 mg of AZT per day, a group of 453 developed 11 AIDS cases, and a group of 457, taking 1500 mg of AZT per day, developed 14 cases. The placebo group of 428 developed 33 AIDS cases.

However, the price for the presumed savings of 22 and 19 AIDS cases with AZT was high, because 19 more cases of anemia, neutropenia, and severe nausea appeared in the 500-mg AZT group, and 72 more such cases appeared in the 1500-mg AZT group, than in the placebo group. This indicates cytocidal effects of AZT on hemopoiesis and on the intestines. Although these AZT-specific diseases were not diagnosed as AIDS, neutropenia generates immunodeficiency. Surprisingly, in view of its toxicity on leukocytes and red cells, a consistent loss of T-cells was not observed in this study. A recent study investigating AZT as AIDS prophylaxis observed leukopenia, e.g., T-cell depletion, in 82% within 1 to 1.5 years of AZT treatment (140a). The study is further compromised by the failure to report and to consider the recreational drug-use histories and the many AZT-treatment adjustments of the subjects analyzed.

(vi) Within 48 weeks on AZT, 172 (56%) out of 308 AIDS patients developed additional AIDS diseases, including pneumonia and candidiasis (125). This indicates that AZT induces AIDS diseases within less than 1 year, and thus much faster than the 10 years HIV is said to need to cause AIDS (54). Likewise, no therapeutic benefits were observed for 365 French (123) and 4 Norwegian AIDS (133) patients after 6 months on AZT.

(vii) The annual lymphoma incidence of AZT-treated AIDS patients was reported to be 9% by the National Cancer Institute and was cal-

culated to be 50% over 3 years (69). The lymphoma incidence of untreated HIV-positive AIDS-risk groups is 0.3% per year and 0.9% per 3 years, derived from the putative average progression rate of 10 years from HIV to AIDS (54, 141,142) and the 3% incidence of lymphoma in AIDS patients (52). Thus, the lymphoma incidence is 30–50 times higher in AZT-treated than in untreated HIV-positive counterparts. In addition, "during the past three years [of AZT therapy] a progressive increase in the number of [AIDS] patients dying from lymphoma, . . ." to a current level of 16%, was noted in 1991 in a group of 346 AIDS patients in London, most of whom were on AZT (143).

It is likely that the chronic levels of the mutagenic AZT, at 10–30 μM (500–1500 mg/person/day), were responsible for the lymphomas. The alternative proposal that HIV-induced immunodeficiency was responsible for the lymphomas (69) is unlikely, since cancers do not reflect a defective immune system (53, 144).

(viii) Ten out of 11 HIV-positive, AZT-treated AIDS patients recovered cellular immunity after discontinuing AZT in favor of an experimental HIV vaccine (145), indicating that AZT sufficed for immunodeficiency.

(ix) Four out of five AZT-treated patients recovered from myopathy 2 weeks after discontinuing AZT; two redeveloped myopathy on renewed AZT treatment (126).

(x) Four patients with pneumonia developed severe pancytopenia and bone marrow aplasia 12 weeks after the initiation of AZT therapy. Three out of four recovered within 4–5 weeks after AZT was discontinued (124), indicating that AZT was sufficient for pancytopenia.

b. Drug Use Sufficient for AIDS Indicator Diseases in the Absence of HIV. (i) Among intravenous drug users in New York, representing a "spectrum of HIV-related diseases," HIV was observed in only 22 out of 50 pneumonia deaths, 7 out of 22 endocarditis deaths, and 11 out of 16 tuberculosis deaths (66).

(ii) Pneumonia was diagnosed in 6 out of 289 HIV-free and 14 out of 144 HIV-positive intravenous drug users from New York (146).

(iii) Among 54 prisoners with tuberculosis in New York State, 47 were street-drug users, but only 24 were infected with HIV (67).

(iv) In a group of 21 heroin addicts, the ratio of helper to suppres-

sor T-cells declined within 13 years from a normal of 2 to less than 1, which is typical of AIDS (50, 51), but only 2 were infected by HIV (147).

(v) Thrombocytopenia and immunodeficiency were diagnosed in 15 intravenous drug users on average 10 years after they became addicted, but 2 were not infected with HIV (148).

(vi) Lymphocyte reactivity and abundance was depressed by long-term injection of drugs not only in 111 HIV-positive but also in 210 HIV-free intravenous drug users from Holland (149).

(vii) The same lymphadenopathy, weight loss, fever, night sweats, diarrhea, and mouth infections were observed in 49 out of 82 HIV-free and 89 out of 136 HIV-positive, long-term intravenous drug users from New York (150), and in about 40% of 113 intravenous drug users from France, of which 69 were HIV-positive and 44 were negative (151). The French group had used drugs for an average of 5 years.

(viii) Among six HIV-free male homosexuals with Kaposi sarcoma, five reported the use of nitrite inhalants (152).

(ix) Similar neurological deficiencies were observed among 12 HIV-infected and 16 uninfected infants from drug-addicted mothers (153).

Thus, the long-term use of recreational and anti-HIV drugs appears necessary in HIV-positives and sufficient in HIV-negatives to induce AIDS indicator and other diseases.

It follows that the drug-AIDS hypothesis is epidemiologically and pathologically better grounded than the virus-AIDS hypothesis. About 32% of American AIDS patients are confirmed intravenous drug users, probably 60% use aphrodisiac drugs orally, and an unknown but large percentage of both behavioral and clinical AIDS-risk groups use AZT. Moreover, the consumption of recreational drugs by AIDS patients is probably underreported, because the drugs are illicit, and because medical scientists and support for research are currently heavily biased in favor of viral AIDS (68, 154, 155). The pathogenicity of these drugs is empirically known for all, and mechanistically for some, drugs, notably for AZT and nitrites (103).

Nonetheless, evidence for the role of drugs in AIDS is rejected by proponents of the virus-AIDS hypothesis (15, 77, 105). This is certainly one reason why despite the current drug-use epidemic, there are no studies that investigate the long-term effects of psychoactive drugs and

AZT in animals, compatible with the time periods and dosages used by AIDS patients (155).

By contrast to the near complete correlation between drugs and AIDS, antibodies to HIV are confirmed in only about 50% of AIDS patients (51, 72), and it is a complete mystery how HIV acts as a pathogen, despite enormous research efforts (14, 15, 54, 156).

The drug-AIDS hypothesis resolves all scientific paradoxes posed by the prevailing virus-AIDS hypothesis:

1. In America, HIV is a long-established, endemic virus, but AIDS is new—because the drug epidemic is new.

2. AIDS is restricted for over 10 years to 10,000 (52) or 0.01% of the over 100 million sexually active heterosexual Americans per year, and to 20,000 (52) or 0.25% of the 8 million homosexuals, estimated at 10% of the adult male population (109, 111). But conventional venereal diseases are on the rise in the U.S. (97), and there is no vaccine or drug against HIV. This is because AIDS is due to drug consumption rather than sexual activity.

3. Over 72% of American AIDS cases are 20- to 44-year-old males (52)—although no AIDS disease is male-specific (50, 51)—because males of this age group consume over 80% of all "hard" psychoactive and aphrodisiac drugs (101, 103, 111, 115, 157, 158).

4. Distinct AIDS diseases occur in distinct risk group—because they use distinct drugs (e.g., users of nitrites get Kaposi sarcoma, users of intravenous drugs get tuberculosis, and users of AZT get leukopenia and anemia).

5. Viral AIDS occurs, on average, 10 years after HIV infection (51, 53, 54), although infectious agents, being self-replicating toxins, typically strike within weeks or months after infection (11, 12). Indeed, HIV is immunogenic, and may be mildly pathogenic in humans within weeks after infection and is then "effectively and rapidly limited" by antiviral immunity (91, 92). This is because HIV infection and AIDS are unrelated events. The duration and toxicity of drug consumption and individual thresholds for dis-

ease determine when AIDS occurs, irrespective of when and whether HIV infects.

6. HIV, as well as many other parenterally and venereally transmitted microbes and viruses, are mere markers for AIDS and AIDS risks (54, 107, 159)—because the higher the consumption of unsterile, injected drugs (140, 151) and sexual contacts mediated by aphrodisiac drugs, the more microbes are accumulated.

7. Some old diseases of hemophiliacs, other recipients of transfusions, and the general American population are called AIDS—if they coincide with perinatal or parenteral HIV infection (54).

8. Old African diseases such as slim disease, fever, diarrhea, and tuberculosis are called AIDS now, although they are clinically and epidemiologically very different from American AIDS. They occur in adolescents and adults of both sexes that are subject to protein malnutrition, parasitic infections, and poor sanitary conditions (53). Only because HIV is endemic in over 10% of Central Africans are over 10% of old African diseases now called AIDS (51, 53, 54).

The drug-AIDS hypothesis predicts that the AIDS diseases of the behavioral AIDS-risk groups in the U.S. and Europe can be prevented by controlling the consumption of recreational and anti-HIV drugs, but not by "safe sex" (51) and "clean injection equipment" (55) for unsterile (!) street drugs. According to the drug-AIDS hypothesis, AZT is AIDS by prescription. Screening of blood for antibodies to HIV is superfluous, if not harmful, in view of the anxiety that a positive test generates among the many believers in the virus-AIDS hypothesis and the toxic AZT prophylaxis, prescribed to many who test "positive." Eliminating the test would also reduce the cost of the approximately 12 million annual blood donations in the U.S. (82) by $11 each (Irwin Memorial Blood Bank, personal communication, 1990) and would lift travel restrictions for antibody-positives to many countries, including the U.S. and China. The drug-AIDS hypothesis is testable epidemiologically and experimentally by studying AIDS drugs in animals.

B. Hepatitis C Virus and Non-A Non-B Hepatitis

Non-A non-B hepatitis is observed primarily in recipients of transfusions and in intravenous drug users (3, 12, 160). It has been postulated to be a viral disease because inoculation of plasma or serum (3–75 ml) from hepatitis patients into chimpanzees induced some biochemical markers of hepatitis, such as alanine aminotransferase, in half of the animals (160). However, none of the animals developed hepatitis (161, 162). Trace amounts of presumably viral RNA have recently been detected in the liver of hepatitis patients. In addition, "nonneutralizing" antibodies to "nonstructural epitopes," from an apparently latent RNA virus, have been identified mostly in asymptomatic carriers (160). Cloning and sequencing indicated that the RNA is directly coding and measures about 10 kb. Therefore, the suspected virus has been tentatively classified as a togavirus (160). Viral RNA was only detectable after amplification with the PCR in 9 out of 15 non-A non-B hepatitis patients, and non-neutralizing antibodies were found in only 7 of the 9 RNA-positive and in 3 of the 6 RNA-negative patients (163). Likewise, liver tissues from chimpanzees inoculated with sera from hepatitis patients contain only one viral RNA molecule per ten cells (160).

In view of this evidence, the putative virus has been termed hepatitis C virus (HCV) to indicate that it is the cause of the hepatitis. Subsequently, the Food and Drug Administration has recommended, and the American Association of Blood Banks has mandated, as of 1990, the testing of the approximately 12 million annual blood donations in the U.S. (82) for antibodies to HCV at an approximate cost of $5 per test. The test was developed by Chiron Co., Emeryville, California (Irwin Memorial Blood Bank, personal communication, August 15, 1991).

However, several arguments cast doubt on the hypothesis that HCV causes hepatitis:

1. Virus-containing sera or plasma from hepatitis patients does not cause hepatitis if inoculated into chimpanzees, indicating that HCV is not sufficient to cause the disease. Moreover, since the virus has not been propagated in culture and isolated in a pure

form, the possibility exists that the biochemical markers of hepatitis that are observed in chimpanzees inoculated with plasma were induced by another agent. Thus, HCV is not likely to be a sufficient cause of hepatitis in humans.

2. The presence of HCV in asymptomatic subjects at the same concentration and activity as in hepatitis patients also indicates that the virus is not sufficient to cause hepatitis.

3. The absence of viral RNA in 6 out of 15 hepatitis C patients indicates that the virus is not necessary for the disease.

It appears that HCV either causes disease by unprecedented mechanisms with as little as one RNA molecule per 10 liver cells in some and even less in other carriers, or that the virus is not the cause of non-A non-B hepatitis. By contrast, the concentration of viral RNAs made by conventional pathogenic viruses, including togaviruses, ranges from 10^3 to over 10^4 per cell (10). Therefore, it seems plausible that a latent passenger virus was identified that survives by establishing chronic asymptomatic infections at very low, nonpathogenic titers (164).

C. Measles Virus, HIV, and Subacute Scleroting Panencephalitis

In 1967, a cytocidal measles virus was proposed to be the cause of a very rare, subacute scleroting panencephalitis of children (165), based on correlations with antibodies to the virus or trace amounts of virus (3, 10, 12). The encephalitis is observed only 1–10 years after an acute primary infection, in the face of antiviral immunity, and in only about 1 out of 1 million children infected by the virus (3, 10, 12). The virus can only be isolated from the brains of 2 out of 8 encephalitis patients after cocultivation of brain cells with susceptible human cells (166). Thus, only a few intact virus particles are present in the brains of some, but apparently not in all, children with encephalitis. Viral gene expression in brain autopsies is 10- to 200-fold lower than in virus-replicating control cells, amounting to as few as 10 mRNAs per cell (167). Moreover, mutations and deletions were observed in these viral RNAs compared to wild-type measles virus (168). Accordingly, some viral RNAs

are not even translated (3). By contrast, the wild-type virus causes measles within weeks after infection, at very high virus titers, and prior to antiviral immunity (10, 12).

The measles virus-encephalitis hypothesis has a number of epidemiological and virological shortcomings:

1. Since the disease does not occur concurrently with, or instead of, the conventional measles disease during a primary infection, and since antiviral immunity does not protect against the disease, measles virus cannot be sufficient to cause the subacute panencephalitis.

2. The virus cannot be a sufficient cause of the disease because only 1 in 10^6 infected persons develops panencephalitis, compared to one in a few if not all who develop measles disease before antiviral immunity (3, 10, 12).

3. Since viruses are self-replicating toxins, all are potentially "fast" pathogens, but encephalitis is observed only 1–10 years after infection, measles virus cannot be sufficient for panencephalitis.

4. The absence of infectious virus in some panencephalitis cases, and the very low concentration of viral RNA in all cases, suggest that measles virus is either not causative, or is causative by a mechanism that is totally different from that causing measles disease. During conventional measles disease, the virus is abundant, making over 1000 RNA molecules per cell in large numbers of cells (3, 10, 12, 167, 168).

In view of these paradoxes, it was suggested that selection of viral mutants would account for the encephalitis-pathogenicity of the virus (3, 167, 168). However, this seems unlikely, because the virus does not replicate sufficiently in encephalitis patients to generate new pathogenic variants, and because natural variants with a neurotropic specificity would then be expected.

About 15 years after the measles virus-encephalitis hypothesis was advanced, others proposed that the encephalitis was caused by a latent

retrovirus closely related to HIV (169). This hypothesis also suffers from the problem that the presumed viral pathogen is latent (169). In addition, an encephalopathy is hard to reconcile with the fact that retroviruses depend on mitosis for infection (170) and the fact that neurons stop dividing soon after birth (1).

D. Phantom Viruses and Neurological Disease

The strong belief in viruses as causes of diseases has in some instances even exceeded their very definition. For example, the Nobel Prize in 1976 was given for hypothetical, slow, and unconventional viruses that would cause neurological diseases such as kuru, Creutzfeld-Jacob's, and Alzheimer's diseases, after long latent periods of up to 30 years (171). Kuru is a now-extinct neurological disease of a small tribe of 35,000 in New Guinea that reportedly was transmitted by ritual cannibalism (3, 12, 171). "Slow and unconventional" viruses have been postulated because 4 out of 7 chimpanzees had developed neurological diseases about 1–2 years after they had been inoculated intracerebrally with brain suspensions from kuru patients (172). The presumed Creutzfeld-Jacob virus failed to induce neurological disease if presumably infected materials were inoculated into the brains of chimpanzees (3). A slow, unconventional virus has also been claimed as the cause of scrapie, a neurological disease of sheep (3, 12).

Since the incubation periods from inoculation of brain suspensions from kuru patients to neurological disease in the animals (1–2 years) and from presumed infection of humans to kuru (up to 30 years) differ significantly, it is not clear whether the diseases were caused by the same agent. Considering the claim that the viruses are naturally transmitted by cannibalism, it seems inappropriate that the traumatic intracerebral inoculation was chosen to test the oral transmission hypothesis. Nevertheless, Gajdusek *et al.* pointed out, "To anyone who had the opportunity of observing the unique syndrome of kuru . . . the similarity of its clinical picture and course to the experimentally induced syndrome . . . is dramatically evident" (172).

The slow virus-neurological disease hypothesis suffers from several shortcomings:

1. None of these hypothetical viruses has ever been isolated and chemically analyzed. Their presumed properties all far exceed the known ranges of conventional viruses and even of known proteins and nucleic acids. For example, the kuru and Creutzfeld-Jacob viruses are said to resist boiling water, ionizing gamma radiation, ultraviolet radiation, and inactivation with formaldehyde (3, 171). Moreover, the viruses are not antigenic, and not visible under the electron microscope, although available preparations are reported to have titers of 10^7 lethal doses per milliliter (3). Paradoxically, the slow, unconventional viruses have since evolved into an infectious protein, termed prion, "derived from a normal cellular protein ... through an unknown posttranslational process" (173).

2. The virus-kuru hypothesis fails to account for the long latent periods between presumed infection and disease and for the restriction of the disease to a very specific risk group.

3. A recent analysis of the original data on kuru transmission casts doubt on the virus-kuru hypothesis, because the evidence for cannibalism was fabricated (174).

In view of this, we agree with a review by Gibbs, a collaborator of Gajdusek, that "many paradoxes [were] thrust on us by the discovery of these unconventional viruses as the etiological agents of chronic, progressive, degenerative diseases of the central nervous system . . . " and that "toxic or genetic determinants and even trauma lead to the same pathogenesis ..." (3). Indeed, it seems plausible that the toxicity and trauma of intracerebral inoculations of human brain suspensions from kuru patients could cause neurological diseases without phantom viruses said to be the etiological agents. The restriction of the slow neurological diseases to specific ethnic groups or to sporadic cases could reflect genetic and acquired deficiencies rather than selective and slow viruses.

III. Viruses as Causes of Clonal Cancer

A. Human T-cell Leukemia Virus and Adult T-cell Leukemia

Human T-cell leukemia virus-I (HTLV-I) was originally discovered in a T-cell line from a leukemic patient (175). This line, termed HUT 102, only produced virus after it had been propagated *in vitro,* in the absence of the virus-suppressing immune system of the host, and after it had been treated with mitogens and mutagens such as iododeoxyuridine, an agent known to activate dormant retroviruses (6). Since the virus was isolated from a cell line that came from an adult patient with T-cell leukemia, the virus was proposed to be the cause of adult T-cell leukemia (ATL), and hence named human T-cell leukemia virus (175, 176). However, a parallel T-cell line, termed HUT 78, derived from another patient with T-cell leukemia, failed to yield a retrovirus (87).

Further support for the hypothesis was derived from epidemiological correlations between antibodies to HTLV-I and ATL in Japan and the U.S. (3, 37, 176). Based on 30,000 blood donations, the American Red Cross has reported that in 1986–1987 about 0.025% or 65,000 Americans were infected with HTLV-I (3, 82), but the American T-cell Leukemia/Lymphoma Registry had recorded in 1990 in the U.S. no more than 90 ATLs. Among these, 75 were non-Caucasians (177), a group in which HTLV-I is often endemic (178). However, the same Registry also reports, "although most cases of ATL are HTLV-I-associated ... many are not" (177). As in the U.S., HTLV-I-free ATLs have been observed in Japan (179). A controlled study comparing the incidence of the leukemia in HTLV-I-positive and -negative control groups has never been published.

By definition, "The diagnosis of ATL is made from the characteristic clinical findings, the detection of serum antibodies to HTLV-I and, when necessary, the confirmation of monoclonal integration of HTLV-I proviral DNA in cellular DNA of ATL cells" (180). According to this tautology, ATL is defined and distinguished from virus-free T-cell leukemias solely by the presence of antibody to HTLV-I or viral DNA.

In addition, HTLV-I is also postulated to cause an HTLV-I-associated myelopathy (HAM), which is a neurological disease also defined only by the presence of HTLV-I (3, 181).

ATL is clonal, originating from a single cell, like virus-free T-cell leukemias. The clonality of the leukemia is defined by chromosome abnormalities, as well as by clonal proviral integration sites (2, 176). However, there are no specific integration sites of HTLV-I in different leukemias (2). In leukemic cells, the virus is always latent, suppressed by antiviral immunity, and sometimes even defective (2). It is for this reason that the virus was originally discovered only *in vitro,* after reactivation from latently infected leukemic cells grown in culture.

HTLV-I, like other non-oncogenic retroviruses (6, 54), is naturally transmitted from mother to child with an efficiency of 22% based on testing for antiviral antibodies (176, 182, 183). Indeed, latent proviruses appear to be transmitted perinatally at a higher efficiency than antibody tests indicate, because the antibody titers increase with age (176) at a much faster rate than could be accounted for even by thousands of sexual contacts (183). Thus, this virus, like all other retroviruses without oncogenes (54), survives from perinatal transmission. Sex is another, although highly inefficient, mode of transmission, depending on an average of over 1000 sexual contacts (183).

Based on epidemiological studies from Japan, HTLV-I is said to cause leukemia in only 1–5% of all virus carriers in a lifetime (182). The annual incidence of the leukemia per HTLV-I carrier in Japan is estimated to be only 1 in 1000 (182, 184). Since HTLV-I is a perinatally transmitted retrovirus, but leukemia typically appears, if at all, only in 50- to 60-year-olds, the latent period from infection to disease is estimated at 55 years (176, 185).

The following epidemiological and virological arguments cast doubt on the HTLV-I-leukemia hypothesis:

1. According to the American Red Cross, "ATL ... as of September 1989, has not been reported in association with transfusion transmitted HTLV-I infection," although about 65,000 Americans were infected with HTLV-I and about 12 million blood donations are annually transfused to millions of recipients in the U.S. (82). Thus, HTLV-I cannot be sufficient to cause leukemia.

2. Since viruses, as self-replicating toxins, are all potentially fast pathogens, but leukemia is only observed about 55 years after

infection, HTLV-I cannot be sufficient for leukemia.

3. Considering that 1% of HTLV-I carriers develop ATL per lifetime in Japan and about 0.1% (90 : 65,000) in the U.S., that the leukemias are clonal deriving from single cells, and that each carrier must contain at least 10^7 latently infected T-cells (because the limit of provirus detection by hybridization is 1 in 1000 cells) and that humans contain 10^{10} to 10^{11} T-cells that go through at least 420 generations in a 70-year lifetime (see Section IV) (37, 186), then only 1 out of 10^2 (Japan) to 10^3 (U .S.) x 10^7 x 420 = 10^{12} infected T-cells become leukemic. Thus, HTLV-I cannot be sufficient for leukemogenesis.

4. Antiviral antibodies that completely neutralize HTLV-I to virtually undetectable levels (2) do not protect against the leukemia. This also indicates that HTLV-I is not sufficient for leukemogenesis.

5. Retroviruses cause either polyclonal tumors via dominant, biochemically active oncogenes (6, 37), or possibly clonal tumors via site-specific integration that generates active virus-cell hybrid oncogenes (31, 40, 42). Yet HTLV-I neither expresses a leukemia-specific gene product that could function as an active oncogene, nor does it integrate at a specific site in different "viral leukemias" (2, 187). Thus, HTLV-I cannot be sufficient for leukemogenesis.

6. The statement of the American T-cell Leukemia/Lymphoma Registry that "although most cases of ATL are HTLV-I associated ... many are not" (177) and the reports of virus-negative leukemias from Japan (179) and other countries (2) indicate that HTLV-I is not even necessary for the disease.

7. The HTLV-I-leukemia hypothesis fails to explain the clonal chromosome abnormalities that are consistently found in all ATLs (2, 188)—except if one makes the additional odd assumption that HTLV-I only transforms cells with a preexisting chromosome abnormality.

Thus, there are no virus-determined diagnostic criteria, besides the presence of antiviral antibodies, nor are there any controlled epidemiological and virological criteria to support the hypothesis that HTLV-I is the cause of ATL. Therefore, *ad hoc* hypotheses have been advanced proposing "a second oncogenic event, such as a chance translocation or a second oncogenic virus . . ." for viral leukemogenesis (187). Others estimate five steps in leukemogenesis, of which HTLV-I is postulated to be an "initiator" (185).

Since not even one transfusion-transmitted leukemia case has been recorded in the U.S., it seems surprising that a blood test for antibodies against HTLV-I has become mandatory for members of the American Association of Blood Banks since February 1989. It raises the cost of each of the approximately 12 million annual blood donations in the U.S. (82) by $5–11 (189; Irwin Memorial Blood Bank, personal communication, 1990). Indeed, an HTLV-I epidemiologist pointed out, "Ironically, this route of [HTLV-I] transmission is numerically the least important," considering the 55-year average latent period from infection to leukemia, "the advanced age of most U.S. blood recipients, and the observation that as many as 60% of transfusion recipients may die within approximately 3 years of transfusion because of their underlying disease" (183). Nevertheless, in terms of blood testing expenses, HTLV-I has reached cost-parity with HIV, which adds another $11 test fee to each blood donation (Irwin Memorial Blood Bank, personal communication, 1990).

An alternative hypothesis suggests that spontaneous or perhaps radiation-induced chromosome abnormalities induce the clonal leukemias (see Section VI). Nuclear radiation from the Hiroshima and Nagasaki bombs is blamed for 147 leukemias (190). By proposing that one out of billions of normal HTLV-I-infected cells is transformed by a spontaneous chromosome abnormality, our hypothesis readily resolves the paradox of the clonal chromosome abnormalities in all "viral" leukemias.

B. Herpes Virus, Papilloma Viruses, and Cervical Cancer

Inspired by the SV40/adenovirus-cancer models, infection by herpes simplex virus (HSV) was postulated in the 1970s to be the cause of cervical cancer based on epidemiological correlations with HSV DNA (3).

The virus is sexually transmitted and is latent in about 85% of the adult population of the U.S. (3). Infection by intact HSV typically kills the cell. However, defective and intact viruses that become latent do not kill cells (3).

The viral DNAs in cervical cancers are defective and integrated with cell DNA. Cervical cancers with defective HSV DNA are clonal, just like virus-free cancers (191–194). In agreement with the SV40/ adenovirus models, HSV does not replicate in the tumors. But, unlike the SV40/adenovirus models, no set of viral genes is consistently present or expressed in human cervical cancers. Therefore, the "hit-and-run" mechanism of viral carcinogenesis was proposed (195). It holds that neither the complete HSV, nor even a part of it, needs to be present in the tumor. Obviously, this is an unfalsifiable, but also an unprovable, hypothesis.

Also inspired by the SV40/adenovirus models, and based on epidemiological correlations, infection by human papilloma virus (HPV) was postulated in the 1980s by zur Hausen to be a causative factor in cervical and anogenital cancers (3, 191, 196).

Papilloma viruses are transmitted by sexual and other contacts, like the herpes viruses, and are widespread or "ubiquitous" in at least 50% of the adult population of the U.S. and Europe (3, 191). For example, using the PCR to amplify sequences of one particular strain of papilloma virus, 46% of 467 women in Berkeley, California, with a median age of 22 were found to carry HPV, but none of them had cervical cancer (199). Many other strains of HPV exist (3, 191) that could not be detected with the assay used in this study (199). Like the SV40/ adenovirus models, HPV does not replicate in the tumors. But, unlike these models, HPV naturally replicates nonlytically (13), forming polyclonal warts with unintegrated viral DNA plasmids (200).

zur Hausen reports that cervical cancers occur in less than 3% of infected women in their lifetime, but the incidence in HPV-free controls was not reported (191). In the U.S., the incidence of cervical cancer in all women, with and without HPV, per 70-year lifetime is about 1% (197). In a controlled study of age-matched women, 67% of those with cervical cancer and 43% of those without were found to be HPV-positive (198). These cancers are observed on average only 20–50 years after infection (191).

Different sets and amounts of viral DNA are integrated into cell DNA of different carcinomas (191), and viral DNA is poorly expressed in some cancers and not expressed at all in others (3, 191, 201). Moreover, different HPV strains are found in different cancers (3, 191, 196). Viral antigens are found in only 1–5% of carcinomas (3). Accordingly, HPV does not replicate in the cancer cells and there are no reports of HPV-specific histological or physiological markers that set HPV DNA-positive apart from negative carcinomas (191). There is also no virus-specific integration site in HPV DNA-positive cancers (191), indicating that no specific cellular gene is activated, or that a tumor suppressor gene is inactivated by integration of viral DNA. HPV DNA-positive tumors are clonal and carry clonal chromosome abnormalities, just like virus-negative tumors (191–194).

The HPV-cancer hypothesis of zur Hausen proposes that HPV encodes a "transforming factor" that is suppressed in normal cells by a cellular interference factor (CIF). Inactivation of both CIF alleles by mutation is postulated to result in viral carcinogenesis (191). The low probability of developing mutations in both suppressor alleles is said to explain the long intervals between infection and cancer. This hypothesis correctly predicts that only a small fraction of infections lead to cancer. It further predicts clonal tumors with active HPV DNA and mutations in both alleles of the suppressor genes, and it predicts no effects on the karyotypes of cells.

Howley *et al.* proposed that a viral protein neutralizes the proteins of the retinoblastoma and p53 tumor suppressor genes, and that neutralization of these suppressor proteins causes cancer (202). The proposal is modeled after the hypothesis that retinoblastoma is caused by a cellular cancer gene, provided that a complementary suppressor gene, termed the retinoblastoma gene, is inactivated (see Section IV). This hypothesis predicts polyclonal tumors.

The following epidemiological and biochemical arguments cast doubt on these HPV-cancer hypotheses:

1. Random allelic mutation of suppressor genes, as postulated by zur Hausen, predicts a few cancers soon, and more long after infection. Since cancers only appear 20–50 years after infection,

cooperation between HPV and mutations cannot be sufficient for carcinogenesis.

2. Further, the proposal of zur Hausen that inactivation of host suppressor genes is necessary for viral transformation is not compatible with HPV survival. Since HPV, like all small DNA viruses, needs all of its 8-kb DNA for virus replication (13), suppression of one or more HPV proteins by normal cellular genes would effectively inhibit virus replication in all normal cells. Conversely, if viral transforming proteins were not suppressed by normal cells, virus-replicating wart cells should be tumorigenic because all viral genes are highly expressed in virus replication (1, 13, 191).

3. The clonality of cervical cancers rules out the Howley hypothesis.

4. The lack of a consistent HPV DNA sequence and of consistent HPV gene expression in HPV DNA-positive tumors is inconsistent with the zur Hausen and Howley hypotheses and indicates that HPV is not necessary to maintain cervical cancer.

5. The presence of HPV in no more than 67% of age-matched women with cervical cancer (198) also indicates that HPV is not necessary for cervical cancer.

6. The hypothesis also fails to explain the presence of clonal chromosome abnormalities consistently seen in cervical cancer (16, 192–194)—except if one makes the additional odd assumption that only cells with preexisting chromosome abnormalities are transformed by HPV.

It follows that neither HPV nor HSV plays a direct role in cervical carcinomagenesis. Moreover, the HPV-cancer hypothesis offers no explanation for the absence of a reciprocal venereal male carcinoma.

Thus, detecting inactive and defective viral DNA from past infections in non-tumorigenic cells with a commercial hybridization test (Vira/Pap, Digene Diagnostics, Silver Spring, Maryland) or with the PCR (199) seems worthless as a predictor of rare carcinomas appear-

ing decades later, in view of the "ubiquity" (191) of these viruses in women and the total lack of evidence that cervical cancer occurs in women with HPV more often than in those without. This test, at $30–150, is currently recommended for the 7 million Pap smears that appear "atypical" in the U·S. per year (Digene Diagnostics, personal communication, 1991). By contrast only 13,000 cervical cancers are observed annually in both HPV-positive and -negative women in the U·S. (197). Indeed, the test may be harmful, considering the anxiety a positive result induces in believers of the virus-cancer hypothesis.

An alternative cervical carcinoma hypothesis suggests that rare spontaneous or chemically induced chromosome abnormalities, which are consistently observed in both HPV and HSV DNA-negative and -positive cervical cancers (192–194), induce cervical cancer. For example, smoking has been identified as a cervical cancer risk (204). The controlled study of age-matched women described above suggests that 52% of the women with cervical cancer were smokers compared to only 27% of those without (198). Indeed, carcinogens may be primary inducers of abnormal cell proliferation rather than HPV or HSV. Since proliferating cells would be more susceptible to infection than resting cells, the viruses would be just indicators, rather than causes of abnormal proliferation. Activation of latent retroviruses like HTLV-I (Section III,A) (2), herpes viruses (12), and lambda phages (205) by chemical or radiation-induced cell damage and subsequent proliferation are classical examples of such indicators. Indeed, Rous first demonstrated that the virus indicates hydrocarbon-induced papillomas; it "... localized in these and urged them on ..." and suggested that enhanced proliferation is a risk factor for carcinogenesis (203).

According to this hypothesis, HPV or HSV DNAs in tumor cells reflect defective and latent viral genomes accidentally integrated into normal or hyperplastic cells, from which the tumor is derived. This hypothesis readily reconciles the clonal chromosome abnormalities with the clonal viral DNA insertions of the "viral" carcinomas. The inactive and defective viral DNA in the carcinomas would be a fossil record of a prior infection that was irrelevant to carcinogenesis.

C. Hepatitis B Virus and Liver Carcinoma

Epidemiological evidence indicates that chronic hepatitis B virus (HBV) carriers in Asia have a 250-fold higher risk of developing hepatomas than do non-carriers (3, 12, 206–208). The virus is typically transmitted perinatally in Asia and Africa (3, 207). In over 95% of infections in Asia and 99.9% in the U.S. and Europe the virus is completely neutralized by antiviral immunity. In people with drug- or disease-induced immunodeficiencies the virus remains chronically active (12). Approximately 1 out of 70 chronic HBV carriers in Asia develop clonal hepatomas and 1 out of 300 develop liver cirrhosis in their lifetime (3, 207). However, the liver tumors appear only in 30- to 60-year-olds. Moreover, chronic HBV carriers in Asia are "more likely" to develop hepatomas than those in Europe and the U.S. (12). Inoculation of HBV into chimpanzees has failed to cause hepatomas (3).

The virus is thought not to kill infected cells and viral DNA is replicated as a plasmid and thus not typically integrated into the host DNA (3, 12). However, molecular studies have detected clonal inserts of HBV DNA randomly integrated into the cellular DNA of liver carcinoma tissues (196, 209). Viral DNA is defective and not replicated in HBV DNA-positive hepatomas (209), like SV40 and adenovirus DNAs in the corresponding viral tumors. By contrast to the SV40/adenovirus models, no subset of viral DNA is consistently found or expressed in HBV-positive tumors (209, 210). Only 11–19% of tumors in HBV positive patients express some viral antigens, compared to 26–61% expressing them in surrounding non-tumorous tissues (211). In addition to clonal inserts of HBV DNA, the hepatomas carry clonal chromosome abnormalities (16, 193, 196).

On the basis of these data, it has been proposed that HBV causes liver carcinoma in a step-wise process that begins with antigenemia, followed by chronic hepatitis, cirrhosis, and cancer (3, 207, 209). However, cirrhosis is not a necessary precursor of a hepatoma (3).

The following epidemiological and biochemical arguments cast doubt on the HBV-hepatoma hypothesis:

1. The long intervals of 30–60 years between infection and hepatomas indicate that HBV is not sufficient to initiate carcinogenesis.

2. The evidence that HBV is naturally transmitted perinatally also indicates that the virus is not sufficient to cause fatal diseases such as cirrhosis and hepatomas, because the viruses that depend on perinatal transmission for survival are not inherently pathogenic.

3. The evidence that the hepatoma risk among chronic HBV carriers in Asia is higher than in the U.S. and Europe also indicates that HBV is not sufficient for carcinogenesis.

4. The clonality of the HBV-positive hepatomas further indicates that HBV is not sufficient for carcinogenesis, because only one out of billions of chronically infected liver cells becomes tumorigenic.

5. The absence of an HBV-specific tumor marker, and of a specific HBV DNA sequence or integration site in viral hepatomas, both indicate that HBV is not necessary to maintain hepatomas.

6. The HBV-hepatoma hypothesis fails to explain the clonal chromosome abnormalities of hepatomas—except if one makes the additional odd assumption that HBV only transforms cells with preexisting chromosome abnormalities.

Thus, there is no convincing evidence that HBV DNA is functionally relevant for the initiation and maintenance of hepatomas. Its presence in the tumor could merely reflect that the tumor had originated from one of probably many liver cells of HBV carriers that contain defective, biochemically inactive viral DNA integrated randomly into their chromosomes (196). Therefore, molecular analysis of HBV DNA and of HBV DNA integration sites (210) is not likely to illuminate carcinogenesis.

However, chronically replicating HBV may function as an indirect carcinogen in the form of a long-term source of intoxication, inducing necrosis and tissue regeneration, a known risk factor for carcinogenesis (1, 196, 203). This view is consistent with the higher-than-normal incidence of hepatomas in persons with chronic HBV infection.

A competing hypothesis suggests that chronic HBV infection may only be an indicator of a chronic nonviral intoxication and immuno-

deficiency. Indeed, nonviral factors are involved in hepatomagenesis because the incidence of the hepatomas per HBV carrier varies with different countries (12). Intoxication could induce tissue regeneration and immune suppression, a classical precondition for opportunistic virus infections (see HPV in Section III, B). According to this view, the hepatoma would be caused by a rare virus-independent mechanism that generates chromosome abnormalities in one of many normal cells with HBV DNA inserts. This hypothesis would readily resolve the presence of the clonal chromosome abnormalities in all "viral" hepatomas. The defective and inactive viral DNAs in the hepatomas would be a fossil record of a prior infection that was irrelevant to carcinogenesis.

D. Epstein-Barr Virus and Burkitt's Lymphoma

In the early 1960s, Burkitt suggested that a B-cell tumor, now called Burkitt's lymphoma, which occurs in 1 out of 10,000 Central African children per year between 4 and 14 years of age, was caused by a virus (3, 12). Although not detectable in biopsies of lymphoma patients, a virus was found with the electron microscope in lymphoma cells grown in culture away from the suppressive immune system of the host (212). The Epstein-Barr virus (EBV) has since been postulated to be the cause of Burkitt's lymphoma (3, 8, 12).

In Central Africa, infection with the virus occurs perinatally in the first months of life in almost 100% of the population (3, 207). In the U.S. and Europe, infection occurs typically during or after puberty in about 50% of healthy adults (3, 213). However, the incidence of lymphomas with EBV in these countries is only less than 1 in 10^6 per year (3). Moreover, only 30% of otherwise indistinguishable lymphomas express EBV antigens (3). In America, Burkitt's lymphomas free of EBV DNA were described in 1973 (214). In China, EBV is also said to cause nasopharyngeal carcinoma in adults (1, 3).

During a primary infection, the virus may induce transient, polyclonal lymphoproliferative diseases, such as mononucleosis, if a large percentage of lymphocytes are infected prior to immunity. After antiviral immunity is established, the virus remains chronically associated with the host in a latent form (3, 12). During the chronic state of infection, viral DNA is detectable with the PCR in about 1 out of 10^5 lym-

phocytes (213) and viral antigens in only about 1 out of 10^7 lymphocytes (12).

In lymphomas, the virus is also suppressed, producing but a few viral antigens (3), as the history of its discovery had first indicated. Burkitt's lymphomas are clonal, deriving from single cells that carry characteristic chromosome translocations that often rearrange the proto-*myc* gene (see Section IV). Since EBV, like other herpes viruses, generally does not integrate into the host chromosome (1, 3), the time of infection of tumor cells (e.g., whether infection occured before, during, or after tumorigenesis) cannot be determined.

The EBV-lymphoma hypothesis suffers from numerous epidemiological and biochemical inconsistencies:

1. The clonality of the lymphomas that emerge from a single tumorigenic cell among billions of non-tumorigenic EBV-infected cells indicates that EBV is not sufficient for tumorigenesis.

2. The long intervals between infection and carcinogenesis, averaging 10 years in Africa, and the incidence of only 1 lymphoma per 10,000 infected persons also indicate that EBV is not sufficient to initiate tumorigenesis.

3. The lymphoma incidence varies over 100-fold between African and European or American EBV carriers, also indicating that EBV cannot be sufficient to cause a lymphoma.

4. The lack of a lymphoma-specific EBV function in symptomatic carriers indicates that EBV is not necessary to maintain lymphomas.

5. The existence of EBV-free Burkitt's lymphomas in American and European patients indicates most directly that EBV is not even necessary for Burkitt's lymphoma.

Thus, EBV appears neither necessary nor sufficient for lymphomagenesis. Nevertheless, it has been argued that EBV plays at least an indirect role in lymphomagenesis, because only a minority of susceptible cells from EBV-positive patients are infected *in vivo,* but virtually all

lymphoma cell lines in culture are infected by the virus (215, 216). However, this could be an artifact of studying cells in culture, because the virus would spread unimpaired by immunity from a few infected, normal, or lymphoma cells to all lymphoma cells that survive in culture.

Since about 100% of the Central African and 30–50% of the American population carries latent EBV, and since EBV-negative Burkitt's lymphomas exist, it is likely that the correlations between EBV and tumors are accidental rather than causal. In view of this, an alternative hypothesis has been advanced, which holds that altered cellular proto-*myc* genes are the cause of Burkitt's lymphoma (see Section IV).

IV. Mutated Oncogenes, Anti-oncogenes, and Cancer

A. Mutated Proto-*myc* Genes and Burkitt's Lymphoma

The transforming gene of the directly oncogenic avian carcinoma virus MC29 contains a specific coding region, now termed *myc* (217), derived from a cellular gene termed proto-*myc* (218). Thus, the viral *myc* gene is a genetic hybrid that consists of a strong retroviral promoter linked to a coding region that is a hybrid of virus- and proto-*myc* derived sequences (219). This viral *myc* gene, like synthetic hybrids in which the native proto-*myc* promoter is replaced with that of a retrovirus (40, 42), is expressed to about 100-fold higher levels in all virus-transformed cells *in vitro* and in viral tumors than the cellular proto-*myc* genes (220–222).

The cellular proto-*myc* gene, located on chromosome 8, is rearranged with immunoglobulin genes from chromosomes 2, 14 and 22 in all (29) or most (30) cell lines derived from Burkitt's lymphomas. However, direct cytogenetic studies show that chromosome 8 is rearranged in only about 50% of primary Burkitt's lymphomas (223–226). Analogous rearrangements have also been observed in the proto-*myc* genes of mouse plasmacytoma cell lines (1, 8, 36). The rearrangements do not alter the coding region of proto-*myc* genes. Most rearrangements link the proto-*myc* coding regions to genetic elements from cellular immunoglobulin genes in the opposite transcriptional orientation (1, 8, 36). Other rearrangements in Burkitt's lymphomas do not affect the location and structure of proto-*myc* on chromosome 8, but instead rearrange regions

3' from proto-*myc* (36, 227–232). Because both retroviral *myc* genes and the rearranged proto-*myc* genes of most, but not all, Burkitt's lymphomas differ from normal proto-*myc* genes in truncations 5' from the coding region, and because both were found in cancers, the viral and rearranged cellular *myc* genes were proposed to be equivalent oncogenes (6, 8, 29, 30).

The transcriptional activity of the rearranged proto-*myc* genes in lymphomas is moderately enhanced, not altered, or even suppressed in Burkitt's lymphoma cells compared to normal proliferating cells (5, 30, 36, 216, 227). It is thus nearly 100-fold lower than that of viral *myc* genes or proto-*myc* genes artificially linked to retroviral promoters (40, 42, 220–222, 233).

Moreover, rearranged proto-*rnyc* genes from Burkitt's lymphomas do not transform any human or rodent cells upon transfection (5, 36, 38)—even if they are artificially linked to retroviral promoters (234, 236). In efforts to develop a system that is more efficient than transfection for introducing mutated proto-*myc* genes into cells or animals, synthetic avian retroviruses with the coding region of the human proto-*myc* gene were constructed (233, 237). Since these viruses transform avian cells, it was concluded that "ungoverned expression of the gene can contribute to the genesis of human tumors" (237). However, transformation of human cells was not demonstrated. Moreover, three independent studies report that murine cells cannot be transformed by authentic avian (238) and synthetic murine retroviruses with *myc* genes (239, 240), signaling a restricted transforming host range of *myc* genes.

Several arguments cast doubt on the hypothesis that rearranged proto-*myc* genes of Burkitt's lymphomas are functionally equivalent to retroviral *myc* genes and thus oncogenic:

1. Rearranged proto-*myc* genes from Burkitt's lymphomas or mouse plasmacytomas lack transforming function in transfection assays, while retroviral *myc* genes and proto-*myc* genes driven by retroviral promoters are sufficient to transform at least avian primary embryo cells (40, 42, 237). This indicates that the proto-*myc* genes from lymphomas and viral *myc* genes are functionally not equivalent.

2. Since expression of rearranged proto-*myc* genes from lymphomas is either the same as, or similar to, that of normal proto-*myc* genes, and their coding regions are identical, rearranged proto-*myc* cannot be sufficient for lymphomagenesis. By contrast, viral *myc* genes are oncogenic, owing to a 100-fold higher level of *myc* expression.

3. Primary Burkitt's lymphomas with normal chromosome 8, and with rearrangements of chromosome 8 that occur 3' from proto-*myc* and thus do not affect the structure and regulation of the proto-*myc* gene, indicate that proto-*myc* translocation is not necessary for Burkitt's lymphomas.

It follows that rearranged proto-*myc* genes of human and animal tumors are transcriptionally and functionally not equivalent to viral *myc* genes, and that they are not necessary for lymphomagenesis.

In view of this, the demonstration (237) that human proto-*myc* transforms avian cells after it had been converted artificially to a retroviral *myc* gene is not relevant to its hypothetical role in human tumors. This claim is all the more questionable because even retrovirus-promoted *myc* genes appear unable to transform non-avian cells. Instead, such experiments model the genesis of a viral *myc* gene from a retrovirus and a cellular proto-*myc* gene by rare illegitimate recombination (37). The critical step in this process is the substitution of the weak cellular promoter by the strong retroviral counterpart (40, 42).

Thus, there is currently only circumstantial evidence for the hypothesis that rearranged proto-*myc* genes play a role in Burkitt's lymphomas. This evidence includes the structural, but not functional, similarity to viral *myc* genes, and the approximately 50% incidence of chromosome-8 rearrangements with breakpoints near proto-*myc* in primary lymphomas. In view of this, rearranged proto-*myc* genes either may be involved in a mechanism of leukemogenesis that is not analogous to the viral model, or they may not be involved at all. Since the incidence of chromosome-8 rearrangements is higher in lymphoma cell lines than in primary lymphomas, it has been pointed out that the rearrangement may favor lymphoma cell growth in culture (225).

In efforts to link the proto-*myc* rearrangements with a role in tumori-

genesis, despite these discrepancies with the one-gene model, it was postulated that rearranged proto-*myc* genes may cooperate with other genes for carcinogenesis (236, 238, 241). To test these *ad hoc* hypotheses, transgenic mice were constructed that carry rearranged proto-*myc* genes linked to artificial promoters and hypothetical helper genes in every cell of their bodies. However, only some of these mice developed clonal tumors late in their lives (236). This indicates that even these combinations are not sufficient for carcinogenesis. Consequently, further helper genes were postulated (236, 241).

An alternative hypothesis suggests that the appearance of certain chromosome abnormalities is sufficient for lymphomagenesis. It is consistent with this proposal that cytogenic studies have identified chromosome abnormalities in all Burkitt's lymphomas, even in those that lack rearranged proto-*myc* genes (224–226). The reason that a high percentage of these rearrangements include proto-*myc* and immunoglobulin genes may be a consequence of the natural functions of these genes in B cells, namely generating antibody diversity in which proto-*myc* genes may play an active or passive role.

B. Rearranged Proto-*abl* Genes and Myelogenous Leukemia

Human myelogenous or granulocytic leukemia develops in two stages. The first is a chronic phase that may last, on average, 3–4 years. During this phase, immature myeloblasts are overproduced in the bone marrow and appear in the blood, but may differentiate into functional cells. This hyperplastic stage is followed by a terminal blast crisis of several months, during which non-functional leukemic cells emerge (242, 243). The leukemic cells of both the chronic and terminal stages in 85–90% of patients are marked by a reciprocal translocation between chromosomes 9 and 22. The rearranged chromosome 22 is termed the Philadelphia chromosome (193). In the remaining 10–15% of cases, chromosome 22 is rearranged with other chromosomes (193, 242–245). The reciprocal translocation between chromosomes 9 and 22 substitutes the 5' end of the coding sequence of the proto-*abl* gene on chromosome 9 with a 5' regulatory and coding element of a gene of unknown function, termed *bcr* (for breakpoint cluster region), from chromosome 22 (33, 246–248). The breakpoints with regard to the proto-*abl* gene vary over

200 kb (249), but those within *bcr* fall in a range of 5.8 kb (8, 247, 248). The transcriptional activity of the proto-*abl* gene is virtually unaffected by the translocation (8, 246).

The proto-*abl* gene is the cellular precursor of the transforming gene of the murine Abelson leukemia virus (6). This virus is sufficient to cause terminal myelogenous leukemia in susceptible mice within 3–5 weeks after infection (250, 251). In this virus, the promoter and 5' coding sequence of proto-*abl* are replaced by retroviral counterparts. Since the 5' proto-*abl* coding regions are substituted by heterologous genetic elements in both the virus and the leukemias, it has been postulated that the structurally altered proto-*abl* gene of the leukemia is a cellular oncogene that is functionally equivalent to the transforming gene of Abelson virus (7, 8, 246, 252). However, the Abelson virus or provirus (253), but not the DNA of human leukemic cells, is capable of transforming the mouse NIH 3T3 cell line *in vitro* (8).

The failure of the *bcr*-proto-*abl* hybrid genes to function like the virus could be a technical problem, because the hybrid genes may not be transfectable due to their large size of over 200 kb (8, 249). Therefore, the transforming function of a cDNA transcribed from the 8.5-kb mRNA of the *bcr*-proto-*abl* was tested in murine retrovirus vectors. In such vectors, as in wild-type Abelson virus (251), the transcriptional activity of the *abl* gene is about 100 times that of normal or rearranged cellular proto-*abl* genes (252, 254, 255). One such recombinant virus induced proliferation of lymphoid mouse cells *in vitro* (254). Another induced clonal lymphomas when introduced into the germline of transgenic mice (255). Finally, a myelogenous leukemia was obtained by infecting bone marrow *in vitro* with the synthetic virus and transplanting this marrow into irradiated syngeneic mice (252). The leukemias appeared after relatively short latent periods of 9 weeks (252), almost as fast as those caused by the wild-type Abelson virus (250). The karyotype of this leukemia was not described (252).

Yet several observations cast doubt on the hypothesis that the rearranged proto-*abl* gene from human chronic myelogenous leukemias is functionally equivalent to the transforming gene of Abelson virus and that it is leukemogenic:

1. The transcriptional activity of the rearranged proto-*abl* gene in the leukemias is about 1% of that of wild-type Abelson virus and those of the synthetic recombinant viruses. Thus, mutated cellular proto-*abl* genes and viral *abl* genes are functionally not equivalent.

2. Given estimates that chromosome translocations occur spontaneously in human cells in 1 out of 10^2 to 10^4 mitoses (37, 256, 257), it can be calculated that a *brc*-proto-*abl* rearrangement would be much more probable than chronic myelogenous leukemia. The probablity that a random reciprocal rearrangement falls within the 200-kb 5' region of proto-*abl* and the 5.8-kb 5' region of *bcr* of the 10^6-kb human genome is $(200 : 10^6) \times (5.8 : 10^6)$ or 10^{-9}. Thus, 1 in 10^9 translocations would generate a Philadelphia chromosome. Considering that humans carry about 10^{10} to 10^{11} lymphocytes (186), which are replaced at least six times per year (53), or 420 times in an average lifetime of 70 years, a human life represents at least 10^{13} mitoses of lymphocytes. Making the conservative assumption that a translocation occurs in 1 out of 10^4 human mitoses (256, 257), about 10^9 ($10^{13} : 10^4$) lymphocytes with rearranged chromosomes are generated in a lifetime. Accordingly, every human should, by the age of 70, develop 1, and possibly 100, lymphocytes with a Philadelphia chromosome ($10^9 : 10^9$) and thus leukemia. However, chronic myelogenous leukemia is observed in only 1 (242) to 2.4 (197, 258) out of 100,000 per year or about 0.1% of people in a 70-year lifetime. Therefore, a rearranged proto-*abl* gene appears not to be sufficient for leukemogenesis.

3. Since in 10–15% of the chronic myelogenous leukemia cases proto-*abl* is not rearranged (193, 244), proto-*abl* mutation is not necessary for leukemogenesis. According to Nowell, "These variants appear to have no significance with respect to the clinical characteristics of the disease, and so it appears that it is the displacement of the sequence of chromosome 22 that is of major importance, rather than the site to which it goes" (193).

Thus, a rearranged proto-*abl* is functionally not equivalent to the

transforming gene of Abelson virus. The rearrangement appears to be more probable than a leukemia, and is not even necessary for the leukemia. It is consistent with the first point that the proto-*abl* translocation is observed in the rather benign, early stage of chronic myelogenous leukemia, in which cells can differentiate into functional myeloblasts (242, 243), whereas the Abelson virus causes a terminal leukemia within several weeks.

Since the transcriptional activity of retroviral *abl* genes is about 100 times that of normal and rearranged proto-*abl* genes, and since it is not known whether even a viral *abl* gene can transform a human cell, the claims that "retrovirus-mediated expression of the *bcr*-proto-*abl* protein provides a murine model system for further analysis of the disease" (252) are not realistic. These claims fail to take into consideration the 100-fold transcriptional discrepancy between the retroviral and cellular *abl* genes and the question of whether the transforming host range of *abl* genes includes human cells. Therefore, synthetic proto-*abl* viruses are just experimental reproductions of the rare spontaneous genesis of retroviral transforming genes from normal cellular genes and retroviruses. The critical step in this process is the recombination of the coding region of a proto-*onc* gene with a retroviral promoter (37).

It follows that the 85–90% incidence of proto-*abl* rearrangements in chronic myelogenous leukemia and the structural similarity of the gene to that of Abelson virus are the only evidence to suggest that proto-*abl* plays a role in human leukemogenesis. In view of this, proto-*abl* either must be involved in human leukemogenesis by a mechanism that is not analogous to that of the viral counterpart, or it may not be involved at all.

An alternative hypothesis suggests that alterations of the normal balance of chromosomes cause the leukemia. According to this hypothesis, the Philadelphia translocation would only affect the growth control of the cell. This is consistent with the rather normal function of cells with the translocation during the 3–4 years prior to the blast crisis. In one case, a person with a Philadelphia chromosome did not develop a leukemia for at least 7 years (P. H. Fitzgerald, personal communication, 1985) (245). Indeed, the blast crisis of myelogenous leukemia is accompanied by further chromosomal abnormalities, which are

observed in leukemia with and without rearranged proto-*abl* genes (193, 244).

C. Point-mutated Proto-*ras* Genes and Cancer

Two laboratories have reported that transfection of the DNA of a human bladder carcinoma cell line transforms morphologically the mouse NIH 3T3 cell line (259, 260). Subsequent cloning proved the transforming DNA to be the coding region of the proto-*ras* gene, the same gene from which the coding region of the *ras* gene of the murine Harvey sarcoma virus is derived. Sequencing indicated that the 3T3 cell-transforming proto-*ras* from the bladder carcinoma cells differs from normal proto-*ras* in a point-mutation in codon 12 that changes the native Gly to Val (23, 26, 261).

Further transfection analyses with the 3T3-cell-transformation assay detected point-mutated proto-*ras* genes in less than 1% to about 20% of most common human tumors (1, 6, 36, 262) and in up to 40% of colon cancers (28, 263, 264). The proto-*ras* genes from these tumors were each from a closely related group that includes the Harvey, Kirsten, and N-*ras* genes. Like the Harvey gene, the Kirsten proto-*ras* gene is named after a sarcomagenic murine retrovirus with a coding region of that gene (6). Regardless of point-mutation, proto-*ras* expression is enhanced 2- to 10-fold in about 50% of tumors compared to normal control tissues (44, 262, 265, 266). Transcription of normal proto-*ras* is also enhanced in normal proliferating cells (36), as, for example, 8-fold in regenerating rat liver cells (267).

1. The Original ras*-Cancer Hypothesis Postulates a First-Order Mechanism of Transformation*

The observations that point-mutated proto-*ras* genes from human and some animal tumors transform mouse 3T3 cells became the basis for the hypothesis that point-mutations of proto-*ras* genes cause cancer (23, 26, 27). The hypothesis derived additional support from the observation that the *ras* genes of Harvey and Kirsten sarcoma viruses also differ from normal proto-*ras* in point-mutations in codon 12 (5, 39, 268). The hypothesis assumes that point-mutations confer to proto-*ras* genes dominant transforming function that is equivalent to that of sarcoma-

genic retroviral *ras* genes (268). Further, it assumes that the 3T3-cell transformation assay measures a preexisting function of mutated cellular proto-*ras* genes. Consequently, point-mutated proto-*ras* genes were termed "dominantly acting oncogens" (4, 5, 9, 46, 259, 260, 269). Subsequently, other proto-*onc* genes, such as proto-*myc* (270, 271) and proto-*src* and the *src* genes of Rous sarcoma virus (275), and even genes that are not structurally related to retroviral oncogenes, such as certain anti-oncogenes (see Section IV, E), were also proposed to derive transforming function from point-mutations (1, 5, 6, 9, 46, 272–274).

Numerous observations designed to test the *ras* point-mutation-cancer hypothesis indicate that point-mutation is not sufficient for carcinogenesis:

1. Point-mutated proto-*ras* genes from tumors do not transform diploid embryo cells from rodents or humans, as retroviral *ras* genes do (238, 276). However, upon simultaneous transfection with other viral oncogenes or cellular genes linked to viral promoters, proto-*ras* genes transform embyro cells (234, 235, 238). This indicates that point-mutation is not sufficient to convert proto-*ras* to a gene that can transform normal cells.

2. Numerical arguments based on relative probabilities of point-mutations versus cancer also indicate that point-mutated proto-*ras* genes are not sufficient for carcinogenesis. The probability of point-mutations is 10^{-9} per nucleotide and per mitosis in eukaryotic cells (37, 38, 47, 277). Since eukaryotes carry about 10^9 nucleotides per cell (278) and consist of 10^{11} (mice) to over 10^{14} (humans) cells, mice carry 10^2 ($10^{11} : 10^9$) and humans carry 10^5 ($10^{14} : 10^9$) cells with the specific point-mutation that changes Gly to Val in codon 12 of proto-*ras* at any time (37, 38). Since the average cell is replaced about 100 times during a human lifetime of 70 years (37, 277), this number must be multiplied by 100. Moreover, since at least 50 different point-mutations in at least five different codons confer transforming function to proto-*ras* in the 3T3 assay (39, 279), mice would contain 5×10^3 and humans have 5×10^6 such cells.

3. Further, the existence of point-mutated proto-*ras* genes in non-tumorigenic, hyperplastic tissues (see Section VI) (280–284) and in transgenic mice (236, 241; R. Finney and J.M. Bishop, 7th Annual Meeting on Oncogenes, Frederick, Maryland, 1991, personal communication) indicates that these mutations are not sufficient for carcinogenesis.

4. Point-mutation is not necessary for the transforming function of Harvey and other murine sarcoma viruses, as mutants without point mutations in *ras* and synthetic retroviruses with normal proto-*ras* coding regions are almost as oncogenic as those with point-mutations (41, 44, 285). This indicates that viral *ras* genes derive transforming function from other virus-specific elements (39, 41, 44) and suggests that point-mutation may not be sufficient for proto-*ras* genes to transform.

5. In primary tumors, point-mutated proto-*ras* genes are expressed at nearly the same level as normal proto-*ras* genes (36, 44, 262, 264, 280, 286). By contrast, point-mutated proto-*ras* genes in cells transformed by transfection are expressed like viral *ras* genes, which is at a level at least 100-fold higher than native proto-*ras* genes (44, 234, 235, 262, 280, 286, 287). Thus, the 3T3-cell-transfection assay creates proto-*ras* expression artifacts that are transcriptionally about 100 times more active than native proto-*ras* genes from tumors. Their activity is similar to that of retroviral *ras* genes.

It appears then that a point-mutated but intact cellular proto-*ras* gene is not sufficient for carcinogenesis. Further, it follows that the transfection assay does not measure a genuine function of pointmutated proto-*ras* genes as they exist in tumors, but measures that of an expression artifact created during the transfection assay. An analogous functional artifact has been observed upon transfection of an antioncogene (see Section IV, E) (287a).

Such artifacts could be generated during transfection by substituting by illegitimate recombination the native proto-*ras* regulatory elements by artificial promoters derived from carrier and helper gene DNA

(44). Indeed, transformation of primary cells by cellular proto-*ras* genes depends on the presence of added viral helper genes or on other cellular genes linked to viral promoters (234, 235, 288, 289), or on the presence of retroviral promoters alone (44). This recombination process is entirely analogous to the generation of retroviral *ras* genes, in which coding regions of normal proto-*ras* genes are recombined by transduction with heterologous retroviral promoters that enhance the transcription over 100-fold compared to proto-*ras* (37, 38, 43, 44). In addition, transfection generates concatenated DNA multimers, an artificial gene amplification that would also enhance the dosage of *ras* transcripts (290–293).

The probable reason that proto-*ras* genes from tumors transform 3T3 cells, but not primary cells, is that mouse NIH 3T3 cells are much more readily transformed by exogenous genes, as well as spontaneously (294), than are embryo cells (238). Thus, the weak promoters acquired from random sources during transfection are sufficient to convert proto-*ras* genes with point-mutations to 3T3-cell transforming genes, but not to genes capable of transforming primary cells.

The reason that point-mutated, but rarely normal, proto-*ras* genes (261) are detected by transfection assays is that point-mutations enhance about 10- to 50-fold the transforming function imparted by heterologous promoters on proto-*ras* genes (39, 44, 285, 295). Thus, proto-*ras* genes derive their transforming function from heterologous promoters, and certain point-mutations merely enhance this transforming function.

2. Ad Hoc ras-*Cancer Hypotheses Postulating Second- and Higher-Order Mechanisms of Transformation*

In view of the evidence that native, point-mutated proto-*ras* genes detected in some tumors are not equivalent to viral *ras* genes and not sufficient for carcinogenesis, *ad hoc ras*-cancer hypotheses have been advanced proposing that cellular *ras* genes with point-mutations depend on helper genes for carcinogenesis (6, 28, 46, 236, 238). However, the hypothetical helper genes have not been identified in most tumors, except for colon cancers.

In the case of colon cancer, it has been postulated that point-mutated

Kirsten and N-*ras* genes depend on the mutation of at least three tumor suppressor genes for transforming function (28, 46, 272). Yet the incidence of these mutations in colon cancers is not convincing proof for their postulated function for the following reasons.

Among primary colon cancers, about 40% carry point-mutated Kirsten *ras* genes (28, 263, 264) and some others contain point-mutated N-*ras* genes (28). In addition 70% of all carcinomas carry deletions or mutations in the presumed tumor suppressor gene DCC (deleted in colon cancer) located on chromosome 18, 75% in the presumed suppressor gene p53 located on chromosome 17 and 30% in the presumed suppressor gene APC (adenomatous polyposis coli) on chromosome 5 (28). Thus, only about 6% (0.4 x 0.7 x 0.75 x 0.3) of the colon cancers studied carry the genetic constellation postulated for colon cancer. About 87% carry various combinations of these mutations, and 7% carry none of the mutations (28). In addition, recent evidence indicates that mutations on chromosome 5 are scattered over several hypothetical suppressors or anti-oncogenes (296). Despite these radical mutational differences among colon carcinomas, the carcinomas do not differ from each other in any known histological or biological properties. In addition, all of these mutations alone, and even together, are also observed in benign colon adenomas (see Section VI) (28). Other tumors with point-mutated proto-*ras* genes are also histologically and morphologically indistinguishable from counterparts without these mutations (262, 297).

In view of such poor correlations and the absence of *ras*-specific tumor markers, a functional test is the only method to prove the hypothesis that point-mutated proto-*ras* genes have transforming function in conjunction with helper genes. However, the only functional test currently available is the 3T3-cell-transfection assay, which generates helper-independent proto-*ras* expression artifacts. Thus, the hypothesis that point-mutated proto-*ras* genes play a role in carcinogenesis is based only on circumstantial evidence, namely, structural, but not functional, similarity to viral *ras* genes. In addition, it is based on epidemiological evidence that mutated genes are more common, or are observed more commonly, in tumors than in normal cells (see Section VI). Moreover, the assumption that mutation of p53 is obligatory for carcinogenesis

has not been confirmed in a recent study that generated developmentally normal mice without p53 genes (319a) (see Section IV, E).

It follows either that unrearranged, point-mutated proto-*ras* genes are oncogenic by a second- or higher-order mechanism of carcinogenesis that is not analogous to the first-order mechanism of viral *ras* genes and of the transfection artifacts of proto-*ras* genes, or that they are not relevant to carcinogenesis. Since constellations of mutated proto-*ras* and helper genes that are tumor-specific have not been found, there is currently no evidence for a role in carcinogenesis.

Therefore, we propose that other events, such as chromosome abnormalities, which are consistently found in colon carcinomas with and without mutated oncogenes or anti-oncogenes (28, 47, 192), may cause colon cancers. The clonal mutations in proto-*ras* and hypothetical helper genes could reflect the origin of tumor cells from non-tumorigenic somatic cells with the same mutations (see Section VI).

D. *int* Genes with Integrated Mouse Retroviruses and Mouse Mammary Carcinomas

Mouse mammary tumor virus (MMTV) is one of the many endogenous retroviruses that are genetically and perinatally transmitted but hardly ever expressed by most strains of mice (5, 6, 298). However, inbred female mice of the C3H and GR strains express high titers of mammary tumor virus in their milk. Approximately 90% of the female offspring of C3H mice develop mammary tumors between the ages of 7–10 months (299, 300). Foster-nursing of C3H offspring by virus-free mothers of other strains reduces the risk of tumors to 20–40% and delays their appearance to 18 to 24 months (299, 301). However, wild mice foster-nursed by a C3H mother fail to develop mammary tumors (over a spontaneous background of 3% at 2 years of age), although they are infected by the virus (302, 303).

Virus replication at high titers enhances reversible, hormone-dependent mammary hyperplasias that are poly- or oligoclonal (304). Out of these hyperplasias, clonal tumors emerge that are hormone-independent (304, 305). Thus, infection by milk-borne virus initiates virus replication, hyperplasias, and frequently tumorigenesis at an earlier age compared to spontaneous virus activation and tumorigenesis—but only

in certain inbred strains of mice. The virus is replicating in both early and late tumors (305). The tumors are clonal, defined by specific virus integration sites and chromosome abnormalities (2). Since only one out of millions of virus-producing mammary cells becomes tumorigenic, tumorigenesis may be virus-independent, or may be due to virus-mediated activation, or inactivation of a cellular gene, in which case, site-specific provirus integration must be postulated.

Site-specific integrations in mammary tumors were originally observed in three different mouse strain-specific loci, termed *int*-1 (34), *int*-2 (306), and *int*-3 (307). In C3H mice, the provirus is primarily observed in *int*-1, in BR6 mice in *int*-2, and in some feral mice in *int*-3. Subsequently, "numerous" (305) *int* loci were observed in mouse mammary carcinomas (308). In light of the observation that proto-*myc* genes in certain chicken leukemias are transcriptionally acitvated by retrovirus insertion (31) these *int* loci have been postulated to be cellular proto-*onc* genes that are activated to cancer genes by the promoter of integrated MMT provirus (1, 6, 8, 34, 306, 308). This hypothesis is compatible with the clonality of the mammary tumors.

Integration sites within a given *int* locus are spread over 20 kb and occur in both transcriptional orientations (1, 2, 8). Viral integrations into *int* loci are also observed prior to tumorigenesis in hormone-dependent hyperplasias (304, 309). Only 1–10 copies of *int* RNAs are found in tumor cells that express *int* genes (310). By comparison, synthetic (39, 40, 42, 44) and natural (31) retrovirus-promoted proto-*onc* genes make about 10^3 to 10^4 copies of RNA per transformed cell. In many viral mammary tumors, the *int* loci are not expressed, and in some tumors the *int* loci are expressed but the MMT provirus is not integrated at or near *int*. For example, *int* loci are expressed in only 2 out of 9 clonal tumors of GR mice (304), and *int* loci are expressed in only 19 out of 46 clonal tumors of C3H mice (305). It has also been reported that *int* loci are expressed in tumors in which MMTV is integrated at non-*int* sites. Accordingly, there is no report of *int*-specific tumor markers.

In view of this, several arguments cast doubt on the *int*-activation hypothesis:

1. Since "numerous" *int* loci are observed in mammary carcinomas,

and since integrations are scattered over 20 kb within a given locus and occur in both orientations, MMTV integration into *int* loci cannot be sufficient for carcinogenesis based on the following numerical arguments. Given random retrovirus integration (6) and 1 x 10^6-kb DNA per mouse genome (278), and assuming only five 20-kb *int* loci, about 1 out of every 10^4 (5 x 20 out of 10^6) infected mammary cells should become tumorigenic. Thus, tumors should appear very soon after infection. Since this is not the case, MMTV integration cannot be sufficient for carcinogenesis.

2. Since MMT proviruses integrate into *int* genes prior to tumorigenesis, provirus-mutated *int* genes cannot be sufficient for tumorigenesis.

3. Since wild mice are susceptible to the virus and produce the same hormones as the inbred mice that develop mammary carcinomas, even the virus-hormone package is not sufficient for tumorigenesis.

4. Provirus integration into different *int* loci in different strains of mice indicates that integration is host-directed. Therefore, the virus is not sufficient for site-specific integration and thus for tumorigenesis, if site-specific integration proves to be relevant for tumorigenesis.

5. Since *int* loci are not expressed in many viral mammary tumors, transcriptional activation of *int* genes by any mechanism is not necessary for carcinogenesis. It is consistent with this view that proviruses are integrated into *int* genes in both directions and integration sites are spread over 20 kb, but retroviral promoters activate transcription in only one direction and only over limited distances (42).

6. Since the same tumors are observed with and without integration into *int* genes, site-specific integration is not necessary for carcinogenesis, because "clonal, hormone-independent tumors . . . seem to be the result of mutations that are unrelated to *int* activation" (304).

7. The retroviral *int*-activation hypothesis fails to account for the clonal chromosome abnormalities of all virus-positive tumors that have been characterized (2)—except if one makes the additional odd assumption that MMTV only transforms cells with preexisting chromosome abnormalities.

It thus appears that the MMTV plays only an indirect role in tumorigenesis as one of several factors that enhance mammary hyperplasias, a known risk factor for carcinogenesis (1, 203). This role is similar to that of other highly expressed animal retroviruses in leukemogenesis. For example, inbred viremic mice and chickens have been described that develop virus-induced hyperplasias from which clonal lymphomas or leukemias emerge (2). Alternatively, high levels of retrovirus expression may just signal a heritable loss of intracellular suppressors which could themselves predispose to overgrowth and thus favor carcinogenesis (2). The incidence of 20–40% carcinomas in foster-nursed C3H mice compared to a background of 3% in other laboratory mice (303) supports this view. This would be analogous to the activation of other retroviruses in cells induced to proliferate by genetic damage from chemicals or radiation (see Section III).

In view of this, we propose that mammary carcinogenesis is a rare, spontaneous event initiated by chromosome abnormalities that occur in one out of millions of virus-infected cells. This hypothesis would explain clonal viral integration sites as accidental consequences of the clonal chromosome abnormality that created a tumor cell from a normal virus-infected cell. It would also explain why the carcinomas are not distinguished by the type of *int* gene that is mutated. The *int*-loci would be strain-preferred provirus integration regions that are not relevant to tumorigenesis.

E. Constitutive Oncogenes, Mutated Anti-oncogenes, and Cancer

There are heritable and spontaneous retinoblastomas (45). Cytogenetic analyses of both have observed that chromosome 13 is either missing or deleted in 20 to 25% (311,312). In addition, other chromosome abnormalities have been observed in all retinoblastomas (311, 312). On this

basis, it was proposed that retinoblastoma arises from the loss of a tumor suppressor or an anti-oncogene, now termed *rb,* that is part of chromosome 13 (45). In the familial cases, the loss of one *rb* allele would be inherited and the second one would be lost due to spontaneous mutation. In the spontaneous cases, somatic mutations would have inactivated both loci. In the retinoblastomas with microscopically intact chromosomes 13, submicroscopic mutations were postulated.

This anti-oncogene hypothesis predicts that normal cells would constitutively express oncogenes that render the cell tumorigenic if both alleles of the corresponding suppressor are inactivated. The hypothesis further predicts that the suppressor genes must be active at all times in normal cells. In 1986, Weinberg *et al.* (313) cloned a human DNA sequence that was missing or altered in about a third of 40 retinoblastomas and in 8 osteosarcomas. Therefore, the gene encoded in this sequence was termed the *rb* gene. Reportedly, the *rb* gene was unexpressed in all retinoblastomas and osteosarcomas, even in those without *rb* deletions (313). The *rb* gene measures almost 200 kb, includes 27 exons and encodes, from an mRNA of 4.7 kb, a 110,000-dalton protein (8, 278).

An analysis of 34 primary retinoblastomas undertaken to test the hypothesis found deletions of the *rb* gene in only 4 of 34 tumors analyzed and transcripts of the *rb* gene were found in 12 out of 17 retinoblastomas and in 2 out of 2 osteosarcomas, casting doubt on the deletion hypothesis (314). The remaining tumors had apparently normal *rb* genes. However, subsequent studies of retinoblastomas have observed point-mutations and small submicroscopic deletions in *rb* genes that did not have macrolesions (273, 274, 315, 316). For example, both Weinberg *et al.* (273) and Lee *et al.* (274) reported a point-mutation in a splice sequence of the *rb* gene. In view of this, it is now believed that point-mutations or other minor mutations of the *rb* genes are sufficient for tumorigenesis (273, 315). However, Gallie *et al.* reported point-mutations and deletions of *rb* genes in only 13 out of 21 tumors (315). In an effort to develop a functional assay, a DNA copy of the mRNA of the *rb* gene was cloned into a retrovirus; infection by this virus inhibited the growth of a retinoblastoma cell line *in vitro* (274, 317). However,

two recent studies show that an intact, synthetic *rb* gene fails to inhibit tumorigenicity of human retinoblastoma and breast cancer cells in nude mice (318, 318a).

Clearly, the point-mutation hypothesis of the *rb* gene would never have emerged if the original chromosome deletion hypothesis had been confirmed. It advanced the anti-oncogene hypothesis into a virtually inexhaustible reservoir of hypothetical cancer genes: Any gene with any mutation in each of both alleles in a cancer cell could be a tumor suppressor or anti-oncogene. According to Weinberg, "... one can cast a broad net for tumor suppressor loci by using a large repertoire of polymorphic DNA markers to survey ... for repeated instances of LOH (loss of heterozygosity). Indeed, this genetic strategy has revolutionized the research field" (287a). Over a dozen deleted or point-mutated anti-oncogenes are now considered to cause osteosarcomas, breast cancer, bladder cancer, lung cancer, colon cancer, Wilms' tumor, and neuroblastoma, in addition to retinoblastoma (8, 9, 46, 287a, 317). For example, a point-mutation in one of three genes of a colon cancer cell would signal an inactivated hypothetical colon cancer suppressor gene (272, 296). Further, the range of the *rb* suppressor gene has since been extended to other cancers, including small cell lung, bladder, prostate, and breast carcinomas, and osteosarcoma (8, 317).

The anti-oncogene hypothesis has been difficult to prove because (a) the oncogenes that are said to be suppressed have not been named or identified (269) and will be difficult to assay because all normal cells or animals should suppress them with the corresponding antioncogenes, and because (b) transfection of an intact *rb* gene (274, 318) has failed to revert transformed cells to normal and to suppress their tumorigenicity (274, 318, 318a). Likewise the hypothetical colon cancer suppressor gene p53 has failed to revert transformed cells to normal (319) and its complete absence has not affected the normal development of mice (319a). Nevertheless, 74% of these p53-free mice developed lymphomas and sarcomas at six months that probably derived from single cells, rather than through a systemic transformation as the anti-oncogene hypothesis would have predicted (319a).

At this time, the hypothesis suffers from the following shortcomings:

1. The probability of point-mutations and minor mutations in both alleles of the *rb* gene appears much higher than the cancers they are said to cause. Since the *rb* gene has 27 exons and each exon is flanked by at least four essential splice nucleotides, at least 108 (4 x 27) point-mutations could inactivate the *rb* gene. In addition, one can assume that point-mutations of at least 10% of the 928 amino acids of the 110,000-dalton *rb* protein would inactivate the gene (8). Thus, at least 200 point-mutations should be able to inactivate *rb*. Since 1 in 10^9 human cells contain any possible point-mutation of the human genome (see Section IV,C), about 1 in 5 x 10^6 would contain an inactive *rb* gene, and 1 in $(5 \times 10^6)^2$ or 2.5 x 10^{13} would contain two inactive *rb* genes in the same cell. This number would be even higher if other mutations such as minor deletions and chromosome nondysjunctions were included.

   Chromosome nondysjunctions are estimated to occur in 1 out of 10^4 human cells (320, 321). The probability of generating a retinoblastoma cell from a point-mutation in one *rb* gene and a missing chromosome 13 would be 1 in 5 x 10^6 x 10^4 or 1 in 5 x 10^{10}. Thus, every adult human consisting of about 10^{14} cells would contain at least 1 and possibly 5 x 10^3 cells in which both *rb* genes are inactivated, and would develop over 100 to 100,000 such cells in a lifetime of 70 years, which represents about 10^{16} cells (37, 277). Since inactive *rb* genes are now said to cause retinoblastomas, osteosarcomas, small cell lung, breast, and bladder carcinomas, etc., and the corresponding tissues represent over 20% of the human body, one would expect at least 20% of humans to develop such a tumor per year.

   Moreover, 1 in 5 x 10^6 cells of every person with one inherited *rb* mutation should have defects in both *rb* alleles due to secondary mutation and 1 in 10^4 cells due to chromosome nondysjunction. A recent review on tumor suppressor genes reports exactly the same probabilities for *rb* mutations as we do (287a). Thus, all persons with an inherited *rb* deletion should develop retinoblastomas and other cancers. Since this is not the case (45), point-mutation or deletion of both *rb* alleles cannot be sufficient for carcinogenesis.

2. Since neither deletion nor minor mutation of *rb* genes is observed in all retinoblastomas or other specific tumors, *rb* deletion or mutation is not necessary for tumorigenesis.

3. The relevance of the growth inhibitory function of the artificial retrovirus with an *rb* coding region to the putative tumor suppressor function of *rb* is unclear for several reasons: (a) Expression from a retroviral promoter enhances the *rb* protein concentration at least 100-fold above physiological levels (274) and thus may not be relevant to its normal function. Similar reservations are expressed by Weinberg: "... many genes ... will antagonize growth when they are forced on a cell by ... gene transfer, but this provides no testimony as to whether these genes are normally used by the cell to down-regulate its own proliferation...." (287a). (b) Recently, elevated rather than reduced *rb* expression was observed in tumor cells (322). (c) Human retinoblastoma cell lines and breast cancer lines transfected with intact and artificially overexpressed *rb* genes are tumorigenic in nude mice, indicating that the *rb* gene does not suppress tumorigenesis by retinoblastoma and mammary carcinoma cells (318, 318a).

It follows that deletion or mutation affecting both alleles of the *rb* and p53 genes is not sufficient and probably not necessary for carcinogenesis since the same retinoblastomas and colon cancers occur in the presence and absence of these genes. An alternative hypothesis suggests that the many chromosome abnormalities associated with retinoblastomas (311,312), other tumors with *rb* mutations (194) and colon cancers are to blame for carcinogenesis (see Section VI).

V. Conclusions

A. Evidence That Latent Viruses and Mutated Cellular Genes Are Pathogenic Is Circumstantial

Compared to classical prototypes, the presumably latent viruses and mutated cellular genes all suffer from activity, infectivity, and specificity gaps: (1) The viruses and genes that are postulated to be pathogenic or

oncogenic are each orders of magnitude less active, and their products less abundant, than the transcriptionally active, pathogenic prototypes that have inspired these hypotheses; (2) infections with the viruses do not cause the postulated diseases, and transfections of appropriate cells with mutated cellular genes do not transform normal cells; (3) the hypothetical pathogens are not disease-specific, because (a) the same latent viruses and mutated cellular genes occur in symptomatic and asymptomatic subjects (see Section VI) and because (b) histologically and clinically indistinguishable diseases occur without them.

Clearly, infection without disease involving limited numbers of cells also occurs with classical viral pathogens and is essential for their survival (3, 12). However, it becomes an important deficiency for hypotheses claiming pathogenicity for viruses that are equally inactive and restricted in diseased and healthy carriers.

Therefore, there is only circumstantial or epidemiological evidence for the role of mutated genes in cancer and latent viruses in disease. Indeed, Bishop writes that "... on the basis of circumstantial evidence of considerable variety, damage to diverse proto-*onc* genes has been implicated in the genesis of human tumors" (7). Varmus pointed out: "Although the dividends of conferring the status of protooncogenes upon these cellular genes have been considerable, it must be acknowledged that the basis for doing so, the genetic definition of v-onc's [retroviral oncogenes], has not been uniformly rigorous" (5). And on the basis of epidemiological correlations, point-mutations in cancer cells are said to be "smoking guns" (272). Yet the same tumors occur without this circumstantial evidence (see Section VI).

Based on just two as yet unconfirmed studies from 1989, Baltimore and Feinberg pointed out that "HIV viremia cannot be said to be 'necessary' for AIDS on the basis of any available data, but the new results are a consistent feature of AIDS" (77). Further, Blattner, Gallo, and Temin (14) argued that "... the strongest evidence that HIV causes AIDS comes from prospective epidemiological studies ..." and Weiss and Jaffe (15) concurred ("the evidence that HIV causes AIDS is epidemiological. ..."), although Gallo (76) conceded that epidemiology is just "one hell of a good beginning" for proving the virus-AIDS hypothesis. But even this beginning is flawed by the tautological defi-

nition of AIDS, which only diagnoses AIDS when antibodies to HIV are found (54) and ignores all AIDS indicator diseases that occur in the absence of HIV, even in AIDS-risk groups (54). For example, half of all American intravenous drug users (55) and 25% of all hemophiliacs (54) are HIV-free, so that their AIDS indicator diseases will not be reportable as AIDS.

The same is true for the epidemiological evidence that HTLV-I causes T-cell leukemia. The leukemia is solely defined by the presence of HTLV-I, although it has been observed in its absence (Section III). In an effort to link human myelopathy with latent HTLV-I, it is proposed that "similarities between HAM (HTLV-I associated myelopathy) and visna [are] the result of still deeper identities" (323). Visna is a neurological disease that occurred in the 1930s in a now extinct strain of sheep. Its cause is believed to have been a latent retrovirus, termed visna virus, that is present in over 50% of healthy sheep in Europe and the U.S. (53). Likewise, there is no controlled study to show that the incidence of cervical cancer is higher in HPV-positive than in matched negative controls (see Section III).

Thus, latent viruses and mutated cellular genes are postulated to be pathogenic only because (i) they structurally resemble active pathogenic viruses or active viral oncogenes, and because (ii) they occur, or are assumed to occur, in the respective diseases more often than in normal tissues (6, 49, 51, 296).

B. Helper Genes and Cofactors to Close the Activity, Infectivity, and Specificity Gaps of Hypothetical Pathogens

Since the latent viruses and mutated cellular genes do not behave like the autonomous pathogens they were originally postulated to be, the original theories have been supplemented by *ad hoc* hypotheses.

For example, it has been postulated that the long latent periods, ranging up to 55 years, of the hypothetical viral pathogens are necessary for various, unproven cofactors to help the latent viruses to cause disease. Accordingly, the viruses have been termed "slow viruses" or "lentiviruses" (3, 12), although the viruses replicate within a few days and are immunogenic within a few weeks after infection (13, 37, 91, 92). Further, it has been postulated that antiviral antibodies consistently

fail to neutralize viruses such as HIV (76, 77) or hepatitis C virus (160), although the respective viruses are almost undetectable for the duration of the diseases they are said to cause. Moreover, helper genes or cofactors are postulated for carcinogenesis by mutated genes that are not transcriptionally activated, including the point-mutated proto-*ras* genes, the *int* genes mutated by provirus insertion, or the rearranged proto-*myc* genes.

In reality, the cofactors are modern euphemisms for new hypotheses. The *ad hoc* hypotheses all assume second- or third-order mechanisms of pathogenesis relying on unproven cofactors for both latent viruses and mutated cellular genes to cause disease. Moreover, these *ad hoc* hypotheses all lack appropriate precedents because all available pathogenic viruses and viral oncogenes are helper-independent first-order pathogens. Yet the *ad hoc* hypotheses are popular because they leave arbitrary but face-saving roles for failing incumbents, which were all originally proposed to cause the diseases by themselves.

In the absence of functional proof, circumstantial and epidemiological evidence is only relevant for causation if the respective viruses and cellular mutations and their hypothetical cofactors are at least disease-specific. This appears not to be the case.

VI. Alternative Hypotheses

A. Latent Viruses as Harmless Passengers

The inactive viruses associated with fatal diseases such as AIDS, hepatitis C, cervical cancer, T-cell leukemia, hepatoma, Burkitt's lymphoma, and encephalitis are all not disease-specific. They are common, like HSV, HPV, EBV, and HBV (3, 12), or rare, like HIV and HTLV-I (54), in healthy persons. The long "latent periods" and the low incidence of "viral" disease among virus carriers indicate that such infections are typically not pathogenic. Although the term "latent period" implies that the virus becomes active thereafter, even this is almost never true (see Section II and III). During the presumably virus-caused diseases, including AIDS, cervical cancer, T-cell leukemia, hepatoma, or panencephalitis, the virus remains typically inactive, leaving pathogenic functions to unnamed cofactors. And there is no cofactor that has been

found only during the disease but not prior to it. It is hardly surprising that latent viruses or fragments of their DNAs are still there if their host develops a nonviral disease. Thus, the latent viruses are innocent bystanders or "passengers," rather than drivers, in nonviral disease processes (159).

B. Drugs as Alternatives to Hypothetical Viral Pathogens

The great triumphs in the pursuit of microbial and viral pathogens in the last 100 years have eclipsed, and even led to the ridicule of, alternative, less spectacular, explanations of disease, such as pathogenic drugs and toxins (15, 324–326). Although we are in the middle of a drug-use epidemic in America, the pathology and epidemiology of recreational drugs, and even of some medical drugs such as AZT, are virtually unstudied by the scientific community (155).

The drug-AIDS hypothesis, described in Section II, A, 2, is one example of how drug use could cause AIDS diseases (54, 60, 103). Psychoactive drugs and medical drugs could explain diseases caused by the depletion of many cells, such as the depletion of T-cells in AIDS or of hepatocytes in hepatitis C, much better than can dormant viruses. Indeed, both of these diseases are observed primarily in drug addicts (54, 103, 160). Drug toxicity is also much more compatible with the restriction of these diseases to risk groups, as, for example, AIDS, which is almost exclusively restricted to users of recreational drugs and anti-HIV drugs such as AZT (like lung cancer is to smokers).

Exogenous toxins could also explain the actions of putative viral tumors, such as nitrite inhalants causing Kaposi sarcomas and AZT causing lymphomas (69, 103), smoking possibly causing cervical cancer (198, 204), nutritional toxins causing hepatomas, and radiation possibly causing T-cell leukemia (190) (see Section III). Toxins would also provide a plausible explanation for the lack of contagiousness of these "viral" diseases. The cumulative effects of drug or nutrient toxicity over time are compatible with the appearance of these diseases relatively late in life and at unpredictable intervals after infection by presumed viral causes. By contrast, viruses as self-replicating toxins all cause diseases soon after infection. In light of this theory, hypothetical linkages between infection by a virus and a subsequent onset of disease via long and

unpredictable latent periods of up to 55 years would dissipate, because infection and pathogenesis are independent events.

C. Mutated Genes and Latent Viruses as Trivial Genetic Scars of Cancer Cells

The spontaneous or virus-induced mutations in tumor cells are also not disease-specific. For example, point-mutated proto-*ras* genes have been observed in chemically induced skin hyperplasias of laboratory mice (280) and in spontaneous liver hyperplasias of B6C3FI mice (281) that all spontaneously revert to normal. Further, they have been observed in reversible skin hyperplasias of humans (282, 327) and in human hemopoietic hyperplasias (238, 284). Moreover, a recent study of transgenic mice concluded that "... expression of the mutant [proto-Ha-*ras*] gene via its own promoter at the normal chromosomal locus is nontransforming" (R. Finney and J.M. Bishop, 7th Annual Oncogene Meeting, Frederick, Maryland, 1991, personal communication). In addition, point-mutations and all other mutations affecting hypothetical tumor suppressor genes are not tumor-specific. They are detected singly and in all combinations, including mutated proto-*ras,* in benign colon adenomas at about the same rates as in malignant carcinomas (28).

Proto-*abl* translocations are seen in functional granulocytes that are overproduced during the chronic, hyperplastic phase of myelogenous leukemia (242, 243) (see Section IV). Hormone-dependent mammary hyperplasias with *int* genes mutated by integrated MMT proviruses have been described (see Section IV). Also, the DNA of hepatitis B virus has been detected and is expressed in non-tumorigenic liver cells more consistently than in hepatomas (196, 211). Inactive and defective HPV DNA is routinely detected in non-tumorigenic tissues with the commercial Vira/Pap test or with the PCR (199). And HTLV-I is almost only detected in normal rather than leukemic carriers (see Section III). Further, viable transgenic mice with mutated proto-*abl,* proto-*myc,* and proto-*ras,* and even with hypothetically cooperating combinations of proto-*myc* and proto-*ras,* have been constructed, and some are commercially bred ("OncoMouse-TM shortens the path to knowledge ...," Dupont Co., Wilmington, DE, 1990) (236). This argues either for even more cofactors or for other mechanisms altogether.

Thus, spontaneous and viral mutations of tumor cells are not disease-specific. These findings confirm the above calculations that the probability of these mutations is much higher than the incidence of cancer and that carcinogenesis even among hyperplasias is still a very rare event. In view of this, we agree with Bishop that "the nomenclature for the affected genes [oncogenes] is unfortunate, since it is based largely on occasional [presumed] pathogenic aberrations. . . ." (9).

Nevertheless, since clonal tumors have been observed to emerge from hyperplasias and transgenic animals at a higher-than-normal rate, their mutated genes and latent viruses could play roles in carcinogenesis that are not analogous to those played by the biochemically active models that led to their discovery. For example, they could alter growth control genes and thus generate hyperplasias. However, even this is speculation because the mutations and latent viruses are not consistently found in hyperplastic cells, with the exception of HPV in papillomas (13) (see Section III). Therefore, they must be presumed innocent until proven guilty (326).

In view of this, we propose that the mutations and latent viruses that are found in tumor cells are trivial genetic scars that were picked up by non-tumorigenic somatic cells during many generations of growth in the presence of mutagens or viruses. Because of detection and reporting biases in favor of disease, the mutations and latent viruses would be reported more often in diseased than in healthy carriers. Further, the mutations and viruses would be more readily and more often observed in cancer cells than in non-tumorigenic somatic tissues, because cancers are clonal populations of cells (192, 193, 328) that provide multiple copies of identical mutations, biological equivalents of the PCR. In contrast, such mutations, including latent and fragmented viral DNAs, would not be detectable in mutationally "heterogenous" populations of normal cells, unless individual cells were cloned or their nucleic acids were amplified.

Since many of these somatic mutations could be incompatible with normal fetal development, they would not be seen in the germline (329) and thus not in an average normal cell. The many congenitally and genetically transmitted animal (6) and human retroviruses, including HTLV-I and HIV (54), would be notable exceptions. Apparently, retro-

viruses are so harmless that they can be accepted as parasites even during development (2).

The hypothesis correctly predicts the same mutations and latent viruses in non-tumorigenic somatic cells and in tumors that emerged from these cells, as, for example, the proto-*ras* and other mutations or the many "tumor" viruses that are shared by tumorigenic and nontumorigenic cells. Further, the hypothesis correctly accounts for the "too many mutations in human tumors" observed by Loeb (47), perhaps those that were considered irrelevant for carcinogenesis by Heidelberger ("I don't care if cells are 90% transformed, I am only interested in the last 10%.") (330). In view of this hypothesis, the latent viruses and non-activating mutations of cellular genes in cancer cells would be genetic trivia.

D. Cancer by Somatic Gene Mutation Unconfirmed

The clonality, irreversibility, and predictable course of most cancers all indicate that cancer has a genetic basis. Yet an autonomous cellular cancer gene, or a complement of interdependent ones, that can be activated by the statistically cheap mutations observed in hypothetical oncogenes and anti-oncogenes is improbable on the following grounds.

(i) Nothing could be more terminal for a multicellular organism than a battery of latent cancer genes that are as easy to "activate" as the over 50 putative cellular oncogenes that have been named or the unnamed oncogenes that are said to be activated by inactivation of suppressor genes (6, 8, 9, 331). The activation of just one dominant oncogene would be sufficient to initiate a clonal cancer and thus to kill the organism. By comparison, activation of a hypothetical death gene would kill only a single cell.

Indeed, since each of these oncogenes is thought to be activated via point-mutations, truncations, and virus insertions and since the probability of such mutational events is as high as 1 in 10^6 per mitosis and gene, and is as high as 1 in 10^9 per mitosis and nucleotide (see above estimates for proto-*ras,* proto-*abl,* and *rb*) (37, 38, 47, 277), multicellular organisms such as humans, with about 10^{16} cells per average 70-year lifespan, would generate at least $50 \times 10^{16} : 10^9 = 5 \times 10^8$ cancer cells per lifetime. This number would be even higher if multiple mutational

sites for the activation of specific oncogenes and for the inactivation of specific anti-oncogenes were considered (6, 8). It would be further enhanced by the multiplicity of certain oncogenes that exist as large families, including proto-*myc* and proto-*ras* (6, 8).

Nevertheless, the numerology of mutations could be reconciled with the real incidence of cancer by postulating adequate numbers of cooperating mutations, as has been attempted in the case of colon cancer (see Section IV). However, this would be analogous to the invention of more and more Ptolomaic epicycles by geocentrists, in the face of Galileo's challenge that the earth was not the center of the solar system. Naturally, the relevance of these efforts to carcinogenesis would depend on functional proof.

(ii) Based on the only proven examples of "mutated cellular" oncogenes, the retroviral oncogenes, a cellular gene would have to become about 100-fold more active than normal to become a cancer gene. However, the odds of truly activating a gene about 100-fold over the level for which it has been optimized during 3 billion years of evolution by spontaneous mutation, must be much lower than the odds of the presumably "activating" point-mutations or truncations or virus insertions that are observed in the hypothetical proto- and anti-oncogenes of tumors. The rare, accidental recombinants with imported retroviral promoters, which in turn have been optimized during virus evolution to override cellular controls, are as yet the only known examples of oncogenic mutations (37).

The odds for activating a cellular gene 100-fold by spontaneous mutations would be particularly low for the many interdependent genes that must determine "how cells govern their replication. . . ." (7), the presumed natural function of proto- and anti-oncogenes (7, 287a). According to Bishop, mutational "damage" to the "relays in regulatory circuitry" (proto-*onc* genes) and "governors of proliferation" (anti-oncogenes) is considered a "gain of function" sufficient to produce cancer (9). These oncogenic functions are postulated to be "dominant because . . . evil overrides good" (9). However, "damage" of the kind observed in putative oncogenes naturally inactivates genes causing diseases such as sickle cell anemia and hemophilia (320, 332). Such damage is a loss of function and thus recessive, because the remaining

"good" gene overrides "evil." Ironically, the same kind of somatic mutations or damages to genes thought to "activate" oncogenes are said to perform conventional gene inactivations when they affect anti-oncogenes.

Indeed, it is one of the most common misconceptions that cancer is a consequence of unrestricted growth, because unrestricted growth produces benign hyperplasias, not cancer. According to Cairns, "It is a common mistake to assume that cancer cells multiply faster than the normal cells from which they were derived .... The fact is that the cells of most cancers divide at about the normal rate, and some even less frequently than their normal counterparts, but they are able to increase in number because a greater proportion of the cells' progeny remain in the dividing pool than is normally allowed" (277).

(iii) There is no functional proof for cellular oncogenes, because according to Stanbridge "... despite intensive efforts to transform normal human fibroblasts or epithelial cells with varying combinations of activated cellular oncogenes, the results have been uniformly negative" (269). Moreover, their presence, unlike that of related viral oncogenes, does not determine the character of a given type of tumor. Likewise, unmutated anti-oncogenes fail to revert tumor cells to normal, and mutated anti-oncogenes fail to distinguish tumors from those in which they are normal (see Section IV).

The somatic mutation hypothesis owes much of its popularity to the fact that, in the 1960s and 1970s, many carcinogens were found to be mutagens (335, 338), although substantial non-correlations between carcinogens and mutagens were also noted (335, 337). In the 1980s, the hypothesis derived further notoriety from the consensus that proto-*onc* genes and anti-oncogenes are the critical targets among the anonymous genes that are mutated by carcinogens (9, 287a). Says Weinberg: "Mutations that potentiate the activities of proto-oncogenes create the oncogenes that force the growth of tumor cells. Conversely, genetic lesions that inactivate suppressor genes liberate the cell ... yielding the unconstrained growth of the cancer cell" (287a). However, not even one of the many somatic mutations observed to date in cancer cells has been shown to function as a cancer gene. According to Pitot: "... that carcinogens are mutagenic or may be converted to mutagens is important

but not direct evidence for the genetic origin of neoplasia" (16).

In sum, the gene mutation hypothesis of cancer is numerically and evolutionarily implausible and is functionally unconfirmed. Similar conclusions were reached by Rous (203, 333) and Rubin (334) after studying oncogenic viruses and cancer for over 50 and 30 years, respectively. Rous concluded: "A favorite explanation has been that oncogens (Rous' term for carcinogens) cause alterations in the genes of the ordinary cells of the body ... somatic mutations as these are termed. But numerous facts, when taken together, decisively exclude this supposition" (203). "A hypothesis is best known by its fruits. What have been those of the somatic mutation hypothesis? ... It acts as a tranquilizer on those who believe in it, and this at a time when every worker should feel goaded now and again by his ignorance of what cancer is" (333). Likewise, Cairns "... suggests that most human cancers are not caused by conventional mutagens ..." (335).

E. Chromosome Abnormalities as Causes of Cancer

But if there are no cellular genes that are converted to cancer genes by somatic mutations, cancer would have to be caused by normal cellular genes. Perhaps a cell could become transformed by gross numerical imbalances of normal genes, e.g., via chromosome abnormalities, just as a computer could be rendered uncontrollable by deleting, duplicating, and misplacing intact chips, or by altering the operating software. To test this hypothesis, it would be necessary to determine how probable such abnormalities are compared to cancer and whether abnormalities exist that are cancer-specific.

Indeed, chromosome abnormalities are the oldest, and, as yet, the only consistent observation made on cancer cells. It was postulated by Boveri in 1914, prior to the discovery of DNA and point-mutations, that cancer would be caused by abnormal chromosomes (194, 336). The clonal origin of tumors, the stemline concept predicted by Boveri and defined by Winge in 1930 (336), is the strongest support for the view that clonal chromosome abnormalities are the causes, rather than consequences, of carcinogenesis.

This abnormal chromosome-cancer hypothesis would explain why

chromosome abnormalities are consistently found in tumors with or without mutated cellular oncogenes and with or without latent viruses.

The hypothesis predicts that diploid cancers that differ from normal cells only in mutated oncogenes or anti-oncogenes are not observed, because certain chromosome abnormalities instead of somatic mutations of specific genes are carcinogenic. Tumor progression would be a consequence of further discontinuous chromosome abnormalities. The hypothesis would readily resolve the paradox that all "viral" tumors presumably caused by HTLV-I, HBV, HPV, HSV, and MMTV have clonal chromosome abnormalities. By contrast, all virus-cancer hypotheses would have to make the odd assumption that only cells with preexisting chromosome abnormalities are transformed by these "tumor" viruses.

Our hypothesis also explains why "... despite intensive efforts to transform normal human fibroblasts or epithelial cells with varying combinations of activated cellular oncogenes, the results have been uniformly negative" (269). In addition, the hypothesis explains why mutated proto-*onc* genes and anti-oncogenes do not distinguish tumors by their presence. According to our hypothesis, accidental somatic mutations generated by chromosome translocations, such as rearranged proto-*myc* or proto-*abl* genes, would be as irrelevant to carcinogenesis as other mutations of specific genes, such as point-mutated *ras* genes. Further, the hypothesis would explain why transgenic mice with activated oncogenes are breedable and why retinoblastoma cells remain carcinogenic for mice, even if they are infected by a retrovirus that overexpresses its presumed suppressor, *rb* anti-oncogene (see Section IV). Our hypothesis would also resolve the discrepancy between the rather high probability and incidence of mutation or "activation" of proto-*onc* genes compared to the much lower probability and incidence of cancer (see Section IV) (37, 337).

We have previously proposed another alternative to the oncogene hypothesis. It holds that cancer genes are generated by substituting the normal promoters of proto-*onc* genes via rare illegitimate recombinations by strong heterologous promoters from viruses or from cellular genes (37). As yet, the retroviral oncogenes are the only proven exam-

ples of this hypothesis (40, 43, 44). The relevance of this hypothesis to virus-free tumors depends on whether the cell contains promoters that are as strong as those of viruses.

Acknowledgments

We thank J. Michael Bishop (San Francisco), Michael Botchan, Eli Canaani (Philadelphia), Asit Chakraborty, Bryan J. Ellison, David Goodrich (San Antonio), Robert Hoffman (San Diego), Ruhong Li, Ranu Nandi, Philip Rosen (Boston), Harry Rubin, Janie Stone, and Charles Thomas, Jr. (San Diego) for critical reviews, critical information, or both; Jane A. Byrd for the final draft of this manuscript and its many precursors; and Cell for providing a free copy of Human Retrovirology: HTLV (176) for a book review that was not published. P.H.D. is supported by Outstanding Investigator Grant 5-R35-CA39915–07 from the National Cancer Institute.

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Chapter Six

AIDS Acquired by Drug Consumption and Other Noncontagious Risk Factors

Pharmacology & Therapeutics 55: 201–277, 1992

Abstract

The hypothesis that human immunodeficiency virus (HIV) is a new, sexually transmitted virus that causes AIDS has been entirely unproductive in terms of public health benefits. Moreover, it fails to predict the epidemiology of AIDS, the annual AIDS risk and the very heterogeneous AIDS diseases of infected persons. The correct hypothesis must explain why: (1) AIDS includes 25 previously known diseases and two clinically and epidemiologically very different epidemics, one in America and Europe, the other in Africa; (2) almost all American (90%) and European (86%) AIDS patients are males over the age of 20, while African AIDS affects both sexes equally; (3) the annual AIDS risks of infected babies, intravenous drug users, homosexuals who use aphrodisiacs, hemophiliacs and Africans vary over 100-fold; (4) many AIDS patients have diseases that do not depend on immunodeficiency, such as Kaposi's sarcoma, lymphoma, dementia and wasting; (5) the AIDS diseases of Americans (97%) and Europeans (87%) are predetermined by prior health risks, including long-term consumption of illicit recreational drugs, the antiviral drug AZT and congenital deficiencies like hemophilia, and those of Africans are Africa-specific. Both negative and positive evidence shows that AIDS is not infectious: (1) the virus hypothesis fails all conventional criteria of causation; (2) over 100-fold different AIDS risks in different risk groups show that HIV is not sufficient for AIDS; (3) AIDS is only "acquired," if at all, years after HIV

is neutralized by antibodies; (4) AIDS is new but HIV is a long-established, perinatally transmitted retrovirus; (5) alternative explanations disprove all assumptions and anecdotal cases cited in support of the virus hypothesis; (6) all AIDS-defining diseases occur in matched risk groups, at the same rate, in the absence of HIV; (7) there is no common, active microbe in all AIDS patients; (8) AIDS manifests in unpredictable and unrelated diseases; and (9) it does not spread randomly between the sexes in America and Europe. Based on numerous data documenting that drugs are necessary for HIV-positives and sufficient for HIV-negatives to develop AIDS diseases, it is proposed that all American/European AIDS diseases, that exceed their normal background, result from recreational and anti-HIV drugs. African AIDS is proposed to result from protein malnutrition, poor sanitation and subsequent parasitic infections. This hypothesis resolves all paradoxes of the virus-AIDS hypothesis. It is epidemiologically and experimentally testable and provides a rational basis for AIDS control.

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> "It's too late to correct," said the Red Queen. "When you've once said a thing, that fixes it, and you must take the consequences."
>
> —Lewis Carroll, *Through the Looking Glass*

1. Virus-AIDS Hypothesis Fails to Predict Epidemiology and Pathology of AIDS

At a press conference in April 1984, the American Secretary of Health and Human Services announced that the Acquired Immunodeficiency Syndrome (AIDS) was an infectious disease, caused by a sexually and parenterally transmitted retrovirus, now termed human immunodeficiency virus (HIV). The announcement predicted an antiviral vaccine within two years (Connor, 1987; Adams, 1989; Farber, 1992; Hodgkinson, 1992).

However, the hypothesis has been a complete failure in terms of public health benefits. Despite unprecedented efforts in research and health care, the hypothesis has failed to generate the promised vaccine, and it has failed to develop a cure (Thompson, 1990; Savitz, 1991; Duesberg, 1992b; Waldholz, 1992). The U.S. Government alone spends annually about $1 billion for AIDS research and about $3 billion for AIDS-related health care (National Center for Health Statistics, 1992). The situation has become so desperate that the director for AIDS research at the National Institutes of Health (NIH) promotes via press release, eight years after HIV was declared the cause of AIDS, an as yet unedited paper, which has no more to offer than a renewed effort at causing AIDS in monkeys: "The best possible situation would be to have a human virus [HIV] that infects monkeys" (Steinbrook, 1992). This is said nine years after the NIH first started infecting chimpanzees with HIV—over 150 so far at a cost of $40,000–50,000 apiece—all of which are still healthy (Hilts, 1992; Steinbrook, 1992) (Section 3.3 and Jorg Eichberg, personal communication).

Moreover, the virus-AIDS hypothesis has failed completely to predict the course of the epidemic (Institute of Medicine, 1988; Duesberg, 1989c, 1991a; Duesberg and Ellison, 1990; Thompson, 1990; Savitz, 1991). For example, the NIH and others have predicted that AIDS would "explode" into the general population (Shorter, 1987; Anderson and May, 1992) and the Global AIDS Policy Coalition from Harvard's International AIDS Center declared in June 1992, "The pandemic is dynamic, volatile and unstable.... An explosion of HIV has recently occurred in Southeast Asia, in Thailand ..." (Mann and the Global AIDS Policy Coalition, 1992). But despite widespread alarm the "general population" has been spared from AIDS, although there is a general increase in unwanted pregnancies and conventional venereal diseases (Institute of Medicine, 1988; Aral and Holmes, 1991). Instead, American and European AIDS has spread, during the last 10 years, steadily but almost exclusively among intravenous drug users and male homosexuals who were heavy users of sexual stimulants and had hundreds of sexual partners (Sections 2.1.3, 3.3.4 and 4.3.2).

The hypothesis even fails to predict the AIDS diseases an infected person may develop and whether and when an HIV-infected person is to develop either diarrhea or dementia, Kaposi's sarcoma or pneumonia (Grimshaw, 1987; Albonico, 1991a,b). In addition the hypothesis fails to explain why the annual AIDS risks differ over 100-fold between different HIV-infected risk groups, i.e. recipients of transfusions, babies born to drug-addicted mothers, American/European homosexuals, intravenous drug users, hemophiliacs and Africans (Section 3.4.4).

Clearly a correct medical hypothesis might not produce a cure or the prevention of a disease, as for example theories on cancer or sickle-cell anemia. However, a correct medical hypothesis must be able to (1) identify those at risk for a disease, (2) predict the kind of disease a person infected or affected by its putative cause will get, (3) predict how soon disease will follow its putative cause and (4) lead to a determination of how the putative agent causes the disease. Since this is not true for the virus-AIDS hypothesis, this hypothesis must be fundamentally flawed. Further, it seems particularly odd that an AIDS vaccine cannot be developed, since HIV induces highly effective virus-neutralizing

antibodies within weeks after infection (Clark *et al.,* 1991; Daar *et al.,* 1991). These are the same antibodies that are detected by the widely used "AIDS-test" (Institute of Medicine, 1986; Duesberg, 1989c; Rubinstein, 1990).

In view of this, AIDS is subjected here to a critical analysis aimed at identifying a cause that can correctly predict its epidemiology, pathology and progression.

2. Definition of AIDS

2.1. AIDS: 2 Epidemics, Sub-Epidemics and 25 Epidemic-Specific Diseases

AIDS includes 25 previously known diseases and two clinically and epidemiologically very different AIDS epidemics, one in America and Europe, the other in Africa (Table 1) (Centers for Disease Control, 1987; Institute of Medicine, 1988; World Health Organization, 1992a). The American/European epidemic falls into four sub-epidemics: the male homosexual, the intravenous drug user, the hemophilia and the transfusion recipient epidemics (Table 1).

2.1.1. *The Epidemics by Case Numbers, Gender and Age*

The American/European AIDS epidemics of homosexuals and intravenous drug users are new, starting with drug-using homosexual AIDS patients in Los Angeles and New York in 1981 (Centers for Disease Control, 1981; Gottlieb *et al.,* 1981; Jaffe *et al.,* 1983a). By December 1991, 206,392 AIDS cases had been recorded in the U.S. and 65,979 in Europe (Table 1) (World Health Organization, 1992a; Centers for Disease Control, 1992b). The U.S. has reported about 30,000—40,000 new cases annually since 1987, and Europe reports about 12,000—16,000 cases annually (World Health Organization, 1992a; Centers for Disease Control, 1992b).

Remarkably for a presumably infectious disease, 90% of all American and 86% of all European AIDS patients are males. Nearly all American (98%) and European (96%) AIDS patients are over 20 years old; the remaining 2% and 4%, respectively, are mostly infants (Table 1) (World Health Organization, 1992a; Centers for Disease Control, 1992b).

Table 1. AIDS Statistics*

Epidemics	American	European	African
AIDS total 1985–1991	206,000	66,000	129,000
AIDS annual since 1990	30–40,000	12–16,000	~20,000
HIV carriers since 1985	1 million	500,000	6 million
Annual AIDS per HIV carrier	3–4%	3%	about 0.3%
AIDS by sex	90% male	86% male	50% male
AIDS by age, over 20 years	98%	96%	?
AIDS by risk group			
male homosexual	62%	48%	
intravenous drugs	32%	.33%	
transfusions	2%	3%	
hemophiliacs	1%	3%	
general population	3%	13%	100%
AIDS by Disease:			
Microbial	50% *Pneumocystis* pneumonia 17% candidiasis 11% mycobacterial disease including 3% tuberculosis 5% toxoplasmosis 8% cytomegalovirus 4% herpes virus	75% opportunistic infections	fever diarrhea tuberculosis slim disease
Microbial total	62% (sum > 62% due to overlap)	75%	about 90%
Non-Microbial	19% wasting 10% Kaposi's 6% dementia 3% lymphoma	5% wasting 12% Kaposi's 5% dementia 3% lymphoma	
Non-microbial total	38%	25%	

*Data from references cited in Section 2. There are small (± 1%) discrepancies between some numbers cited here and the most recent surveys cited in the text, because some calculations are based on previous surveys.

There is very little AIDS among teenagers, as only 789 American teenagers have developed AIDS over the last 10 years, including 160 in 1991 and 170 in 1990 (Centers for Disease Control, 1992b).

Since 1985, 129,066 AIDS cases have been recorded in Africa (World Health Organization, 1992b), mainly from the people of Central Africa (Blattner, 1991). Unlike the American and European cases, the African cases are distributed equally between the sexes (Quinn *et al.,* 1986; Blattner *et al.,* 1988; Institute of Medicine, 1988; Piot *et al.,* 1988; Goodgame, 1990) and range "in age from 8 to 85 years" (Widy-Wirski *et al.,* 1988).

An AIDS crisis that was reported to "loom" in Thailand as of 1990 (Anderson, 1990; Smith, 1990) and that was predicted to "explode" now (Mann and the Global AIDS Policy Coalition, 1992) has generated only 123 AIDS patients from 1984 until June 1991 (Weniger *et al.,* 1991).

2.1.2. *AIDS Diseases*

The majority of American (62%) and European (75%) AIDS patients have microbial diseases or opportunistic infections that result from a previously acquired immunodeficiency (World Health Organization, 1992a; Centers for Disease Control, 1992b). In America these include *Pneumocystis* pneumonia (50%), candidiasis (17%) and mycobacterial infections such as tuberculosis (11%), toxoplasmosis (5%), cytomegalovirus (8%) and herpes virus disease (4%) (Table 1) (Centers for Disease Control, 1992b). *Pneumocystis* pneumonia is often described and perceived as an AIDS-specific pneumonia. However, *Pneumocystis carinii* is a ubiquitous fungal parasite that is present in all humans and may become active upon immune deficiency like many others (Freeman, 1979; Pifer, 1984; Williford Pifer *et al.,* 1988; Root-Bernstein, 1990a). Since bacterial opportunists of immune deficiency, like tuberculosis bacillus or pneumococcus, are readily defeated with antibiotics, fungal and viral pneumonias predominate in countries where antibiotics are readily available. This is particularly true for risk groups that use antibiotics chronically as AIDS prophylaxis (Callen, 1990; Bardach, 1992). Indeed, young rats treated for several weeks simultaneously with antibiotics and immunosuppressive cortisone all developed *Pneumocystis* pneumonia spontaneously (Weller, 1955).

Contrary to its name, AIDS of many American (38%) and European (25%) patients does not result from immunodeficiency and microbes (Section 3.5.8). Instead, these patients suffer dementia (6%/5%), wasting disease (19%/5%), Kaposi's sarcoma (10%/12%) and lymphoma (3%/3%) (Table 1) (World Health Organization, 1992a; Centers for Disease Control, 1992b).

The African epidemic includes diseases that have been long established in Africa, such as fever, diarrhea, tuberculosis and "slim disease" (Table 1) (Colebunders *et al.*, 1987; Konotey-Ahulu, 1987; Pallangyo *et al.*, 1987; Berkley *et al.*, 1989; Evans, 1989a; Goodgame, 1990; De Cock *et al.*, 1991; Gilks, 1991). Only about 1% are Kaposi's sarcomas (Widy-Wirski *et al.*, 1988). The African AIDS definition is based primarily on these Africa-specific diseases (Widy-Wirski *et al.*, 1988) "because of limited facilities for diagnosing HIV infection" (De Cock *et al.*, 1991).

2.1.3. *AIDS Risk Groups and Risk-group Specific AIDS Diseases*

Almost all American (97%) and European (87%) AIDS patients come from abnormal health risk groups whose health had been severely compromised prior to the onset of AIDS: 62% of American (47% of European) AIDS patients are male homosexuals who have frequently used oral aphrodisiac drugs (Section 4), 32% (33%) are intravenous drug users, 2% (3%) are critically ill recipients of transfusions and 1% (3%) are hemophiliacs (Institute of Medicine, 1988; Brenner *et al.*, 1990; Centers for Disease Control, 1992b; World Health Organization, 1992a). About 38% of the American teenage AIDS cases are hemophiliacs and recipients of transfusions, 25% are intravenous drug users or sexual partners of intravenous drug users and 25% are male homosexuals (Centers for Disease Control, 1992b). Approximately 70% of the American babies with AIDS are born to drug-addicted mothers ("crack babies") and 13% are born with congenital deficiencies like hemophilia (Centers for Disease Control, 1992b). Only 3% of the American and 13% of the European AIDS patients are from "undetermined exposure categories," i.e. from the general population (Table 1) (World Health Organization, 1992a; Centers for Disease Control, 1992b). Some of the differences between European and American statistics may reflect dif-

ferences in national AIDS standards between different European countries and the U.S. and differences in reporting between the World Health Organization (WHO) and the American Centers for Disease Control (CDC) (World Health Organization, 1992a). By contrast to the American and European AIDS epidemics, African AIDS does not claim its victims from sexual, behavioral or clinical risk groups.

The AIDS epidemics of different risk groups present highly characteristic, country-specific and sub-epidemic-specific AIDS diseases (Table 1 and Table 2):

1. About 90% of the AIDS diseases from Africa are old African diseases that are very different from those of the American/European epidemic (Section 2.1.2, Table 1). The African diseases do not include *Pneumocystis* pneumonia and candidiasis (Goodgame, 1990), although *Pneumocystis* and *Candida* are ubiquitous microbes in all humans including Africans (Freeman, 1979; Pifer, 1984).

2. The American/European epidemic falls into several sub-epidemics based on sub-epidemic-specific diseases:

   a) American homosexuals have Kaposi's sarcoma 20 times more often than all other American AIDS patients (Selik *et al.*, 1987; Beral *et al.*, 1990).

   b) Intravenous drug users have a proclivity for tuberculosis (Sections 4.5 and 4.6).

   c) "Crack" (cocaine) smokers exhibit pneumonia and tuberculosis (Sections 3.4.5 and 4.6).

   d) Ninety-nine percent of all hemophiliacs with AIDS have opportunistic infections, of which about 70% are fungal and viral pneumonias, but less than 1% have Kaposi's sarcoma (Evatt *et al.*, 1984; Centers for Disease Control, 1986; Selik *et al.*, 1987; Koerper, 1989).

   e) Nearly all recipients of transfusions have pneumonia (Curran *et al.*, 1984; Selik *et al.*, 1987).

f) HIV-positive wives of hemophiliacs exhibit only pneumonia and a few other AIDS-defining opportunistic infections (Section 3.4.4.5).

g) American babies exclusively have bacterial diseases (18%) and a high rate of dementia (14%) compared to adults (6%) (Table 1) (Centers for Disease Control, 1992b).

h) Users of the cytotoxic DNA chain terminator AZT, prescribed to inhibit HIV, develop anemia, leukopenia and nausea (Section 4.6.2).

3. The Thai mini-epidemic of 123 is made up of intravenous drug users (20%), heterosexual male and female "sex workers" (50%) and male homosexuals (30%) (Weniger *et al.*, 1991). Among the Thais 24% have tuberculosis, 22% have pneumonia and other opportunistic infections common in Thailand and 10% have had septicemia, which is indicative of intravenous drug consumption (Weniger *et al.*, 1991).

2.2. The HIV-AIDS Hypothesis, or the Definition of AIDS

Based on epidemiological data collected between 1981 and 1983, AIDS researchers from the CDC (Centers for Disease Control, 1986) "found in gay culture—particularly in its perceived "extreme" and "non-normative" aspects (that is "promiscuity" and recreational drugs)—the crucial clue to the cause of the new syndrome" (Oppenheimer, 1992). Accordingly the CDC had initially favored a "lifestyle" hypothesis for AIDS.

However, by 1983 immunodeficiency was also recorded in hemophiliacs, some women and intravenous drug users. Therefore, the CDC adopted the "hepatitis B analogy" (Oppenheimer, 1992) and re-interpreted AIDS as a new viral disease, transmitted sexually and parenterally by blood products and needles shared for the injection of intravenous drugs (Francis *et al.*, 1983; Jaffe *et al.*, 1983b; Centers for Disease Control, 1986; Oppenheimer, 1992). In April 1984 the American Secretary of Health and Human Services and the virus researcher Robert Gallo announced at a press conference that the new AIDS virus was found.

The announcement was made, and a test for antibody against the virus—termed the "AIDS test"—was registered for a patent, before even one American study had been published on this virus (Connor, 1987; Adams, 1989; Crewdson, 1989; Culliton, 1990; Rubinstein, 1990). Since then most medical scientists have believed that AIDS is infectious, spread by the transmission of HIV.

According to the virus-AIDS hypothesis the 25 different AIDS diseases and the very different AIDS epidemics and sub-epidemics are all held together by a single common cause, HIV. There are two strains of HIV that are 50% related, HIV-1 and HIV-2. But as yet only one American-born AIDS patient has been infected by HIV-2 (O'Brien *et al.*, 1992). Since nearly all HIV-positive AIDS cases recorded to date are infected by HIV-1, this strain will be referred to as HIV in this article. The HIV-AIDS hypothesis proposes: (a) that HIV is a sexually, parenterally and perinatally transmitted virus, (b) that it causes immunodeficiency by killing T-cells, but on average only 10 years after infection in adults and two years after infection in infants—a period that is described as the "latent period of HIV" because the virus is assumed to become reactivated in AIDS—and (c) that all AIDS diseases are consequences of this immunodeficiency (Coffin *et al.*, 1986; Institute of Medicine, 1986, 1988; Gallo, 1987; Blattner *et al.*, 1988; Gallo and Montagnier, 1988; Lemp *et al.*, 1990; Weiss and Jaffe, 1990; Blattner, 1991; Goudsmit, 1992).

Because of this belief, 25 previously known, and in part entirely unrelated diseases have been redefined as AIDS, provided they occur in the presence of HIV. HIV is in practice only detectable indirectly via antiviral antibodies, because of its chronic inactivity even in AIDS patients (Section 3.3). These antibodies are identified with disrupted HIV, a procedure that is termed the "AIDS test" (Institute of Medicine, 1986; Rubinstein, 1990). Virus isolation is a very inefficient and expensive procedure, designed to activate dormant virus from leukocytes. It depends on the activation of a single, latent HIV from about 5 million leukocytes from an antibody-positive person. For this purpose the cells must be propagated *in vitro* away from the virus-suppressing immune system of the host. Virus may then be detected weeks later in the culture medium (Weiss *et al.*, 1988; Duesberg, 1989c).

Antibodies against HIV were originally claimed to be present in most (88%) AIDS patients (Sarngadharan *et al.,* 1984), but have since been confirmed in no more than about 50% of the American AIDS patients (Institute of Medicine, 1988; Selik *et al.,* 1990). The rest are presumptively diagnosed based on disease criteria outlined by the CDC (Centers for Disease Control, 1987; Institute of Medicine, 1988). Because of confidentiality laws more tests are probably done than are reported to the CDC.

Since the "AIDS test" became available in 1985, over 20 million tests have been performed annually in the U.S. alone on blood donors, servicemen and applicants to the Army, AIDS patients and many others, and millions more are performed in Europe, Russia, Africa and other countries (Section 3.6). On the basis of such widespread testing, clearly the most comprehensive in the history of virology, about 1 million, or 0.4% of mostly healthy Americans (Curran *et al.,* 1985; Institute of Medicine, 1988; Duesberg, 1991a; Vermund, 1991; Centers for Disease Control, 1992a), 0.5 million, or 0.2% of Western Europeans (Mann *et al.,* 1988; Blattner, 1991; World Health Organization, 1992a), 6 million, or 10% of mostly healthy Central Africans (Curran *et al.,* 1985; Institute of Medicine, 1988; Piot *et al.,* 1988; Goodgame, 1990; Blattner, 1991; Anderson and May, 1992) and 300,000 or 0.5% of healthy Thais (Weniger *et al.,* 1991) are estimated to carry antibodies to HIV (Table 1). According to the CDC the incidence of HIV-2 is "relatively high" in Western Africa with a record of 9% in one community, but "exceedingly low" in the U.S. where not even one infection was detected among 31,630 blood donors (O'Brien *et al.,* 1992).

2.3. Alternative Infectious Theories of AIDS

In view of the heterogeneity of the AIDS diseases and the difficulties in reducing them to a common, active microbe, several investigators have proposed that AIDS is caused by a multiplicity of infectious agents such as viruses and microbes, or combinations of HIV with other microbes (Sonnabend *et al.,* 1983; Konotey-Ahulu, 1987, 1989; Stewart, 1989; Cotton, 1990; Goldsmith, 1990; Lemaitre *et al.,* 1990; Root-Bernstein, 1990a,c; Balter, 1991; Lo *et al.,* 1991).

However, the proponents of infectious AIDS who reject HIV as the

sole cause or see it as one of several causes of AIDS have failed to establish a consistent alternative to or cofactor for HIV. Instead, they typically blame AIDS on viruses and microbes that are widespread and either harmless or not life-threatening to a normal immune system, such as *Pneumocystis,* cytomegalovirus, herpes virus, hepatitis virus, tuberculosis bacillus, *Candida,* mycoplasma, treponema, gonococci, toxoplasma and cryptosporidiae (Section 3.5.7) (Freeman, 1979; Mims and White, 1984; Pifer, 1984; Evans, 1989c; Mills and Masur, 1990; Bardach, 1992). Since such microbes are more commonly active in AIDS patients than in others, they argue that either chronic or repeated infections by such microbes would generate fatal AIDS (Sonnabend *et al.,* 1983; Stewart, 1989; Mills and Masur, 1990; Root-Bernstein, 1990a,c).

Yet all of these microbes also infect people with normal immune systems either chronically or repeatedly without causing AIDS (Freeman, 1979; Mims and White, 1984; Evans, 1989c; Mills and Masur, 1990). It follows that pathogenicity by these microbes in AIDS patients is a consequence of immunodeficiency acquired by other causes (Duesberg, 1990c, 1991a). This is why most of these infections are termed opportunistic.

3. Discrepancies Between AIDS and Infectious Disease

3.1. Criteria of Infectious and Noninfectious Disease

The correct hypothesis explaining the cause of AIDS must predict the fundamental differences between the two main AIDS epidemics and the bewildering heterogeneity of the 25 AIDS diseases. In addition, the cause of American/European AIDS should make clear why—in an era of ever-improving health parameters, population growth and decreasing mortality (The Software Toolworks World Atlas™, 1992; Anderson and May, 1992)—suddenly a subgroup of mostly 20- to 45-year-old males would die from diverse microbial and nonmicrobial diseases. The mortality from all infectious diseases combined has been reduced to less than 1% in the Western World (Cairns, 1978) through advanced sanitation and nutrition (Section 6) (McKeown, 1979; Moberg and Cohn, 1991; Oppenheimer, 1992). Further, 20- to 45-year-olds are the

least likely to die from any disease (Mims and White, 1984). Their relative immunity to all diseases is why they are recruited as soldiers. The correct AIDS hypothesis would also have to explain why only a small group of about 20,000 Africans have developed AIDS diseases annually since 1985 (Table 1), during a time in which Central Africa enjoyed the fastest population growth in the world, i.e. 3% (The Software Toolworks World Atlas™, 1992).

The sudden appearance of AIDS could signal a new microbe, i.e. infectious AIDS. Yet the suddenness of AIDS could just as well signal one or several new toxins, such as the many new psychoactive drugs that have become popular in America and Europe since the Vietnam War (Section 4).

Based on common characteristics of all orthodox infectious diseases, infectious AIDS would be predicted to:

(1) Spread randomly between the sexes. This is just as true for venereal as for other infectious diseases (Judson *et al.,* 1980; Haverkos, 1990).

(2) Cause primary disease within weeks or months after infection, because infectious agents multiply exponentially in susceptible hosts until stopped by immunity. They are self-replicating, and thus fast acting toxins. (Although "slow" viruses are thought to be pathogenic long after neutralization by antiviral immunity (Evans, 1989c), slow pathogenicity by a neutralized virus has never been experimentally proven (Section 6.1).)

(3) Coincide with a common, active and abundant microbe in all cases of the same disease. (Inactive microbes or microbes at low concentrations are harmless passengers, e.g. lysogenic bacteriophages, endogenous and latent retroviruses (Weiss *et al.,* 1985), latent herpes virus or latent ubiquitous *Pneumocystis* and *Candida* infections (Freeman, 1979; Pifer, 1984; Williford Pifer *et al.,* 1988). Hibernation is a proven microbial strategy of survival, which allows indefinite coexistence with the host without pathogenicity.)

(4) Coincides with a microbe that lyses or renders nonfunctional more cells than the host can spare or regenerate.

(5) Generate a predictable pattern of symptoms.

By contrast non-infectious AIDS, caused by toxins, would be predicted to:

(1) Spread nonrandomly, according to exposure to toxins. For example, lung cancer and emphysema were observed much more frequently in men than in women 20 years ago, because men consumed much more tobacco than women 30–40 years ago (Cairns, 1978).

(2) Follow intoxication after variable intervals as determined by lifetime dosage and personal thresholds for disease. These intervals would be considerably longer than those between microbes and disease, because microbes are self-replicating toxins. For example, lung cancer and emphysema are "acquired" only after 10–20 years of smoking, and liver cirrhosis is "acquired" only after 10–20 years of alcoholism.

(3) Manifest toxin-specific and intoxication site-specific diseases, e.g. cigarettes causing lung cancer and alcohol causing liver cirrhosis.

3.2. AIDS Not Compatible with Infectious Disease

All direct parameters of AIDS are incompatible with classical criteria of infectious disease:

(1) Unlike conventional infectious diseases, including venereal diseases (Judson *et al.,* 1980), American/European AIDS is nonrandomly (90%) restricted to males, although no AIDS disease is male-specific (Table 1).

(2) The long and unpredictable intervals between infection and "acquiring" primary AIDS symptoms—averaging two years in infants and 10 years in adults, and termed "latent periods of HIV"—stand in sharp contrast to the short intervals of days or weeks between infection and primary disease observed with all classical viruses, including retroviruses (Duesberg, 1987; Duesberg and Schwartz, 1992). These short intervals reflect the time periods, that all exponentially growing microbes with generation times of half-hours, and viruses including HIV (Clark *et al.,* 1991; Daar *et al.,* 1991) with generation times of 8–48 hr need to reach immunogenic and thus potentially pathogenic concentrations (Fenner *et al.,* 1974; Freeman, 1979; Mims and White, 1984). Once stopped by immunity, conventional viruses and microbes are no longer

pathogenic. Thus long latent periods between immunity against a microbe and a given disease are incompatible with conventional microbial causes, including HIV (Section 3.5.14). The discrepancy of eight years between the hypothetical "latent periods of HIV" in infants and adults presents a secondary paradox.

Nevertheless, HIV could possibly play a role in AIDS if it were consistently reactivated by an "acquired immunodeficiency"—10 years after it was neutralized by antibodies (Section 3.4.2)—just as *Candida, Pneumocystis* and cytomegalovirus play roles in AIDS if they are activated by "acquired immunodeficiency." However, HIV is nearly always inactive even during acquired immunodeficiency (Sections 3.3.1 and 3.5.6). In the absence of HIV reactivation during AIDS, long hypothetical latent periods are simply statistical artifacts. They are conceived to link HIV with AIDS and to buy time for the real causes of AIDS to generate AIDS-defining diseases.

(3) There is no active microbe common to all AIDS patients, and no common group of target cells are lysed or rendered nonfunctional (Sections 3.3 and 3.5.10).

(4) There is no common, predictable pattern of AIDS symptoms in patients of different risk groups. Instead, different risk groups have characteristic AIDS diseases (Sections 2.1.3, 3.4.4 and 3.4.5).

Thus AIDS does not meet even one of the classical criteria of infectious disease. In a recent response to these arguments, Goudsmit, a proponent of the HIV-AIDS hypothesis, confirmed that "AIDS does not have the characteristics of an ordinary infectious disease. This view is incontrovertible" (Goudsmit, 1992). Likewise, the epidemiologists Eggers and Weyer conclude that "the spread of AIDS does not behave like the spread of a disease that is caused by a single sexually transmitted agent" (Eggers and Weyer, 1991) and hence have "simulated a cofactor [that] cannot be identified with any known infectious agent" (Weyer and Eggers, 1990). Anderson and May (1992) had to invent "assortative scenarios" for different AIDS risk groups to reconcile AIDS with infectious disease. Indeed, AIDS would never have been accepted as infectious without the numerous unique assumptions that have been made to accommodate HIV as its cause (Sections 3.5 and 6.1).

3.3. No Proof for the Virus-AIDS Hypothesis

Despite research efforts that exceed those on all other viruses combined and have generated over 60,000 papers on HIV (Christensen, 1991), it has not been possible to prove that HIV causes AIDS. These staggering statistics illustrate that the virus-AIDS hypothesis is either not provable or is very difficult to prove.

Proof for pathogenicity of a virus depends either on (1) meeting Koch's classical postulates, (2) preventing pathogenicity through vaccination, (3) curing disease with antiviral drugs or (4) preventing disease by preventing infection. However, the HIV-hypothesis fails all of these criteria.

3.3.1. *Virus Hypothesis Fails to Meet Koch's Postulates*

Koch's postulates may be summarized as follows: (i) the agent occurs in each case of a disease and in amounts sufficient to cause pathological effects; (ii) the agent is not found in other diseases; and (iii) after isolation and propagation in culture, the agent can induce the disease anew (Merriam-Webster, 1965; Weiss and Jaffe, 1990).

But:

(i) HIV is certainly not present in all AIDS patients, and even antibody against HIV is not found in all patients who have AIDS-defining diseases. HIV is not even present in all persons who die from multiple indicator-diseases plus general immune system failure—the paradigm AIDS cases (Sections 3.4 and 4.5). In addition, HIV is never present "in amounts sufficient to cause pathological effects" based on the following evidence:

(1) On average only 1 in 500 to 3000 T-cells, or 1 in 1500 to 8000 leukocytes of AIDS patients are infected by HIV (Schnittman *et al.*, 1989; Simmonds *et al.*, 1990). (About 35% of leukocytes are T-cells (Walton *et al.*, 1986).) A recent study, relying on in situ amplification of a proviral HIV DNA fragment with the polymerase chain reaction, detects HIV DNA in 1 of 10 to 1 of 1000 leukocytes of AIDS patients. However, the authors acknowledge that the *in situ* method cannot distinguish between intact and defective proviruses and may include false-

positives, because it does not characterize the amplified DNA products (Bagasra *et al.,* 1992). Indeed the presence of 1 provirus per 10 or even 100 cells is exceptional in AIDS patients. This is why direct hybridization with viral DNA, a technique that is capable of seeing 1 provirus per 10 to 100 cells, typically fails to detect HIV DNA in AIDS patients (Duesberg, 1989c). According to one study, "The most striking feature ... is the extremely low level of HIV provirus present in circulating PBMCs (peripheral blood mononuclear cells) in most cases" (Simmonds *et al.,* 1990).

Since on average only 0.1% (1 out of 500 to 3000) of T-cells are ever infected by HIV in AIDS patients, but at least 3% of all T-cells are regenerated (Sprent, 1977; Guyton, 1987) during the two days it takes a retrovirus to infect a cell (Duesberg, 1989c), HIV could never kill enough T-cells to cause immunodeficiency. Thus even if HIV killed every infected T-cell (Section 3.5.10), it could deplete T-cells only at 1/30 of their normal rate of regeneration, let alone activated regeneration. The odds of HIV causing T-cell deficiency would be the same as those of a bicycle rider trying to catch up with a jet airplane.

(2) It is also inconsistent with a common pathogenic mechanism that the fraction of HIV-infected leukocytes in patients with the same AIDS diseases varies 30- to 100-fold. One study reports that the fraction of infected cells ranges from 1 in 900 to 1 in 30,000 (Simmonds *et al.*, 1990), and another reports that it ranges from 1 in 10 to 1 in 1000 (Bagasra *et al.,* 1992). In all conventional viral diseases the degree of pathogenicity is directly proportional to the number of infected cells.

(3) It is entirely inconsistent with HIV-mediated pathogenicity that there are over 40-times more HIV-infected leukocytes in many healthy HIV carriers than in AIDS patients with fatal AIDS (Simmonds *et al.,* 1990; Bagasra *et al.,* 1992). Simmonds *et al.* report that there are from 1 in 700 to 1 in 83,000 HIV-infected leukocytes in healthy HIV carriers and from 1 in 900 to 1 in 30,000 in AIDS patients. Bagasra *et al.* report that there are from 1 in 30 to 1 in 1000 infected leukocytes in healthy carriers and from 1 in 10 to 1 in 1000 in patients with fatal AIDS. Thus there are healthy persons with 43 times (30,000:700) and 33 times (1000:30) more HIV-infected cells than in AIDS patients.

(4) In terms of HIV's biological function, it is even more important

that the levels of HIV RNA synthesis in AIDS are either extremely low or even nonexistent. Only 1 in 10,000 to 100,000 leukocytes express viral RNA in 50% of AIDS patients. In the remaining 50% no HIV expression is detectable (Duesberg, 1989c; Simmonds *et al.*, 1990). The very fact that amplification by the polymerase chain reaction must be used to detect HIV DNA or RNA (Semple *et al.*, 1991) in AIDS patients indicates that not enough viral RNA can be made or is made in AIDS patients to explain any, much less fatal, pathogenicity based on conventional precedents (Duesberg and Schwartz, 1992). The amplification method is designed to detect a needle in a haystack, but a needle in a haystack is not sufficient to cause a fatal disease, even if it consists of plutonium or cyanide.

(5) In several AIDS diseases, that are not caused by immunodeficiency (Section 3.5.8), HIV is not even present in the diseased tissues, e.g. there is no trace of HIV in any Kaposi's sarcomas (Salahuddin *et al.*, 1988) and there is no HIV in neurons of patients with dementia, because of the generic inability of retroviruses to infect nondividing cells like neurons (Sections 3.5.8 and 3.5.10) (Duesberg, 1989c).

As a result, there is typically no free HIV in AIDS patients (Section 3.5.6). Indeed, the scarcity of infectious HIV in typical AIDS patients is the reason that neutralizing antibodies, rather than virus, have become the diagnostic basis of AIDS. It is also the reason that on average 5 million leukocytes of HIV-positives must be cultured to activate ("isolate") HIV from AIDS patients. Even under these conditions it may take up to 15 different isolation efforts (!) to get just one infectious virus out of an HIV carrier (Weiss *et al.*, 1988). The scarcity of HIV and HIV-infected cells in AIDS patients is also the very reason for the notorious difficulties experienced by leading American (Hamilton, 1991; Palca, 1991a; Crewdson, 1992) and British (Connor, 1991, 1992; Weiss, 1991) AIDS researchers in isolating, and in attributing credit for isolating HIV from AIDS patients.

(ii) HIV does not meet Koch's second postulate, because it is found not just in one, but in 25 distinct diseases, many as unrelated to each other as dementia and diarrhea, or Kaposi's sarcoma and pneumonia (Table 1, Section 2.1.2).

(iii) HIV also fails Koch's third postulate, because it fails to cause AIDS when experimentally inoculated into chimpanzees which make antibodies against HIV just like their human cousins (Blattner *et al.*, 1988; Institute of Medicine, 1988; Evans, 1989b; Weiss and Jaffe, 1990). Up to 150 chimpanzees have been inoculated since 1983 and all are still healthy (Duesberg, 1989c) (Jorg Eichberg, personal communication, see Section 1). HIV also fails to cause AIDS when accidentally introduced into humans (Duesberg, 1989c, 1991a).

There is, however, a legitimate limitation of Koch's postulates, namely that most microbial pathogens are only conditionally pathogenic (Stewart, 1968; McKeown, 1979; Moberg and Cohn, 1991). They are pathogenic only if the immune system is low, allowing infection or intoxication of the large numbers of cells that must be killed or altered for pathogenicity. This is true for tuberculosis bacillus, cholera, influenza virus, polio virus and many others (Freeman, 1979; Mims and White, 1984; Evans, 1989c).

However, even with such limitations HIV fails the third postulate. The scientific literature has yet to prove that even one health care worker has contracted AIDS from the over 206,000 American AIDS patients during the last 10 years, and that even one of thousands of scientists has developed AIDS from HIV, which they propagate in their laboratories and companies (Section 3.5.16) (Duesberg, 1989c, 1991a). AIDS is likewise not contagious to family members living with AIDS patients for at least 100 days in the same household (Friedland *et al.*, 1986; Sande, 1986; Hearst and Hulley, 1988; Peterman *et al.*, 1988). However the CDC has recently claimed that seven health care workers have developed AIDS from occupational infection (Centers for Disease Control, 1992c). But the CDC has failed to provide any evidence against nonoccupational causation, such as drug addiction (see Section 4). Indeed thousands of health care workers, e.g. 2586 by 1988 (Centers for Disease Control, 1988), have developed AIDS from nonprofessional causes. In addition the CDC has failed to report the AIDS diseases of the seven patients and those of their putative donors, has failed to report their sex (see next paragraph) and whether these patients developed AIDS only after AZT treatment (see Section 4) (Centers for Disease Control, 1992c).

The failure of HIV to meet the third postulate is all the more definitive since there is no antiviral drug or vaccine. Imagine what would happen if there were 206,000 polio or viral hepatitis patients in our hospitals and no health care workers were vaccinated!

Contrary to expectations that health care workers would be the first to be affected by infectious AIDS, the AIDS risk of those health care workers that have treated the 206,000 American AIDS patients is in fact lower than that of the general population, based on the following data. The CDC reports that about 75% of the American health care workers are females, but that 92% of the AIDS patients among health care workers are males (Centers for Disease Control, 1988). Thus the AIDS risk of male health care workers is 35 times higher than that of females, indicating nonprofessional AIDS causes.

Moreover, the CDC reports that the incidence of AIDS among health care workers is percentagewise the same as that in the general population, i.e. by 1988, 2586 out of 5 million health care workers, or 1/2000 had developed AIDS (Centers for Disease Control, 1988), by the same time 110,000 out of the 250 million Americans, or 1/2250, had developed AIDS (Centers for Disease Control, 1992b). Since health care workers are nearly all over 20 years old and since there is virtually no AIDS in those under 20 (Table 1), but those under 20 make up about 1/3 of the general population, it can be estimated that the AIDS risk of health care workers is actually 1/3 lower (1/3 times 1/2000) than that of the general population—hardly an argument for infectious AIDS.

In view of this, leading AIDS researchers have acknowledged that HIV fails Koch's postulates as the cause of AIDS (Blattner *et al.,* 1988; Evans, 1989a,b; Weiss and Jaffe, 1990; Gallo, 1991). Nevertheless, they have argued that the failure of HIV to meet Koch's postulates invalidates these postulates rather than HIV as the cause of AIDS (Section 6.1) (Evans, 1989b, 1992; Weiss and Jaffe, 1990; Gallo, 1991). But the failure of a suspected pathogen to meet Koch's postulates neither invalidates the timeless logic of Koch's postulates nor any claim that a suspect causes a disease (Duesberg, 1989b). It only means that the suspected pathogen cannot be proven responsible for a disease by Koch's postulates—but perhaps by new laws of causation (Section 6).

3.3.2. *Anti-HIV Immunity Does Not Protect Against AIDS*

Natural antiviral antibodies, or vaccination, against HIV—which completely neutralize HIV to virtually undetectable levels—are consistently diagnosed in AIDS patients with the "AIDS test." Yet these antibodies consistently fail to protect against AIDS diseases (Section 3.5.11) (Duesberg, 1989b,c, 1991a; Evans, 1989a,b). According to Evans, "The dilemma in HIV is that antibody is not protective" (Evans, 1989a).

By contrast, all other viral diseases are prevented or cured by antiviral immunity. Indeed, since Jennerian vaccination in the late 18th century, antiviral immunity has been the only protection against viral disease. In view of this HIV researchers have argued that antibodies do not neutralize this virus (Section 3.5.11) instead of considering that HIV may not be the cause of AIDS.

3.3.3. *Antiviral Drugs Do Not Protect Against AIDS*

All anti-HIV drugs fail to prevent or cure AIDS diseases (Section 4).

3.3.4. *All AIDS-defining Diseases Occur in the Absence of HIV*

The absence of HIV does not prevent AIDS-defining diseases from occurring in all AIDS risk groups, it only prevents their diagnosis as AIDS (Sections 3.4.4, 4.5 and 4.7).

Thus, there is no proof for the virus-AIDS hypothesis—not even that AIDS is contagious. Instead, the virus-AIDS hypothesis is based only on circumstantial evidence, including epidemiological correlations and anecdotal cases (Sections 3.4 and 3.5).

3.4. Noncorrelations Between HIV and AIDS

Leading AIDS researchers acknowledge that correlations are the only support for the virus-AIDS hypothesis. For example, Blattner *et al.* state, "... overwhelming seroepidemiologic evidence (is) pointing toward HIV as the cause of AIDS ... Better methods ... show that HIV infection is present in essentially all AIDS patients" (Blattner *et al.,* 1988). According to an editorial in *Science,* Baltimore deduces from studies reporting an 88% correlation between antibodies to HIV and AIDS: "This was the kind of evidence we are looking for. It distinguishes between a virus that was a passenger and one that was the cause"

(Booth, 1988). The studies Baltimore relied on are those published by Gallo *et al.* in *Science* in 1984 that are the basis for the virus-AIDS hypothesis (Gallo *et al.,* 1984; Sarngadharan *et al.,* 1984), but their authenticity has since been questioned on several counts (Beardsley, 1986; Schupach, 1986; Connor, 1987; Crewdson, 1989; Hamilton, 1991; Palca, 1991a; Crewdson, 1992). Weiss and Jaffe concur that "the evidence that HIV causes AIDS is epidemiological . . ." (Weiss and Jaffe, 1990), although Gallo concedes that epidemiology is just "one hell of a good beginning" (Gallo, 1991). In view of correlations it is argued that "persons infected with HIV will develop AIDS and those not so infected will not" (Evans, 1989a), or that "HIV . . . is the *sine qua non* for the epidemic" (Gallo, 1991).

But correlations are only circumstantial evidence for a hypothesis. According to Sherlock Holmes, "Circumstantial evidence is a very tricky thing. It may seem to point very straight to one thing, but if you shift your point of view a little, you may find it pointing in an equally uncompromising manner to something entirely different" (Doyle, 1928). The risk in epidemiological studies is that the cause may be difficult to distinguish from noncausal associations. For example, yellow fingers are noncausally and smoking is causally associated with lung cancer. "In epidemiological parlance, the issue at stake is that of confounding" (Smith and Phillips, 1992). This is true for the "overwhelming sero-epidemiologic evidence" claimed to support the virus-AIDS hypothesis on the following grounds.

3.4.1. *Only about Half of American AIDS is Confirmed HIV-antibody-positive*

In the U.S. antibodies against HIV are only confirmed in about 50% of all AIDS diagnoses; the remainder are presumptively diagnosed (Institute of Medicine, 1988; Selik *et al.,* 1990). Several studies indicate that the natural coincidence between antibodies against HIV and AIDS diseases is not perfect, because all AIDS defining diseases occur in all AIDS risk groups in the absence of HIV (Section 4). Ironically, the CDC never records the incidence of HIV in its *HIV/AIDS Surveillance Reports* (Centers for Disease Control, 1992b).

It follows that the reportedly perfect correlation between HIV and

AIDS is in reality an artifact of the definition of AIDS and of allowances for presumptive diagnoses (Centers for Disease Control, 1987; Institute of Medicine, 1988). Since AIDS has been defined exclusively as diseases occurring in the presence of antibody to HIV (Section 2.2), the diagnosis of AIDS is biased by its definition toward a 100% correlation with HIV. That is why "persons infected by HIV will develop AIDS and ... those not so infected will not" (Evans, 1989a), and why HIV is the *"sine qua non"* of AIDS (Gallo, 1991).

3.4.2. *Antibody-positive, but Virus-negative AIDS*

The correlations between AIDS and HIV are in fact not correlations with HIV, but with antibodies against HIV (Sarngadharan *et al.,* 1984; Blattner *et al.,* 1988; Duesberg, 1989c). But antibodies signal immunity against viruses, signal neutralization of viruses, and thus protection against viral disease—not a prognosis for a future disease as is claimed for antibodies against HIV. For example, antibody-positive against polio virus and measles virus means virus-negative, and thus protection against the corresponding viral diseases. The same is true for antibodies against HIV: antibody-positive means very much virus-negative. Residual virus or viral molecules are almost undetectable in most antibody-positive persons (Sections 3.3 and 3.5.6). Thus antibodies against HIV are not evidence for a future or current HIV disease unless additional assumptions are made (Section 3.5.11).

3.4.3. *HIV: Just One of Many Harmless Microbial Markers of Behavioral and Clinical AIDS Risks*

In addition to antibodies against HIV, there are antibodies against many other passenger viruses and microbes in AIDS risk groups and AIDS patients (Sections 2.3 and 4.3.2). These include cytomegalovirus, hepatitis virus, Epstein-Barr virus, Human T-cell Leukemia Virus-I (HTLV-I), herpes virus, gonorrhea, syphilis, mycoplasma, amoebae, tuberculosis, toxoplasma and many others (Gallo *et al.,* 1983; Sonnabend *et al.,* 1983; Blattner *et al.,* 1985; Mathur-Wagh *et al.,* 1985; Darrow *et al.,* 1987; Quinn *et al.,* 1987; Messiah *et al.,* 1988; Stewart, 1989; Goldsmith, 1990; Mills and Masur, 1990; Root-Bernstein, 1990a,c; Duesberg, 1991a; Buimovici-Klein *et al.,* 1988). In addition, there are between 100 and

150 chronically latent retroviruses in the human germ line (Martin *et al.,* 1981; Nakamura *et al.,* 1991). These human retroviruses are in every cell, not just in a few like HIV, and have the same genetic structure and complexity as HIV and all other retroviruses (Duesberg, 1989c). According to Quinn *et al.,* "Common to African patients with AIDS and outpatient controls and American patients with AIDS and homosexual men was the finding of extremely high prevalence rates of antibody to CMV (range, 92–100%), HSV (range, 90–100%), hepatitis B virus (range, 78–82%), hepatitis A virus (range, 82–95%), EBV capsid antigen (100%), syphilis (11–23%), and *T. gondii* (51–74%). In contrast, the prevalence of antibody to each of these infectious agents was significantly lower among the 100 American heterosexual men ..." (Quinn *et al.,* 1987). Thus, the incidence of many human parasites, both rare and common, is high in typical AIDS patients and in typical AIDS risk groups (Sections 2.3 and 5). However, none of these microbes are fatal and nearly all are harmless to a normal immune system (Section 2.3).

Most of these parasites, including HIV, have been accumulated by AIDS risk behavior and by clinical AIDS risks (Blattner *et al.,* 1985; Institute of Medicine, 1988; Stewart, 1989). Such behavior includes the long-term injection of unsterile, recreational "street" drugs and large numbers of sexual contacts promoted by oral and injected aphrodisiac drugs (Section 4) (Dismukes *et al.,* 1968; Darrow *et al.,* 1987; Des Jarlais *et al.,* 1987; Espinoza *et al.,* 1987; Moss, 1987; Moss *et al.,* 1987; van Griensven *et al.,* 1987; Des Jarlais *et al.,* 1988; Messiah *et al.,* 1988; Chaisson *et al.,* 1989; Weiss, S.H., 1989; Deininger *et al.,* 1990; McKegney *et al.,* 1990; Stark *et al.,* 1990; Luca-Moretti, 1992; Seage *et al.,* 1992). Clinical risk groups, such as hemophiliacs, accumulate such viruses and microbes from occasionally contaminated transfusions (Section 3.4.4).

It follows that a high correlation between AIDS and antibodies against one particular virus, such as HIV, does not "distinguish between a virus that was a passenger and one that was a cause" (Baltimore, see above) (Booth, 1988). It is an expected consequence or marker of behavioral and clinical AIDS risks, particularly in countries where the percentage of HIV carriers is low (Duesberg, 1991a). In addition to HIV, many other microbes and viruses which are rare and inactive, or just inactive, in the general population, such as hepatitis virus, are "spe-

cific" for AIDS patients, and thus markers for AIDS risks (Sections 2.2, 2.3 and 4.3.2). For example, 100% of AIDS patients within certain cohorts, not just 50% as with HIV (Section 2.2), were shown to have antibodies against, or acute infections of, cytomegalovirus (Gottlieb *et al.*, 1981; Francis, 1983; van Griensven *et al.*, 1987; Buimovici-Klein *et al.*, 1988). A comparison of 481 HIV-positive with 1499 HIV-negative homosexual men in Berlin found that the HIV-positives were "significantly more often carriers of antibodies against hepatitis A virus, hepatitis B virus, cytomegalovirus, Epstein-Barr virus and syphilis" (Deininger *et al.*, 1990). And the frequent occurrence of antibodies against hepatitis B virus in cohorts of homosexual AIDS patients, termed "hepatitis cohorts," was a precedent, that helped to convince the CDC to drop the "lifestyle" hypothesis of AIDS in favor of the "hepatitis analogy" (Francis *et al.*, 1983; Centers for Disease Control, 1986; Oppenheimer, 1992) (Section 2.2).

The higher the consumption of unsterile, injected drugs, the more sexual contacts mediated by aphrodisiac drugs and the more transfusions received, the more accidentally contaminating microbes will be accumulated (Sections 3.4.4.5, 4.3.2 and 4.5). In Africa antibodies against HIV and hepatitis virus are poor markers for AIDS risks, because millions carry antibodies against these viruses (Table 1) (Quinn *et al.*, 1987; Evans, 1989c; Blattner, 1991). Thus it is arbitrary to consider HIV the AIDS "driver" rather than just one of the many innocent microbial passengers of AIDS patients (Francis, 1983), because it is neither distinguished by its unique presence nor by its unique biochemical activity.

3.4.4. *Annual AIDS Risks of Different HIV-infected Risk Groups, Including Babies, Homosexuals, Drug Addicts, Hemophiliacs and Africans, Differ over 100-fold*

If HIV were the cause of AIDS the annual AIDS risks of all infected persons should be similar, particularly if they are from the same country. Failure of HIV to meet this prediction would indicate that HIV is not a sufficient cause of AIDS. The occurrence of the same AIDS-defining diseases in HIV-free controls would indicate that HIV is not even necessary for AIDS.

3.4.4.1. *Critically ill recipients of transfusions.* The annual AIDS risk of HIV-infected American recipients of transfusions (other than hemophiliacs) is about 50%, as half of all recipients die within one year after receiving a transfusion (Table 2) (Ward *et al.,* 1989).

Table 2. Annual AIDS Risks of HIV-infected Groups*

HIV-infected group	Annual AIDS in percent	Group-specific diseases
American recipients of transfusions	50	pneumonia, opportunistic infections
American babies	25	dementia, bacterial
Male homosexuals using sexual stimulants	4–6	Kaposi's sarcoma
Intravenous drug users	4–6	tuberculosis, wasting
American hemophiliacs	2	pneumonia, opportunistic infections
German hemophiliacs	1	pneumonia, opportunistic infections
American teenagers	0.16–1.7	hemophilia-related
American general population	0. 1–1	opportunistic infections
Africans	0.3	fever, diarrhea, tuberculosis
Thais	0.05	tuberculosis

*Based on controlled studies, it is proposed that the health risks of all HIV-infected AIDS risk groups are the same as those of matched HIV-free controls (Sections 3.4.4, 4 and 5). The virus hypothesis simply claims the specific morbidity of each of these groups for HIV.

Since the AIDS risk of transfusion recipients is much higher than the national 3–4% average, nonviral factors must play a role (Table 1). Indeed, about 50% of American recipients of transfusions without HIV also die within 1 year after receiving a transfusion (Hardy *et al.,* 1985; Ward *et al.,* 1989), and over 60% within 3 years (Bove *et al.,* 1987). Moreover, the AIDS risk of transfusion recipients increases 3–6 times faster with the

volume of blood received than their risk of infection by HIV (Hardy *et al.,* 1985; Ward *et al.,* 1989). This indicates that the illnesses that necessitated the transfusions are responsible for the mortality of the transfusion recipients. Yet the virus hypothesis claims the relatively high mortality of American transfusion patients for HIV without considering HIV-free controls. The hypothesis also fails to consider that the effects of HIV on transfusion mortality should be practically undetectable in the face of the high mortality of transfusion recipients and its postulate that HIV causes AIDS on average only 10 years after infection.

3.4.4.2. *HIV-infected babies.* The second highest annual AIDS risk is reported for perinatally infected American babies, whose health has been compromised by maternal drug addiction or by congenital diseases like hemophilia (Section 2.1.3). They develop AIDS diseases on average two years after birth (Anderson and May, 1988; Blattner *et al.,* 1988; Institute of Medicine, 1988; Blattner, 1991). This corresponds to an annual AIDS risk of 25% (Table 2).

Since the AIDS risk of babies is much higher than the national average of 3–4% (Table 1), nonviral factors must play a role in pediatric AIDS. Based on correlations and controlled studies documenting AIDS-defining diseases in HIV-free babies, it is proposed below that maternal drug consumption (Section 4) and congenital diseases, like hemophilia (Section 3.4.4.5), are the causes of pediatric AIDS. Indeed, before AIDS surfaced, many studies had shown that maternal drug addiction was sufficient to cause AIDS-defining diseases in newborns (Section 4.6.1). In accord with this proposal it is shown that HIV is naturally a perinatally transmitted retrovirus—and thus harmless (Section 3.5.2).

3.4.4.3. *HIV-positive homosexuals.* The annual AIDS risk of HIV-infected male homosexuals with hundreds of sex partners, who frequently use aphrodisiac drugs (Section 4), was originally estimated at about 6% (Mathur-Wagh *et al.,* 1985; Anderson and May, 1988; Institute of Medicine, 1988; Lui *et al.,* 1988; Moss *et al.,* 1988; Turner *et al.,* 1989; Lemp *et al.,* 1990; van Griensven *et al.,* 1990; Blattner, 1991). As more HIV-positives became identified, lower estimates of about 4% were reported

(Table 2) (Rezza *et al.*, 1990; Biggar and the International Registry of Seroconverters, 1990; Munoz *et al.*, 1992).

Since the annual AIDS risk of such homosexual men is higher than the national average, group-specific factors must be necessary for their specific AIDS diseases. Based on correlations with drug consumption and studies of HIV-free homosexuals, it is proposed here that the cumulative consumption of sexual stimulants and psychoactive drugs determines the annual AIDS risk of homosexuals (Sections 4.4 and 4.5). Indeed, all AIDS-defining diseases were observed in male homosexuals from behavioral risk groups before HIV was discovered and have since been observed in HIV-free homosexuals from AIDS risk groups (Sections 4.5 and 4.7).

In the spirit of the virus-AIDS hypothesis, many of these HIV-free homosexual AIDS cases have been blamed on various retrovirus-like particles, papilloma viruses, other viruses and microbes by researchers who have not investigated drug use, particularly not oral drug use. These cases include 153 immunodeficient HIV-free homosexuals with T4/T8-cell ratios below 1 (Drew *et al.*, 1985; Weber *et al.*, 1986; Novick *et al.*, 1986; Collier *et al.*, 1987; Bartholomew *et al.*, 1987; Buimovici-Klein *et al.*, 1988) and 23 HIV-free Kaposi's sarcomas (Afrasiabi *et al.*, 1986; Ho *et al.*, 1989b; Bowden *et al.*, 1991; Safai *et al.*, 1991; Castro *et al.*, 1992; Huang *et al.*, 1992) (see also Note added in proof).

3.4.4.4. *HIV-positive intravenous drug users.* Application of the annual AIDS risk of male homosexual risk groups led to valid predictions for the annual AIDS risk of intravenous drug users (Lemp *et al.*, 1990). Therefore the annual AIDS risk of HIV-infected intravenous drug users was originally estimated to be 6% (Table 2) (Lemp *et al.*, 1990; Blattner, 1991; Goudsmit, 1992). More recent studies have concluded that the annual AIDS risk of intravenous drug users is about 4% (Table 2) (Rezza *et al.*, 1990; Munoz *et al.*, 1992).

These findings argue against a sexually transmitted cause, because sexual transmission predicts a much higher AIDS risk for homosexuals with hundreds of sexual partners than for intravenous drug users (Section 4) (Weyer and Eggers, 1990; Eggers and Weyer, 1991). Indeed, numerous controlled studies have indicated that the morbidity and mor-

tality of intravenous drug users is independent of HIV (Sections 4.4, 4.5 and 4.7). On the basis of such studies it is proposed that the lifetime dose of drug consumption determines the annual AIDS risk of intravenous drug users (Section 4).

3.4.4.5. *HIV-positive hemophiliacs.* The hemophiliacs provide the most accessible group to test the virus hypothesis, because the time of infection can be estimated and because the role of other health risks can be controlled by studying HIV-free hemophiliacs.

About 15,000, or 75% of the 20,000 American hemophiliacs have HIV from transfusions received before the "AIDS test" was developed in 1984 (Tsoukas *et al.,* 1984; Hardy *et al.,* 1985; Institute of Medicine, 1986, 1988; Stehr-Green *et al.*, 1988; Goedert *et al.,* 1989; Koerper, 1989). Based on limited data and antibodies against selected viral antigens, it is generally estimated that most of these infections occurred between 1978 and 1984 (Evatt *et al.,* 1985; Johnson *et al.,* 1985; McGrady *et al.,* 1987; Goedert *et al.,* 1989). This high rate of infection reflects the practice, developed in the 1960s and 1970s, of preparing factor VIII from blood pools collected from large numbers of donors (Johnson *et al.,* 1985; Aronson, 1988; Koerper, 1989). Since only about 300 of the 15,000 HIV-infected American hemophiliacs have developed AIDS annually over the last 5 years (Morgan *et al.,* 1990; Centers for Disease Control, 1992a,b), the annual AIDS risk of HIV-infected American hemophiliacs is about 2% (Table 2). Data from Germany extend these results: about 50% of the 6000 German hemophiliacs are HIV-positive (Koerper, 1989), and only 37 (1%) of these developed AIDS-defining diseases during 1991 and 303 (1% annually) from 1982 until 1991 (Bundesgesundheitsamt (Germany), 1991; Leonhard, 1992). An international study estimated the annual AIDS risk of adult hemophiliacs at 3% and that of children at 1% over a 5-year period of HIV-infection (Biggar and the International Registry of Seroconverters, 1990).

According to the virus-AIDS hypothesis, one would have expected that by now (about one 10-year-HIV-latent-period after infection) at least 50% of the 15,000 HIV-positive American hemophiliacs would have developed AIDS or died from AIDS. But the 2% annual AIDS risk indicates that the average HIV-positive hemophiliac would have to

wait for 25 years to develop AIDS diseases from HIV, which is the same as their current median age. The median age of American hemophiliacs has increased from 11 years in 1972, to 20 years in 1982 and to over 25 years in 1986, despite the infiltration of HIV in 75% (Johnson *et al.,* 1985; Institute of Medicine, 1986; Koerper, 1989). Thus, one could make a logical argument that HIV, instead of decreasing the lifespan of hemophiliacs, has in fact increased it.

Considering the compromised health of many hemophiliacs compared to the general population, it is also surprising, that the 1–2% annual AIDS risk of HIV-infected hemophiliacs is lower than the 3–4% risk of the average HIV-infected, nonhemophilic European or American (Table 1). There is even a bigger discrepancy between the annual AIDS risks of hemophiliacs and those of intravenous drug users and male homosexuals, which are both about 4–6% (Table 2). In an effort to reconcile the relatively low annual AIDS risks of hemophiliacs with that of homosexuals, the hematologists Sullivan *et al.* (1986) noted "The reasons for this difference remain unclear." And Biggar and colleagues (1990) noted that "AIDS incubation ... was significantly faster" for drug users and homosexuals than for hemophiliacs.

In view of the many claims that HIV causes AIDS in hemophiliacs, it is even more surprising that there is not even one controlled study from any country showing that the morbidity or mortality of HIV-positive hemophiliacs is higher than that of HIV-negative controls.

Instead, controlled studies show that immunodeficiency in hemophiliacs is independent of HIV, and that the lifetime dosage of transfusions is the cause of AIDS-defining diseases of hemophiliacs. Studies describing immunodeficiency in HIV-free hemophiliacs are summarized in Table 3 (Tsoukas *et al.,* 1984; AIDS Hemophilia French Study Group, 1985; Ludlam *et al.,* 1985; Gill *et al.,* 1986; Kreiss *et al.,* 1986; Madhok *et al.,* 1986; Sullivan *et al.,* 1986; Sharp *et al.,* 1987; Matheson *et al.,* 1987; Antonaci *et al.,* 1988; Mahir *et al.,* 1988; Aledort, 1988; Jin *et al.,* 1989; Jason *et al.,* 1990; Lang, *et al.,* 1989; Becherer *et al.,* 1990). One of these studies even documents an AIDS-defining disease in an HIV-free hemophiliac (Kreiss *et al.,* 1986). Immunodeficiency in these studies is typically defined by a T4 to T8-cell ratio of about 1 or less than 1, compared to a normal ratio of 2.

Most of the studies listed in Table 3 and additional ones conducted before HIV had been discovered have concluded or noted that immunodeficiency is directly proportional to the number of transfusions received over a lifetime (Menitove *et al.,* 1983; Kreiss *et al.,* 1984; Johnson *et al.,* 1985; Hardy *et al.,* 1985; Pollack *et al.,* 1985; Prince, 1992; Ludlum *et al.,* 1985; Gill *et al.,* 1986). According to the hematologists Pollack *et al.* (1985) "derangement of immune function in hemophiliacs results from transfusion of foreign proteins or a ubiquitous virus rather than contracting AIDS infectious agent." The "ubiquitous virus" was a reference to the virus-AIDS hypothesis but a rejection of HIV, because in 1985 HIV was extremely rare in blood concentrates outside the U.S., but immunodeficiency was observed in Israeli, Scottish and American hemophiliacs (Pollack *et al.,* 1985). Madhok *et al.* also arrived at the conclusion that "clotting factor concentrate impairs the cell mediated immune response to a new antigen in the absence of infection with HIV" (Madhok *et al.,* 1986). Aledort observed that "chronic recipients ... of factor VIII, factor IX and pooled products ... demonstrated significant T-cell abnormalities regardless of the presence of HIV antibody" (Aledort, 1988). Even those who claim that clotting factor does not cause immunodeficiency show that immunodeficiency in hemophiliacs increases with both the age and the cumulative dose of clotting factor received during a lifetime (Becherer *et al.,* 1990).

One controlled study showed directly that protein impurities of commercial factor VIII, rather than factor VIII or HIV, were immunosuppressive among factor VIII-treated, HIV-positive hemophiliacs. Over a period of two years the T-cells of HIV-positive hemophiliacs treated with commercial factor VIII declined two-fold, while those of matched HIV-positive controls treated with purified factor VIII remained unchanged (Table 3) (de Biasi *et al.,* 1991).

Before AIDS, a multicenter study investigating the immune systems of 1551 hemophiliacs treated with factor VIII from 1975 to 1979 documented lymphocytopenia in 9.3% and thrombocytopenia in 5% (Eyster *et al.,* 1985). Accordingly, AIDS-defining opportunistic infections, including 60% pneumonias and 20% tuberculosis, have been recorded in hemophiliacs between 1968 and 1979 (Johnson *et al.,* 1985). These transfusion-acquired immunodeficiencies could more than account for

Table 3. Immunosuppression in HIV-negative and -positive Hemophiliacs

Study	Immunosuppression (T4/T8 about or less than 1) HIV-negative	HIV-positive
1. Tsoukas *et al.* (1984)	6/14	9/15
2. Ludlam *et al.* (1985)	15	—
3. French Study Group (1985)	33	55
4. Sullivan *et al.* (1986)	28	83
5. Madhok *et al.* (1986)	9	10
6. Kreiss *et al.* (1986)	6/17	22/24
7. Gill *et al.* (1986)	8/24	30/32
8. Sharp *et al.* (1987)	5/12	—
9. Matheson *et al.* (1987)	5	3
10. Mahir *et al.* (1988)	6	5
11. Antonaci *et al.* (1988)	15	10
12. Aledort (1988)	57	167
13. Jin *et al.* (1989)	12	7
14. Lang *et al.* (1989)	24	172
15. Becherer *et al.* (1990)	74	136
16. Jason *et al.* (1990)	31	—
17. de Biasi *et al.* (1991)	—	10/20

*In a normal immune system, the T4 to T8 T-cell ratio is about 2, in immunodeficient persons and in many AIDS patients it is about 1 or below 1. Studies which list the fraction of immunodeficient hemophiliacs in HIV-positive and HIV-negative groups indicate, that HIV-positives are more likely to be immunodeficient. This is because HIV is a marker for the number of transfusions received and transfusion of foreign proteins causes immune deficiency. The study by de Biasi et al. (1991) showed that among 20 HIV-positive hemophiliacs only those 10 who received commercially purified factor VIII, but not those who received further purified factor VIII developed immunodeficiency over a period of two years. See text for references.

the 2% annual incidence of AIDS-defining diseases in HIV-positive hemophiliacs recorded now (Centers for Disease Control, 1992b). An American hematologist who recorded opportunistic infections in hemophiliacs occurring between 1968 and 1979, including 2 candidiasis and 66 pneumonia deaths, commented in 1983 "... it seems possible that many of the unspecified pneumonias in hemophiliacs in the past would be classified today as AIDS" (Aronson, 1983).

It follows that long-term transfusion of foreign proteins causes immunodeficiency in hemophiliacs with or without HIV. The virus hypothesis has simply claimed normal morbidity and mortality of hemophiliacs for HIV, by ignoring HIV-free controls.

Nevertheless several investigators comparing HIV-negative to HIV-positive hemophiliacs have noted that immunodeficiency is more often associated with HIV-positives (Table 3), and have observed that HIV correlates with the number of transfusions received (Tsoukas *et al.,* 1984; Kreiss *et al.,* 1986; Sullivan *et al.,* 1986; Koerper, 1989; Becherer *et al.,* 1990). According to Kreiss *et al.* "seropositive hemophiliac subjects, on average, had been exposed to twice as much concentrate ... as seronegative[s]" (Kreiss *et al.,* 1986). And according to Goedert *et al.* "the prevalence of HIV-1 antibodies was directly associated with the degree of severity (of hemophilia)" (Goedert *et al.,* 1989). Thus HIV appears just to be a marker of the multiplicity of transfusions, rather than a cause of immunodeficiency.

The conclusion that long-term transfusion of foreign proteins causes immunodeficiency makes three testable predictions:

(1) It predicts that hemophiliacs with "AIDS" would be older than average hemophiliacs. Indeed, the median age of hemophiliacs with AIDS in the U.S. (Evatt *et al.,* 1984; Koerper, 1989; Stehr-Green *et al.,* 1989), England (Darby *et al.,* 1989) and other countries (Biggar and the International Registry of Seroconverters, 1990; Blattner, 1991) is significantly higher (about 34 years in the U.S.; Johnson *et al.,* 1985; Koerper, 1989; Becherer *et al.,* 1990) than the average age of hemophiliacs (20–25 years in the U.S., see above). Goedert *et al.* reported that the annual AIDS risk of 1- to 17-year-old hemophiliacs was 1.5%, that of 18- to 34-year-old hemophiliacs was 3% and that of 64-year-old hemo-

philiacs was 5% (Goedert *et al.,* 1989). This confirms that the cumulative dose of transfusions received is the cause of AIDS-defining diseases among hemophiliacs. According to the hematologist Koerper, "this may reflect lifetime exposure to a greater number of units of concentrate, . . ." and to Evatt *et al.,* "This age bias may be due to differences in duration of exposure to blood products . . ." (Evatt *et al.,* 1984; Koerper, 1989).

By contrast, AIDS caused by an autonomous infectious pathogen would be largely independent of the age of the recipient. Even if HIV were that pathogen, the hemophiliac population with AIDS should have the same age distribution as the hemophiliac population over 10 years, because HIV is thought to take 10 years to cause AIDS and nearly all hemophiliacs were infected about 10 years ago (Johnson *et al.,* 1985; McGrady *et al.,* 1987; Koerper, 1989).

(2) Foreign protein-mediated immunodeficiency further predicts that all AIDS diseases of hemophiliacs are opportunistic infections. If hemophilia AIDS were due to HIV only 62% of their AIDS diseases would be opportunistic infections, because 38% of all American AIDS patients have diseases, that are not dependent on, and not consistently associated with, immunodeficiency (Table 1, Section 3.5.8). These include wasting disease (19%), Kaposi's sarcoma (10%), dementia (6%) and lymphoma (3%) (Table 1).

The AIDS pathology of hemophiliacs confirms the prediction of the foreign protein-hypothesis exactly. In America 99% of the hemophiliacs with AIDS have opportunistic infections, of which about 70% are fungal and viral pneumonias, and less than 1% have Kaposi's sarcoma (Evatt *et al.,* 1984; Selik *et al.,* 1987; Stehr-Green *et al.,* 1988; Goedert *et al.,* 1989; Koerper, 1989; Becherer *et al.,* 1990). The small percentage of Kaposi's sarcoma is due to the nitrite inhalants used by male homosexual hemophiliacs as sexual stimulants (Section 4). There are no reports of wasting disease and dementia in hemophiliacs.

(3) If hemophilia AIDS is due to transfusion of foreign proteins, the wives of hemophiliacs should not contract AIDS from their mates. But if it were due to a parenterally or sexually transmitted virus, hemophilia AIDS would be sexually transmissible. Indeed, AIDS researchers claim that the wives of hemophiliacs develop AIDS from sexual transmission

of HIV (Lawrence *et al.,* 1990; Weiss and Jaffe, 1990; Centers for Disease Control, 1992b). For example AIDS researcher Fauci asks: "How about the 60-year-old wife of a hemophiliac who gets infected? Is she cruising, too?" (Booth, 1988).

However, (a) statistical scrutiny and (b) a controlled study unconfirm the hypothesis that hemophilia AIDS is sexually transmissible: (a) The CDC reports that 94 wives of hemophiliacs have been diagnosed with unnamed AIDS diseases since 1985 (Centers for Disease Control, 1992b). If one considers that there have been 15,000 HIV-positive hemophiliacs in the U.S. since 1985 and assumes that a third are married, then there are 5000 wives of HIV-positive hemophiliacs. About 13 of these women have developed AIDS annually during the 7 years (94:7) from 1985 to 1991 (Centers for Disease Control, 1992b). By contrast, at least 80 of these women would be expected to die per year, considering the human lifespan of about 80 years and that on average at least 1.6% of all those over 20 years of age die annually. Thus, until controls show that among 5000 HIV-negative wives of hemophiliacs only 67 (80–13) die annually, the claim that wives of hemophilics die from sexual transmission of HIV is unfounded speculation.

Moreover, it has been pointed out that all AIDS-defining diseases of the wives of hemophiliacs are typically age-related opportunistic infections, including 81% pneumonia (Lawrence *et al.,* 1990). Kaposi's sarcoma, dementia, lymphoma and wasting syndrome are not observed in wives of hemophiliacs (Lawrence *et al.,* 1990). Thus the virus-AIDS hypothesis seems to claim, once more, normal morbidity and mortality of the wives of hemophiliacs for HIV.

(b) To test the hypothesis that immunodeficiency of hemophiliacs is sexually transmissible the T4 to T8 cell-ratio of 41 spouses and female sexual partners of immunodeficient hemophiliacs were analyzed (Kreiss *et al.,* 1984). Twenty-two of the females had relationships with hemophiliacs with T-cell ratios below 1 and 19 with hemophiliacs with ratios of 1 and greater. The mean duration of relationships was 10 years, the mean number of sexual contacts was 111 during the previous year, and only 12% had used condoms (Kreiss *et al.,* 1984). Since the T-cell ratios of all spouses were normal, averaging 1.68—exactly like those of 57 normal controls, the authors concluded that "there is no evidence to

date for heterosexual or household-contact transmission of T-cell subset abnormalities from hemophiliacs to their spouses . . ." (Kreiss *et al.*, 1984).

It follows that the foreign protein-hypothesis, but not the HIV-hypothesis, correctly predicts (1) the pathology, (2) the age bias, (3) the noncontagiousness of hemophilia AIDS and (4) HIV-free immunodeficiency in hemophiliacs. It also explains the discrepancies between the annual AIDS risks of hemophiliacs and other risk groups (Table 2).

Since the virus hypothesis has become totally dominant in 1988, no new studies have described HIV-free immunodeficient hemophiliacs (Table 3) and the question whether HIV-free immunodeficient hemophiliacs ever developed AIDS-defining diseases became a taboo. The study by Jason *et al.* described data collected in the mid 1980s, the studies by Jin *et al.* and Becherer *et al.* collected data before 1988 and the one by de Biasi *et al.* compared the effects of purified to unpurified factor VIII only in HIV-positive hemophiliacs (Table 3).

In response to the argument that hemophiliacs only began to develop AIDS diseases when HIV appeared (Centers for Disease Control, 1986; Oppenheimer, 1992), it is proposed that "new" AIDS-defining diseases among hemophiliacs are an indirect consequence of extending their life with factor VIII treatment. Long-term treatment with factor VIII has prolonged the median life of hemophiliacs from 11 in 1972 to 25 in 1986. But contaminating foreign proteins received over periods of 10 years of treatment have also caused immunodeficiencies, and various viral and microbial contaminants have caused infections in some, and HIV infection in 75%. HIV has been a marker for the number of transfusions and factor VIII treatments received, just like hepatitis virus infection was a marker of the number of transfusions received until it was eliminated from the blood supplies (Anonymous, 1984; Koerper, 1989). Prior to factor VIII therapy most hemophiliacs died as adolescents from internal bleeding (Koerper, 1989).

3.4.4.6. *HIV-positive teenagers.* The annual AIDS risk of HIV-infected American teenagers can be calculated as follows: There are about 30 million American teenagers, of which 0.03% (10,000) (Burke *et al.*, 1990) to 0.3% (100,000) (St Louis *et al.*, 1991) are HIV-positive. Since only

160 developed AIDS in 1991 and only 170 in 1990 (Centers for Disease Control, 1992b), their annual AIDS risk is between 0.16% and 1.7% (Table 2).

Thus the AIDS risk of teenagers with HIV is less than the national average of 3–4%. There are no statistics to indicate that the annual risk for AIDS-defining diseases of the HIV-infected teenage population is higher than that of HIV-free controls (Section 3.5.2). Since most American teenagers with AIDS are either hemophiliacs (38%), intravenous drug users (25%) or male homosexuals (25%) (Section 2.1.3), it is proposed that the associated risk factors, rather than HIV, are the cause of teenage AIDS (Sections 3.4.4.5 and 4).

3.4.4.7. *HIV-positive general U.S. population.* The CDC reports that 3% of all American AIDS cases are from the general population, corresponding to 900--1200 of the 30,000~40,000 annual AIDS cases (Table 1) (Centers for Disease Control, 1992b). Since at least 0.03% to 0.3%, or 80,000 to 800,000, of the general American population of 250 million are infected (Section 3.5.2) (U.S. Department of Health and Human Services, 1990; Burke *et al.,* 1990; Morgan *et al.,* 1990; St Louis *et al.,* 1991), the annual AIDS risk of the general population must be between 0.1% and 1% (Table 2). Thus the annual AIDS risk of HIV-infected Americans of the general population is similar to that of teenagers.

There are no statistics to indicate that the annual AIDS risk of the general HIV-infected population is higher than the annual risk for AIDS-defining diseases in HIV-free controls. Because the incidence of AIDS in the general population is exceedingly low, it is proposed again that it reflects the normal, low incidence of AIDS-defining diseases, rather than HIV-mediated diseases.

3.4.4.8. *HIV-positive Africans.* The annual AIDS risks of HIV-infected Africans is only 0.3% (Tables 1 and 2), because 6 million HIV carriers generated 129,000 AIDS cases from 1985 to the end of 1991 (Table 1). There are no controlled studies indicating that the risk for AIDS-defining diseases of HIV-infected Africans differs from that of HIV-negative controls.

Since the annual AIDS risk of HIV-infected Africans is (1) 10-times

lower than the average American and European risk, (2) up to 100-fold less than that of American/European risk groups, (3) the same for both sexes unlike that in America and Europe and (4) very low considering that the annual mortality in Africa is around 2% and that AIDS includes the most common African diseases, it is proposed that African AIDS is just a new name for indigenous African diseases (Section 2.1.2).

Instead of a new virus, malnutrition, parasitic infections and poor sanitary conditions have all been proposed as causes of African AIDS-defining diseases (Editorial, 1987; KonoteyAhulu, 1987, 1989; Rappoport, 1988; Adams, 1989). Further, it has been proposed that the incidence of tuberculosis, diarrhea, fever and other African AIDS-defining diseases may be the same in Africans with and without HIV (Editorial, 1987). And prior to the discovery of HIV, protein malnutrition was identified by the AIDS researchers Fauci *et al.* as the world's leading cause of immunodeficiency, particularly in underdeveloped countries (Seligmann *et al.,* 1984).

Indeed, recent studies document that only 2168 out of 4383 (49.5%) African AIDS patients with slim disease, tuberculosis and other Africa-specific diseases, who all met the WHO definition of AIDS, were infected by HIV. These patients were from Abidjan, Ivory Coast (De Cock *et al.,* 1991; Taelman *et al.,* 1991), Lusaka, Zambia and Kinshasa, Zaire (Taelman *et al.,* 1991). Another study reports 135 (59%) HIV-free AIDS patients from Ghana out of 227 diagnosed by clinical criteria of the WHO. These patients suffered from weight loss, diarrhea, chronic fever, tuberculosis and neurological diseases (Hishida *et al.,* 1992). An earlier study documents 116 HIV-negatives among 424 African patients that meet the WHO definition of AIDS (Widy-Wirski *et al.,* 1988). According to an African AIDS doctor, "Today, because of AIDS, it seems that Africans are not allowed to die from these conditions any longer" (Konotey-Ahulu, 1987). Another asks "What use is a clinical case definition for AIDS in Africa?" (Gilks, 1991).

The 10-fold difference between the average annual AIDS risks of Africans and Americans/ Europeans (Table 1) can thus be resolved as follows: (1) The high AIDS risk of HIV-positive Americans and Europeans is the product of the low absolute numbers of HIV carriers in the U.S. and Europe compared to Africa (Table 1) and of the concentra-

tion of HIV in AIDS risks groups, e.g. consumers of recreational drugs and the antiviral drug AZT (Section 4) and recipients of transfusions (Section 3.4.3). (2) The low AIDS risk of Africans is a product of large absolute numbers of HIV carriers and their relatively low, spontaneous and malnutrition-mediated AIDS risks.

3.4.4.9. *HIV-positive Thais.* Given that there have been only 123 Thai AIDS cases in the last 1–2 years and an estimated 300,000 HIV carriers in Thailand (Weniger *et al.,* 1991), the annual AIDS risk of HIV-infected Thais can be calculated to be less than 0.05% (Table 2). Since most of these 123 were either intravenous drug users or "sex workers" (Section 2.1.3), it is proposed that these specific health risks are their cause of AIDS (Section 4), rather than the HIV that they share, unspecifically, with 300,000 healthy Thais.

The over 100-fold range in the annual AIDS risks of different AIDS risks groups, summarized in Table 2, clearly indicates that HIV is not sufficient to cause AIDS. It confirms and extends an earlier CDC conclusion: "The magnitude of some of the differences in rates is so great that even gross errors in denominator estimates can be overcome" (Hardy *et al.,* 1985). Moreover, analysis of the specific health risks of each risk group has identified nonviral health risks that are necessary and sufficient causes of AIDS (Table 3 and Section 4.5).

3.4.5. *Specific AIDS Diseases Predetermined by Prior Health Risks*

If HIV were the cause of AIDS, every AIDS case should have the same risk of having one or more of the 25 AIDS diseases. However, the data listed above (Section 2.1) and in Table 2 indicate that per AIDS case different risk groups have very specific AIDS diseases:

(1) Male homosexuals have 20 times more Kaposi's sarcoma than all other American and European AIDS risk groups.

(2) Hemophiliacs and other recipients of transfusions have fungal and viral pneumonia and other opportunistic infections, and practically no Kaposi's sarcoma or dementia.

(3) The AIDS diseases of the "general population" are either spontaneous, hemophilia- or age-related opportunistic infections. Typical

examples are cited below (Section 3.5.16).

(4) Babies exclusively have bacterial infections (18%) and a high rate of dementia (14%), compared to adults (6%) (Table 1).

(5) Africans develop Africa-specific AIDS diseases 10 times more and Kaposi's sarcoma 10 times less often than Americans or Europeans.

The epidemiological data summarized in Section 3.4 indicate that HIV is sufficient to determine neither the annual AIDS risk, nor the type of AIDS disease an infected person may develop. Instead, prior health risks including drug consumption, malnutrition and congenital diseases like hemophilia and their treatments and even the country of residence, predetermine AIDS diseases. The correlations between HIV and AIDS that are claimed to support the virus-AIDS hypothesis are not direct, not complete, not distinctive and, above all, not controlled. Controlled studies indicate that the incidence of AIDS-defining diseases in intravenous drug users, male homosexuals practicing risk behavior and hemophiliacs is independent of HIV.

Therefore, it is proposed that various group-specific health risk factors, including recreational and antiviral drugs (Section 4) and malnutrition, are necessary and sufficient causes of AIDS. The existence of risk group-specific AIDS-defining diseases in the absence of HIV confirms this conclusion (Sections 3.4.4 and 4.5).

3.5. Assumptions and Anecdotal Cases that Appear to Support the Virus-AIDS Hypothesis

The following assumptions and anecdotal cases are frequently claimed to prove the virus-AIDS hypothesis. Despite the popularity of these claims they are either uncontrolled for alternative explanations or they are natural coincidences between HIV infection and naturally-occurring diseases.

3.5.1. *HIV is Presumed New Because AIDS is New*

HIV is presumed new in all countries with AIDS, because AIDS is new (Blattner *et al.,* 1988; Gallo and Montagnier, 1988; Weiss and Jaffe, 1990). The presumed newness of HIV is used as a primary argument for the virus-AIDS hypothesis: ... the time of occurrence of AIDS in each country is correlated with the time of introduction of HIV into

that country; first HIV is introduced, then AIDS appears" (Blattner *et al.*, 1988) or: "In every country and city where AIDS has appeared, HIV infection preceded it just by a few years" (Weiss and Jaffe, 1990).

However, according to Farr's law, the age of a microbe in a population is determined by changes in its incidence over time (Bregman and Langmuir, 1990). If a microbe is spreading from a low to a high incidence it is new; however, if its incidence in a population is constant, it is old (Fig. 1) (Freeman, 1979; Duesberg, 1991a). Figure 1 shows the incidences of long established microbes in the U.S. population, i.e. *Candida* and *Pneumocystis* each at about 100% (Freeman, 1979; Pifer, 1984;

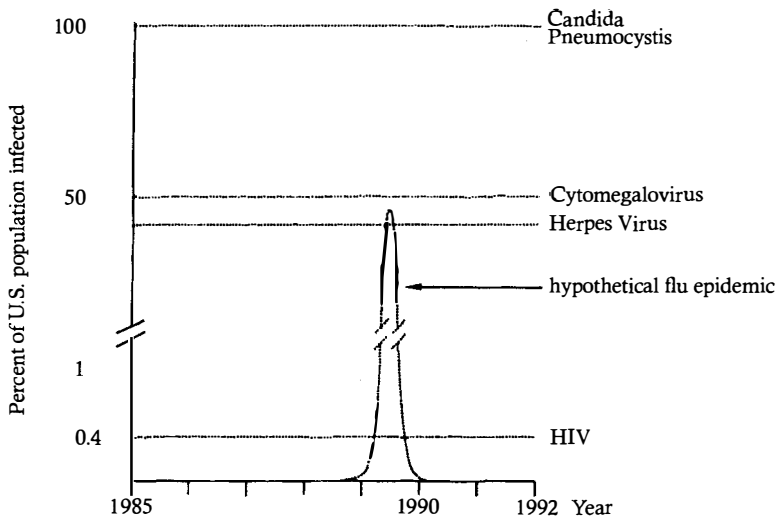

Figure 1. Determination of the age of a microbe in a population based on Farr's law. Farr's law holds that a microbe entering a population spreads exponentially until a susceptible pool is saturated. Subsequently those microbes that are incompatible with long term survival of the host are eliminated exponentially, to generate a bell-shaped curve. The rise and fall of a hypothetical flu epidemic caused by a new strain of influenza virus is an example. But microbes that can coexist with their host become established. Examples are *Candida,* Pneurnocystis (Freeman, 1979), cytomegalovirus, herpes virus (Evans, 1989c) and HIV (see text), these are shown at the percentages at which they are established in the American population.

Williford Pifer *et al.,* 1988), and cytomegalovirus and herpes virus at about 50% and 40%, respectively (Evans, 1989c). In addition, it shows the typical exponential rise and subsequent fall of a hypothetical epidemic by a new influenza virus strain (Freeman, 1979).

Ever since antibodies against HIV were first detected by the "AIDS test" in 1985, the number of antibody-positive Americans has been fixed at a constant population of 1 million, or 0.4% (Section 2.2. and Table 1). The U.S. Army also reports that from 1985 to 1990 an unchanging 0.03% of male and female applicants have been HIV-positive (Burke *et al.,* 1990). This is the predicted distribution of a long established virus (Fig. 1). Since there are over 250 million uninfected Americans, and since there is no antiviral vaccine or drug to stop the spread of HIV, the non-spread of HIV in the U.S. in the last 7 years is an infallible indication that the American "HIV epidemic" is old. The Central African HIV epidemic has also remained fixed at about 10% of the population since 1985 (Section 2.2). Likewise, HIV has remained fixed at 500,000 Europeans since 1988 (World Health Organization, 1992a). The non-spread of HIV confirms exactly the conclusion reached below that HIV behaves in a population as a quasi-genetic marker (Section 3.5.2). Hence, the assumption that HIV is new in the U.S. or in Africa is erroneous.

Indeed HIV existed in the U.S. long before its fictitious origin in Africa (Gallo, 1987; Gallo and Montagnier, 1988; Anderson and May, 1992) and its fictitious entry into this country in the 1970s (Shilts, 1987). For example, in the U.S. in 1968 an HIV-positive, male homosexual prostitute died from Kaposi's sarcoma and immunodeficiency (Garry *et al.,* 1988), and 45 out of 1129 American intravenous drug users were found to be HIV-positive in 1971 and 1972 (Moore *et al.,* 1986).

The putative novelty of HIV is an anthropocentric interpretation of new technology that made it possible to discover HIV and many other latent retroviruses like HTLV-I (Duesberg and Schwartz, 1992). Indeed, the technology to detect a latent virus like HIV only became available around the time AIDS appeared. Given a new virus-scope, the assertion that HIV is new is just like claiming the appearance of "new" stars with a new telescope. Thus the claims that "... first HIV is introduced, then AIDS appears" (Blattner *et al.,* 1988) and that "HIV ... preceded it (AIDS)" (Weiss and Jaffe, 1990) are ironically more true than the

proponents of the virus hypothesis had anticipated. HIV preceded AIDS by many, perhaps millions, of years.

3.5.2. *HIV—Assumed to be Sexually Transmitted—Depends on Perinatal Transmission for Survival*

AIDS is said to be a sexually transmitted disease, because HIV is thought to be a sexually transmitted virus (Section 2.2). However, HIV is not by nature a sexually transmitted virus. Sexual transmission of HIV is extremely inefficient. Based on studies measuring heterosexual and homosexual transmission, it depends on an average of 1000 heterosexual contacts and 100–500 homosexual contacts with antibody-positive people (Rosenberg and Weiner, 1988; Lawrence *et al.,* 1990; Blattner, 1991; Hearst and Hulley, 1988; Peterman *et al.,* 1988). According to Rosenberg and Weiner, "HIV infection in non-drug using prostitutes tends to be low or absent, implying that sexual activity alone does not place them at high risk" (Rosenberg and Weiner, 1988). Moreover, unwanted pregnancies and venereal diseases, but not HIV infections, have increased significantly in the U.S. since HIV has been known (Institute of Medicine, 1988; Aral and Holmes, 1991). This argues directly against sexual transmission of HIV.

Sexual transmission is so inefficient because there is no free, non-neutralized HIV anywhere in antibody-positive persons, particularly not in semen (Section 3.3). In a group of 25 antibody-positive men, only one single provirus of HIV could be found in over 1 million cells of semen in one of the men and no HIV at all was found in the semen of the other 24 (Van Voorhis *et al.,* 1991). Likewise, HIV could only be isolated or reactivated from ejaculates of 9 out of 95 antibody-positive men by cocultivation with 2 million phytohemagglutinin-activated leukocytes (Anderson *et al.,* 1992). No virus or microbe could survive if it depended on a transmission strategy that is as inefficient as 1 in 1000 contacts.

Indeed, HIV depends on perinatal, instead of sexual, transmission for survival—just like other animal and human retroviruses. Therefore, the efficiency of perinatal transmission must be high. This appears to be the case. Based on HIV-tracking via the "AIDS test," perinatal transmission from the mother is estimated to be 13–50% efficient (Blattner

et al., 1988; Blattner, 1991; Duesberg, 1991a; Institute of Medicine, 1988; European Collaborative Study, 1991). This number does not include paternal HIV transmission to the baby via semen, for which there are currently no data. The real efficiency of perinatal transmission must be higher than the antibody-tests suggest, because in a fraction of recipients HIV only becomes immunogenic when its hosts are of an advanced age (Quinn *et al.,* 1986; St Louis *et al.,* 1991). During the antibody-negative phase, latent HIV can be detected by the polymerase chain reaction (Rogers *et al.,* 1989, European Collaborative Study, 1991). This is also true for other perinatally transmitted human (Blattner, 1990; Duesberg, 1991a) and animal retroviruses (Rowe, 1973; Duesberg, 1987).

HIV survival via perinatal transmission leads to two predictions: (1) HIV cannot be inherently pathogenic—just like all other perinatally transmitted viruses and microbes (Freeman, 1979; Mims and White, 1984). No microbe-host system could survive if the microbe were perinatally transmitted and at once fatal. (2) HIV must function as a quasi-genetic marker, because it is quasi-nontransmissible by sex, or other natural horizontal modes of transmission, just like known murine retrovirus prototypes (Rowe, 1973; Duesberg, 1987). Both predictions are confirmed:

(1) Overwhelming statistical evidence from the U.S. and Africa documents that the risk for AIDS-defining diseases for HIV-positive babies, in the absence of other risk factors (Sections 3.4.4 and 4), is the same as that of HIV-free controls:

(a) "AIDS tests" from applicants to the U.S. Army and the U.S. Job Corps indicate that between 0.03% (Burke *et al.,* 1990) and 0.3% (St Louis *et al.,* 1991) of the 17- to 19-year-old applicants are HIV-infected but healthy. Since there are about 90 million Americans under the age of 20, there must be between 27,000 and 270,000 (0.03%–0.3% of 90 million) HIV carriers. In Central Africa there are even more, since 1–2% of healthy children are HIV-positive (Quinn *et al.,* 1986).

Most, if not all, of these adolescents must have acquired HIV from perinatal infection for the following reasons: sexual transmission of HIV depends on an average of 1000 sexual contacts, and only 1 in 250 Americans carries HIV (Table 1). Thus, all positive teenagers would

have had to achieve an absurd 1000 contacts with a positive partner, or an even more absurd 250,000 sexual contacts with random Americans to acquire HIV by sexual transmission. It follows that probably all of the healthy adolescent HIV carriers were perinatally infected, as for example the 22-year-old Kimberly Bergalis (Section 3.5.16).

The AIDS risk of perinatally infected babies of the general population can be estimated as follows. Between 27,000 and 270,000 Americans under the age of 20 carry HIV. But only about 4260 AIDS cases have been recorded in this age group in the last 10 years (Centers for Disease Control, 1992b). Therefore, between 85% and 98% of HIV-infected youths do not develop AIDS up to 20 years after perinatal infection (Section 2.1). Since the above number includes the AIDS babies from drug-addicted mothers (Sections 3.4.2 and 4), the AIDS risk of HIV-infected babies from mothers that don't use drugs probably reflects normal infant mortality.

(b) A controlled study from Africa compared 218 newborns from HIV-positive mothers to 218 from HIV-negative mothers, and the "rates of prematurity, low birth weight, congenital malformations and neonatal mortality were comparable in the two groups" (Lepage *et al.*, 1991). The mothers were matched for age and parity and the "frequency of signs and symptoms was not statistically different in the two groups."

(2) The incidence of HIV in American teenagers of different ethnic backgrounds is predictable on genetic grounds. It is about 10-fold higher in blacks than in whites, i.e. 0.3% compared to 0.03% (U.S. Department of Health and Human Services, 1990; Burke *et al.*, 1990; Blattner, 1991; Palca, 1991b; St Louis *et al.*, 1991; Vermund, 1991). HIV was even 50-fold more common in black mothers in inner-city hospitals in New York (36%) than in whites (0.7%) (Landesmann *et al.*, 1987). This reflects the 25- to 50-fold higher incidence of HIV in the blacks' African ancestors (10%) compared to the whites' European ancestors (0.2 to 0.4%) (Section 2.2, Table 1). Likewise, the different ethnic groups of the Caribbean reflect the distinct HTLV-I incidences of their ancestors in Africa, Europe and Japan, despite generations of coexistence on the Caribbean islands (Blattner, 1990). The unchanging incidence of HIV in the American population (Fig. 1) also confirms the view that HIV is a quasi-genetic marker. Since there is virtually no horizontal transmis-

sion of retroviruses, murine retroviruses have functioned as classical genetic markers of mice that could only be distinguished from cellular genes by fastidious genetic crosses (Rowe, 1973).

Thus the assumption that AIDS is sexually transmitted by HIV is not consistent with the natural perinatal mode of HIV transmission. If natural transmission of HIV caused a disease, AIDS would be a pediatric disease. Instead, HIV is merely a marker of either an average of 1000 sexual contacts and thus of many other possible AIDS risks associated with very high sexual activity or of long-term intravenous drug use (Sections 3.4.3 and 5).

3.5.3. *AIDS Assumed to be Proportional to HIV Infection*

The incidence of AIDS is assumed to be proportional to the incidence of HIV via a constant factor. For example, a 10-fold higher incidence of AIDS in American and European males compared to females is assumed to reflect a 10-fold higher incidence of HIV in men (Blattner *et al.*, 1988; Blattner, 1991; Goudsmit, 1992).

However, there is no evidence that the incidence of HIV is 10 times higher in males than in females of the general American and European population, although this is the case for AIDS (Table 1). Indeed, the most recent claim for a 90% bias of HIV for males of the general population (Blattner, 1991) is only supported by a reference to an editorial (Palca, 1991b), which itself provides nothing more than an unreferenced cartoon showing global patterns of HIV infection. According to a CDC epidemiologist, estimates of how HIV is distributed between the sexes of the general population are "approximations" based on the distribution of AIDS (Tim Dondero, CDC, personal communication; see also Anderson and May, 1992)—a tautology.

Proportionality between HIV and AIDS via a constant is also incompatible with the following statistics. The U.S. Army (Burke *et al.*, 1990) and the U.S. Job Corps (St Louis *et al.*, 1991) report, based on millions of tests, that HIV has been equally distributed between the sexes among 17- to 21-year-olds of the general population over the last five years for which data were available (Sections 3.5.1 and 3.5.2). Since testing 17- to 19-year-olds annually for 5 years is equivalent to testing 17- to 24-year-olds, the U.S. Army data predict that among 17- to 24-year-olds,

AIDS risks should be distributed equally between the sexes. However, the CDC documents that 85% of the AIDS cases among 17- to 24-year-olds were males (Centers for Disease Control, 1992b).

In response to this, some proponents of the virus-AIDS hypothesis have speculated that teenage homosexuals exclude themselves from the Army. However, Randy Shilts, a homosexual writer, reports that just the opposite is true (Shilts, 1991). Moreover, most teenagers are not as yet aware of a definite homosexual persuasion and are not likely to understand the implications nor to fear the consequences of a positive "AIDS test."

The over 100-fold discrepancies between the AIDS risks of different HIV-infected risk groups also disprove the claim that the incidence of AIDS is proportional via a constant to the incidence of HIV (Table 2). The proportionality between HIV and AIDS only holds if the analysis is restricted to groups with the same AIDS risks. In groups with the same percentage of HIV but with different AIDS risks, AIDS segregates specifically with nonviral AIDS risks, e.g. illicit recreational drugs, the antiviral drug AZT (Section 4) and frequent transfusions (Section 3.4.4).

3.5.4. *AIDS Assumed to be Homosexually Transmitted in the U.S. and Europe*

In view of a sexually transmitted AIDS virus, it is paradoxical that AIDS is 90% male in America and 86% male in Europe (Sections 3.1 and 3.2). Therefore it is assumed that "the virus first got its footing in the U.S." in male homosexuals (Booth, 1988) and has remained with homosexuals because it is transmitted preferentially by anal intercourse and because homosexuals have no sex with heterosexuals (Centers for Disease Control, 1986; Shilts, 1987; Blatter *et al.,* 1988; Institute of Medicine, 1988; Blattner, 1991; Bardach, 1992; Project Inform, 1992).

However, this assumption is inconsistent with the fact that about 10% of all males and females prefer anal intercourse (Bolling and Voeller, 1987; Turner *et al.,* 1989) and that American and European heterosexuals have sufficient access to HIV. The females would be infected by HIV-positive, heterosexual intravenous drug users, hemophiliacs, and bisexual males. Thus, if HIV were transmitted by anal intercourse, about the same percentage of women as men should develop AIDS, particu-

larly since the efficiencies of transmission of anal and vaginal intercourse are approximately the same, e.g. between 1 to 100 and 1 to 500 for anal and 1 to 1000 for vaginal intercourse (Blattner, 1991) (see also Section 3.5.2). Yet, despite widespread alarm, this has not occurred in the last 10 years in the U.S. (Table 1), although the first women with AIDS had been diagnosed as early as in 1981 (Centers for Disease Control, 1986; Guinan and Hardy, 1987). The risk of women for both HIV infection and AIDS is the same for those who practice anal intercourse as for those who practice other types of intercourse (Guinan and Hardy, 1987).

The preferred anal-transmission hypothesis is also incompatible with the sexually equal distribution of HIV and AIDS in Africa. Since it is postulated that HIV appeared in America and Africa at about the same time 10–20 years ago (Institute of Medicine, 1986; Blattner *et al.,* 1988; Gallo and Montagnier, 1988), HIV should have reached the same equilibria between the sexes in all countries.

Instead it is shown below that the male bias for AIDS in America and Europe reflects male-specific behavior, including the facts that over 75% of all intravenous drug users are males and that long-term consumption of sexual stimulants, like amylnitrite and ethylchloride inhalants, is almost entirely restricted to male homosexuals (Section 4). HIV is just a marker of the many sexual stimulants used to achieve 500–1000 sexual contacts (Section 4). The difference between the AIDS risks of men in America and Europe, namely drugs, and those of Africans, namely country-specific, but not sex-specific, risk factors (Section 3.4.4.8) resolves the paradox between the different sexual distributions of AIDS in these countries.

3.5.5. *AIDS Assumed to be Heterosexually Transmitted by African "Life-style"*

AIDS in Africa is assumed to affect both genders equally, because HIV is distributed equally between the sexes by "prostitution" (Institute of Medicine, 1988), lack of "circumcision" (Klein, 1988; Marx, 1989; Blattner, 1991), African "lifestyle" (Quinn *et al.,* 1987; Blattner *et al.,* 1988; Goodgame, 1990) and "voodoo rituals" (Gallo, 1991). These assumptions are compatible with the sexually equal distributions of HIV and AIDS in Africa.

However, AIDS in Africa is hard to reconcile with the known efficiency of sexual transmission of HIV. Since it takes 1000 HIV-positive sexual contacts to transmit HIV and about 10% of all Central Africans, or 6 million, are HIV-positive (Section 2.2), 6 million Africans would have had to achieve on average at least 10,000 sexual contacts with random Africans to pick up HIV. Since this is highly improbable, it is also highly improbable that sexual transmission of HIV is the cause of AIDS in Africa. The true reason for the sexually equal distribution of HIV in Africa is perinatal transmission of HIV (Section 3.5.2). Nonsexual, country-specific risk factors are the reason for the "sexually" equal distribution of AIDS in Africa (Section 3.4.4.8).

3.5.6. *HIV Claimed to be Abundant in AIDS Cases*

HIV is said to be abundant or viremic in AIDS patients (Baltimore and Feinberg, 1989; Coombs *et al.,* 1989; Ho *et al.,* 1989a; Semple *et al.,* 1991) and thus compatible with orthodox viruses which cause disease only at high titers (Duesberg and Schwartz, 1992). In other words HIV is assumed to meet Koch's first postulate (Section 3.3). The assumption is based on two papers which reported HIV titers of 10^2 to 10^3 infectious units per mL of blood in 75% of AIDS patients and in 25–50% of asymptomatic HIV carriers (Coombs *et al.,* 1989; Ho *et al.,* 1989a). The authors and an accompanying editorial, *HIV Revealed, Toward a Natural History of the Infection* (Baltimore and Feinberg, 1989), concluded that these findings established HIV viremia as an orthodox criterion of viral pathogenicity. Viremia of similar titers was recently also implied in some AIDS patients and asymptomatic carriers based on an indirect assay that amplifies HIV RNA *in vitro* (Semple *et al.,* 1991).

However, several arguments cast doubt on the claim that HIV viremia is relevant for AIDS:

(1) Since viremia was observed in 25–50% of asymptomatic HIV carriers (Coombs *et al.,* 1989; Ho *et al.,* 1989a; Semple *et al.,* 1991), it cannot be sufficient for AIDS.

(2) Since no viremia was observed in 25% of the AIDS cases studied by two groups (Coombs *et al.,* 1989; Ho *et al.,* 1989a), it is not necessary for AIDS.

(3) Viremia initiated from a previously suppressed virus and observed

years after infection is a classical consequence, rather than the cause of immunodeficiency. Indeed, many normally latent parasites become activated and may cause chronic "opportunistic infections" in immunodeficient persons, as for example *Candida, Pneumocystis,* herpes virus, cytomegalovirus, hepatitis virus, tuberculosis bacillus, toxoplasma (Sections 2.3 and 3.4.3)—and sometimes even HIV. It is consistent with this view that HIV viremia is observed more often in AIDS patients than in asymptomatic carriers (Duesberg, 1990c).

(4) The HIVs that make up the "viremias" are apparently not infectious *in vivo,* because only a negligible fraction of leukocytes, on average only 1 in 1500 to 8000, of AIDS patients are infected (Section 3.3). The probable reason is that the "viremias" consist of viruses that are neutralized by the antiviral antibodies of "seropositive" AIDS patients (Duesberg, 1992d). Since viruses, as obligatory cellular parasites, can only be pathogenic by infecting cells, these noninfectious viremias cannot be relevant to the cause of AIDS. If assayed *in vitro,* in the absence of free antiviral antibodies, antibodies may dissociate from neutralized viruses and thus render the virus infectious for cells in culture. This explains the discrepancy between the noninfectious "viremias" *in vivo* and the relatively high infectivity recorded *in vitro* (Coombs *et al.,* 1989; Ho *et al.,* 1989a).

Thus HIV viremia is a rare, predictable consequence of immunodeficiency rather than its cause.

3.5.7. *HIV to Depend on Cofactors for AIDS*

Conceding that HIV is not sufficient to cause AIDS, it is assumed to depend on cofactors. Montagnier (Goldsmith, 1990; Lemaitre *et al.,* 1990; Balter, 1991) and Lo (Lo *et al.,* 1991) have proposed mycoplasmas that were discovered in their laboratories; Gallo has proposed two viruses, herpes virus-6 and HTLV-I, which were both discovered in his laboratory (Cotton, 1990; Gallo, 1990, 1991; Lusso *et al.,* 1991). Others have proposed cytomegalovirus, Epstein-Barr virus (Quinn *et al.,* 1987; Evans, 1989a; Root-Bernstein, 1990c), "age" (Evans, 1989a; Goedert *et al.,* 1989; Weiss and Jaffe, 1990; Biggar and the International Registry of Seroconverters, 1990), unidentified "coagents" (Weyer and Eggers, 1990; Eggers and Weyer, 1991), "clinical illness promotion fac-

tors" (Evans, 1989b, 1992) and even "pre-existing immune abnormalities" (Ludlam *et al.*, 1985; Marion *et al.*, 1989; Ludlam, 1992) as cofactors of HIV.

However, cofactor hypotheses only replace HIV-specific AIDS problems with the following HIV-plus-cofactor-specific AIDS problems:

(1) Since HIV is extremely rare and dormant in most antibody-positive AIDS patients (Sections 2.2 and 3.3), it is hard to imagine how its various AIDS-allies could benefit from their dormant "cofactor" HIV.

(2) Since HTLV-I is just as dormant and unable to kill cells as HIV (Duesberg, 1987; Blattner, 1990; Duesberg and Schwartz, 1992), it is even harder to imagine how one dormant virus could help another dormant virus to generate the biochemical activity that would be necessary to cause a fatal disease.

(3) Since mycoplasma (Freeman, 1979; Cotton, 1990; Goldsmith, 1990; Balter, 1991), herpes virus-6 (Cotton, 1990; Lusso *et al.*, 1991), cytomegalovirus and Epstein-Barr virus (Mims and White, 1984; Evans, 1989c) are each very common, if not ubiquitous, parasites (Freeman, 1979; Froesner, 1991), AIDS should develop in most people as soon as they are infected by HIV. Likewise, "aged" people should develop AIDS as soon as they are infected by HIV. Yet not more than 3–4% of HIV-antibody-positive Americans or Europeans and 0.3% of antibody-positive Africans develop AIDS per year (Tables 1 and 2).

Moreover, if infectious cofactors helped HIV to cause AIDS, the AIDS risk of Africans would be expected to be higher than that of Americans. This is because the incidence of hypothetical, microbial cofactors in Africans without AIDS was found to be the same as in those with AIDS, while the incidence of microbial cofactors in Americans without AIDS risks was significantly lower than in those with AIDS (Section 3.4.3) (Quinn *et al.*, 1987). Even the cofactor HIV was present in 6% of African AIDS-free controls (Quinn *et al.*, 1987). Yet the annual AIDS risk of HIV-infected Africans is 10-times lower than that of Americans (Table 1).

(4) Contrary to the claims that "age" is an AIDS cofactor of HIV, the virus-AIDS hypothesis postulates that the latent period for HIV is longer in adults (10 years) than in children (2 years) (Section 2.2). How-

ever, the proposal that "age" is a cofactor for HIV becomes more compelling the more the hypothetical "latent period" of HIV grows. Clearly, if a 70-year-old will be infected by a virus with a "latent period" of 10 years, "age" will be a predictable cofactor (see, for example, hemophiliacs, Section 3.4.4.5 and Paul Gann, Section 3.5.16).

(5) The claims that HIV depends on "clinical illness promotion factors" (Evans, 1992) or on a "pre-existing immune abnormality" (Marion *et al.,* 1989; Ludlam, 1992) for AIDS are euphemisms for saying that HIV cannot cause AIDS until something else does (Duesberg, 1989b). The additional hypothesis that a "pre-existing immune abnormality" (Ludlam, 1992) or a "prior immune dysfunction" (Marion *et al.,* 1989) makes a subject more susceptible to HIV is erroneous, because a pre-existing immune deficiency only affects the progression of an infection, but not the risk of infection.

In view of this, I share Gallo's concerns about cofactors of HIV, which he expresses with a quotation from Lewis Thomas: "Multifactorial is multi-ignorance. Most factors go away when we learn the real cause of a disease" (Gallo, 1991). The "cofactor" HIV may be no exception. Until any one of these hypothetical cofactors is actually shown to depend on HIV to cause AIDS, HIV must be considered just one of many innocent bystanders found in AIDS patients (Section 3.4.3).

3.5.8. *All AIDS Diseases to Result from Immunodeficiency*

All AIDS diseases are said to reflect a primary immunodeficiency (Coffin *et al.,* 1986; Institute of Medicine, 1986; Blattner *et al.,* 1988).

However, immunodeficiency is not a common denominator of all AIDS diseases. About 38% of all AIDS diseases, i.e. dementia, wasting disease, Kaposi's sarcoma and lymphoma (Table 1), are neither caused by, nor necessarily associated with, immunodeficiency. Cancer is not a consequence of immunodeficiency (Stutman, 1975; Duesberg, 1989c). Indeed, Kaposi's sarcoma frequently has been diagnosed in male homosexuals in the absence of immunodeficiency. For example, the immune systems of 20 out of 37 HIV-positive homosexuals with Kaposi's sarcoma were normal when their disease was first diagnosed (Spornraft *et al.,* 1988). Another study also describes 19 male homosexual Kaposi's sarcoma patients with normal immune systems (Mur-

ray *et al.,* 1988). Likewise, Kaposi's sarcomas have been diagnosed in HIV-free male homosexuals with normal immune systems (Afrasiabi *et al.,* 1986; Archer *et al.,* 1989; Friedman-Kien *et al.,* 1990; Marquart *et al.,* 1991).

Dementia and wasting disease also are not consequences of immunodeficiency (Duesberg, 1989c, 1991a). Thus, the assumption that all AIDS diseases are caused by immunodeficiency is erroneous.

3.5.9. *HIV to Induce AIDS via Autoimmunity and Apoptosis*

In view of the extremely low number of HIV-infected cells in AIDS patients (Section 3.3), HIV has recently been proposed to cause AIDS by inducing autoimmunity (Hoffmann, 1990; Maddox, 1991a; Mathé, 1992) or apoptosis (Laurent-Crawford *et al.,* 1991; Goudsmit, 1992). According to these new ideas HIV is assumed either to confuse the immune system into attacking itself or to persuade the immune cells to commit suicide, termed apoptosis. The autoimmune hypothesis postulates homology between HIV and human cells, and currently relies only on mouse and monkey models (Hoffmann, 1990; Maddox, 1991a), and on precedents for autoimmunity induced in humans as a consequence of graft rejection and blood transfusions (Root-Bernstein, 1990a,b; Mathe, 1992). One autoimmunologist claims that "each of Duesberg's paradoxes might be understood in the context of the model without sacrificing the idea that HIV is usually involved in pathogenesis" (Hoffmann, 1990). This strategy of crediting me rather than the virus-AIDS hypothesis for its paradoxes shifts the discussion from a problem with science to a problem with a scientist (Booth, 1988; Weiss and Jaffe, 1990).

However, both the autoimmune and the apoptosis hypotheses are incompatible with human AIDS on several grounds:

(1) Autoimmunity or apoptosis cannot account for all those AIDS diseases that are not caused by immunodeficiency, e.g. Kaposi's sarcoma, dementia, wasting disease and lymphoma (Section 3.5.8).

(2) Autoimmunity or apoptosis fail to explain risk group-specific AIDS diseases (Section 2.1.3, Tables 1 and 2).

(3) Autoimmunity and apoptosis fail to explain the long average intervals, "latent periods," from conventional immunity against HIV,

detected by the "AIDS test," to hypothetical autoimmunity 10 years later (Section 3.2).

(4) Autoimmunity and apoptosis fail to explain the over 100-fold discrepancies between the annual AIDS risks of different HIV-infected groups (Table 2).

(5) HIV-induced autoimmunity or apoptosis fail to explain the consistent 90% bias of American/European AIDS for males (Section 2.1, Table 1).

(6) In view of the autoimmunity or apoptosis hypothesis, it is paradoxical that 80% of antibody-positive Americans (1 million minus the 206,000 who have developed AIDS) and 98% of antibody-positive Africans (6 million minus the 129,000 who have developed AIDS) have not developed AIDS since 1984 (Table 1). Obviously, these figures are not even corrected for the normal and drug-induced incidence of AIDS-defining diseases in those groups (Section 3.4.4, Table 2).

(7) There is no sequence homology between HIV and human DNA detectable by hybridization to predict autoimmunity (Shaw *et al.*, 1984). Therefore, autoimmunologists argue that antibodies against those antibodies, which are directed at the viral proteins that bind to cellular receptors, would also react with cellular receptors and thus cause AIDS (Hoffmann, 1990). However, if this were true, all viruses should cause AIDS.

Thus the HIV-autoimmunity and apoptosis hypotheses of AIDS are (a) not compatible with essential parameters of human AIDS and (b) arbitrary, because they are not based on an autoimmunogenic or apoptogenic property of HIV that is distinct from all other viruses.

3.5.10. *HIV Assumed to Kill T-cells*

Based on an early observation by Gallo *et al.* HIV is assumed to cause immunodeficiency by specifically killing T-cells (Gallo *et al.*, 1984; Weiss and Jaffe, 1990). Gallo's observation was restricted to primary T-cells (Gallo *et al.*, 1984) but not to established T-cell lines (Rubinstein, 1990). However, according to Montagnier, the discoverer of HIV, "In a search for a direct cytopathic effect of the virus on (primary) T-lymphocytes, no gross changes could be seen in virus-producing cultures, with regard to cell lysis or impairment of cell growth" (Montagnier *et al.*, 1984).

Others have confirmed that HIV does not kill infected, primary T-cells *in vitro* (Hoxie *et al.,* 1985; Anand *et al.,* 1987; Langhoff *et al.,* 1989; Duesberg, 1989c). Moreover HIV-infected primary T-cells are considered the natural "reservoir" of HIV *in vivo* (Schnittman *et al.,* 1989).

Thus Gallo's controversial observation probably reflects the notorious difficulties experienced by his laboratory in maintaining primary blood cells alive in culture instead of a genuine cytocidal function of HIV (Crewdson, 1989; Culliton, 1990; Rubinstein, 1990; Hamilton, 1991). Gallo showed in a later study from his laboratory that about 50% of uninfected T-cells died within 12 days in culture (Gallo, 1990).

Indeed, the assumption that HIV is cytocidal is incompatible with generic properties of retroviruses and with specific properties of HIV:

(1) The hallmark of retrovirus replication is to convert the viral RNA into DNA and to deliberately integrate this DNA as a parasitic gene into the cellular DNA (Weiss *et al.,* 1985). This process of integration depends on mitosis to succeed, rather than on cell death (Rubin and Temin, 1958; Duesberg, 1989c). The resulting genetic parasite can then be either active or passive, just like other cellular genes (Duesberg, 1987). Transcription of viral RNA from chromosomally integrated proviral DNA also only works if the cell survives infection, because dying cells are not transcriptionally active. Thus, this strategy of replication depends entirely on the survival of the infected cell.

Noncytocidal replication is the reason that retroviruses were all considered potential carcinogens before AIDS (Weiss *et al.,* 1985; Duesberg, 1987). For example, Gallo's first candidate for an AIDS virus is called Human T-cell Leukemia Virus-I (Gallo *et al.,* 1983), and Gallo's second candidate for an AIDS virus was originally described at a press conference in April 1984 by Gallo and the Secretary of Health and Human Services as "a variant of a known human cancer virus called HTLV III" (Crewdson, 1989; Rubinstein, 1990). It used to be called Human T-cell Leukemia Virus-III by Gallo (Gallo *et al.,* 1984; Shaw *et al.,* 1984) before it was renamed HIV in 1986 (Coffin *et al.,* 1986).

(2) Limited cytotoxicity of HIV has been observed soon after infection of cells *in vitro* (Duesberg, 1989c; Bergeron and Sodroski, 1992). Therefore, it has been proposed that multiple copies of unintegrated

proviral DNA, generated by multiple infections before all cellular receptors are blocked by newly replicated viruses, could kill T-cells (Bergeron and Sodroski, 1992). However, cells infected by every retrovirus, including HIV (Bergeron and Sodroski, 1992), survive multiple unintegrated proviral DNAs during the early phase of the infection (Weiss *et al.,* 1985). Rare cell death during this phase of infection is a consequence of cell fusion, which is mediated by viruses on the surface of infected cells binding to receptors of uninfected cells. In some conditions retrovirus-mediated fusion occurs so reliably that it has been used to quantitate retroviruses in tissue culture. However, virus-mediated fusion is blocked by antiviral antibodies and thus not relevant to the loss of T-cells in persons with antibodies against HIV (Duesberg, 1989c).

Alternatively, it has been proposed that HIV proteins are directly toxic because of structural similarities with scorpion and snake poisons (Gallo, 1991; Garry *et al.,* 1991; Garry and Koch, 1992). However, no such toxicity is observed in millions of asymptomatic HIV carriers, and there is no reason that it should occur, if it did, only after latent periods of 10 years.

(3) The propagation of HIV in indefinitely growing human T-cells for the "AIDS test" was patented by Gallo *et al.* in 1984 (Rubinstein, 1990) and was recently confirmed by Montagnier (Lemaître *et al.,* 1990). It is totally incompatible with Gallo's claim that HIV kills T-cells. Such HIV-producing T-cells have been growing in many laboratories and companies since 1984 producing virus at titers of up to 10^6 virus particles per mL, which is many orders of magnitude more than is ever observed in humans with or without AIDS (Duesberg, 1989c, 1991a).

In view of this, Gallo postulates that T-cell lines in culture have all acquired resistance to HIV killing (Gallo, 1991). However, there is no precedent for this *ad hoc* hypothesis, as no other cytocidal virus has ever been observed that is cytocidal *in vivo* and in primary cells *in vitro,* but is noncytocidal in cell lines in culture. It is also implausible that a potentially life-saving cellular mutation, such as resistance to the hypothetical "AIDS virus," would be restricted just to cells in culture, particularly if these mutations occur so readily that they are found in all T-cell lines. There is not even one T-cell line that is consistently killed by HIV.

(4) HIV, like all other retroviruses, does not specifically infect T-cells.

It also infects monocytes, epithelial cells, B-cells, glial cells and macrophages, etc. and none of these are killed by HIV (Levy, 1988; Duesberg, 1991a). Most other retroviruses also infect T-cells, which is why so many of them are suspected "T-cell leukemia" viruses (Weiss *et al.,* 1985; Duesberg, 1987; Blattner, 1990).

Thus, the assumption that HIV causes AIDS by killing T-cells is not tenable.

3.5.11. *Antibodies Assumed not to Neutralize HIV*

Antibodies against HIV, detected by a positive "AIDS test," are claimed not to protect against AIDS because they do not neutralize HIV (Institute of Medicine, 1988; Evans, 1989a; Weiss and Jaffe, 1990; Gallo, 1991). "It is a test for anti-HIV antibodies and not, as Duesberg states, 'neutralizing antibodies'" (Baltimore and Feinberg, 1990).

However, antiviral immunity completely neutralizes HIV and restricts it to undetectable levels in healthy HIV-carriers as well as in AIDS patients (Section 3.3.1) (Duesberg, 1989b,c). Indeed, two recent studies have just confirmed that HIV activity is "rapidly and effectively limited" by antiviral immunity (Clark *et al.,* 1991; Daar *et al.,* 1991) to less than 1 in 1000 T-cells (Section 3.3). By contrast, HIV replicates in the absence of antiviral immunity in human T-cells in culture to titers of 10^6 virus particles per mL (Section 3.5.10). Thus, the assumption that HIV causes AIDS because of inadequate antiviral immunity is unconfirmed. Baltimore's, Feinberg's and Evans' paradox "that antibody is not protective" (Evans, 1989a) is their failure to recognize the non-role of HIV in AIDS (Section 3.3.2).

3.5.12. *HIV Claimed to Cause AIDS in 50% Within 10 Years*

All HIV-infected persons are said to die from AIDS after a medium latent period of 10 years (Anderson and May, 1988; Institute of Medicine, 1988; Moss *et al.,* 1988; Lemp *et al.,* 1990; Blattner, 1991; Duesberg, 1991a).

However, according to statistics from the CDC, only about 30,000–40,000, or 3–4%, of a reservoir of 1 million HIV-infected Americans develop AIDS annually (Table 1). Likewise, 3% of infected Europeans develop AIDS per year (Table 1). Accordingly, 50% of

HIV-infected Americans and Europeans would have to wait 12–16 years and 100%, 24–33 years to develop AIDS. During this time, many would die from other causes. Since only 0.3% of infected Africans develop AIDS diseases annually (Tables 1 and 2), 50% of Africans would have to wait about 150 years and 100% would have to wait 300 years to develop AIDS.

Thus, it is presumptuous to claim that HIV causes AIDS in 50% of infected persons after median latent periods of 10 years, particularly since the virus has only been known for nine years.

3.5.13. *HIV Said to Derive Pathogenicity from Constant Mutation*

During its long latent periods, HIV is claimed to acquire pathogenicity by mutation, for example by generating variants that escape immunity (Hahn *et al.,* 1986; Levy, 1988; Eigen, 1989; Gallo, 1990; Weiss and Jaffe, 1990; Anonymous, 1992; Anderson and May, 1992) or by generating defective variants (Eigen, 1989; Haas, 1989; Weiss, R.A., 1989).

However, a recent study just demonstrated that the replicative and functional properties of HIVs from AIDS patients are the same as those from asymptomatic carriers (Lu and Andrieu, 1992). Indeed, most essential structural and replicative proteins of a virus cannot be mutated without eliminating its viability. Functionally relevant mutations of any virus are also severely restricted by the necessity to remain compatible with the host (Duesberg, 1990b). Moreover, there is no precedent for an immune system that has been able to neutralize a virus completely and is then unable to catch up with an occasional subsequent mutation. If viruses in general could evade the immune system by mutation, the immune system would be a useless burden to the host.

Likewise, the proposals that defective HIVs could generate pathogenicity is untenable. Defective viruses are only viable in the presence of nondefective helper viruses and thus unlikely to survive in natural transmission from host to host at low multiplicity of infection, particularly with helper viruses that never achieve high titers like HIV (Duesberg, 1989a).

There are, however, examples of new antigenic variants of retroviruses (Beemon *et al.,* 1974) or influenza viruses (Duesberg, 1968), that have arisen upon rare double infection by two antigenically distinct

virus strains via genetic recombination. Yet antigenically new variants of HIV have never been observed in American and European AIDS patients, as all HIV strains diagnosed to date crossreact with the very same standard HIV-1 strain that is patented in America and Europe for the "AIDS test" (Connor, 1991, 1992; Palca, 1991a; Weiss, 1991).

Moreover, if recombination or spontaneous mutation could generate pathogenic HIV mutants from nonpathogenic strains, one would expect all those who are infected by HIV from AIDS patients to develop AIDS within weeks after infection. Such HIV mutants should be pathogenic just as soon as conventional, nonpathogenic HIV strains are immunogenic. But this is not observed.

Thus, the assumption that HIV acquires pathogenicity by mutation during the course of the infection is not tenable.

3.5.14. *HIV Assumed to Cause AIDS with Genes Unique Among Retroviruses*

AIDS researchers assert that HIV causes AIDS with unique genetic information that all other animal and human retroviruses lack and that these unique genes would regulate HIV down during the "latent period" and up during AIDS (Gallo and Montagnier, 1988; Haseltine and Wong-Staal, 1988; Institute of Medicine, 1988; Eigen, 1989; Temin, 1990; Fauci, 1991; Gallo, 1991). Further, it is claimed that HIV-infected cells export factors encoded by these genes that promote neoplastic growth of uninfected cells to cause, for example, Kaposi's sarcoma (Salahuddin *et al.,* 1988; Ensoli *et al.,* 1990; Gallo, 1990); at the same time such genes are said to export "scorpion poison"-related toxins that kill uninfected neurons to cause dementia (Gallo, 1991; Garry *et al.,* 1991; Garry and Koch, 1992). By contrast, all other known bacterial, animal and human viruses, including retroviruses, are only able to kill or alter those cells they infect, because viruses are manufactured inside cells and would not benefit from proteins released to uninfected cells.

However, the claims of unique retroviral HIV genes with unique control functions raises several unresolvable problems:

(1) Despite its presumed unique properties HIV has the same genetic complexity, i.e. 9000 nucleotides, and the same genetic structure as all

other retroviruses (Beemon *et al.,* 1974; Wang *et al.,* 1976; Institute of Medicine, 1988). It shares with other retroviruses the three major genes *gag-pol-env,* which are linked in this order in all animal and human retroviruses (Wang *et al.,* 1976). Although "novel" genes that overlap with the major retroviral genes have been discovered in HIV by computerized sequence analysis, and by new protein detection technology (Varmus, 1988), such genes have also been found with the same technology in other retroviruses that do not cause AIDS, such as HTLV-I, other human retroviruses, bovine retroviruses, simian retroviruses and sheep retroviruses (Varmus, 1988; Weiss, 1988; Duesberg, 1989c; Palca, 1990). Thus there is no unique genetic material and no uncommon genetic structure in HIV RNA that could indicate where this unique AIDS-specific information of HIV is hiding.

(2) Since all retroviral genes share just one common promoter, it would be impossible to differentially activate one HIV gene while the others are latent. Thus the idea that different viral genes would regulate latency and virulence, as with lambda phage, is not compatible with HIV (Haseltine and Wong-Staal, 1988; Eigen, 1989; Temin, 1990; Fauci, 1991). Since all HIV genes share the same promotor, latent HIV can only be activated by the host—just like all other latent retroviruses. In addition HIV cannot make specific AIDS factors, while its major genes are dormant. Since viral RNA synthesis *in vivo* is only detectable in 1 out of 10,000 to 100,000 leukocytes and then only in half of all AIDS patients (Section 3.3), HIV cannot make Kaposi's sarcomagenic and neurotoxic factors in amounts sufficient to cause fatal tumors and dementias. This is why such factors have not been detectable *in vivo* (Weiss and Jaffe, 1990; Gallo, 1991).

Thus, based on the structure, information and function of its RNA, HIV is a profoundly conventional retrovirus. It does not contain unique genes that distinguish it from other retroviruses, nor can its genes be differentially regulated at the transcriptional level.

3.5.15. *Simian Retroviruses to Prove that HIV Causes AIDS*

Animal retroviruses may cause diseases in experimental animals that overlap with the wide spectrum of AIDS diseases. Such systems are now studied for analogies to gain experimental support for the virus-

AIDS hypothesis (Blattner *et al.,* 1988; Weiss and Jaffe, 1990; Goudsmit, 1992). For example, a retrovirus isolated from macaques (Fultz *et al.,* 1990), termed simian immunodeficiency virus (SIV), that is 40% related to HIV, is said to cause AIDS-like diseases in rhesus monkeys (Kestler *et al.,* 1990; Temin, 1990). According to an editorial in *Science,* "if SIV infection is all that is needed to cause simian AIDS, that's one more indication that HIV is all that is needed to cause human AIDS" (Palca, 1990).

However, the presumed role of SIV in the diseases of infected monkeys is very different from that of HIV in human AIDS:

(1) According to one study, about half of the infected monkeys developed diseases within several months to one year after infection (Kestler *et al.,* 1990). By contrast only 3–4% of HIV-infected Americans or Europeans and 0.3% of infected Africans develop AIDS annually (Table 1).

(2) In the same study, the absence of antiviral antibodies predicted the incidence of diseases in monkeys, while the opposite is claimed for humans infected with HIV. Another study has confirmed that the monkey's risk of disease is directly proportional to the titer of SIV (Fultz *et al.,* 1990).

(3) The simian retroviruses barely reduce the T-cell levels of ill monkeys (Kestler *et al.,* 1991), while HIV is claimed to deplete T-cells in humans.

(4) The spectrum of diseases observed in the SIV-infected monkeys is different from AIDS, including bacteremia and lacking, among others, Kaposi's sarcoma and dementia (Kestler *et al.,* 1990; Fultz *et al.,* 1990).

(5) In follow-up studies, SIV failed to cause disease in rhesus and mangabey monkeys despite extensive sequence variation which is thought to enhance pathogenicity of the virus (Fultz *et al.,* 1990; Burns and Desrosiers, 1991; Villinger *et al.,* 1991).

(6) Since SIV has never caused any disease in wild monkeys, although about 50% are naturally infected (Duesberg, 1987, 1989c; Blattner *et al.,* 1988; Fultz *et al.,* 1990; Burns and Desrosiers, 1991; Villinger *et al.,* 1991), SIV is not an appropriate model for the hypothesis that HIV causes AIDS in naturally infected humans.

It would appear that SIV causes disease in monkeys like all viruses

cause disease soon after infection and in the absence of effective immunity. This is not a model for the hypothesis that HIV causes AIDS 10 years after it is neutralized by antibodies. Indeed, in the vast literature on retroviruses there is not even one proven example of a latent retrovirus that, in the presence of antiviral immunity, has ever caused a disease in any animal, including chickens, mice, cattle, and monkeys (Weiss *et al.,* 1985; Duesberg, 1987, 1989c).

Moreover, the observation that a retrovirus that is 60% unrelated to HIV causes disease in monkeys cannot prove that HIV causes AIDS in humans, even if all parameters of infection were completely analogous. It can only prove that under analogous conditions other retroviruses may also cause disease, which has been demonstrated with numerous avian and murine retroviruses long ago (Weiss *et al.,* 1985).

3.5.16. *Anecdotal AIDS Cases from the General Population*

Rare AIDS cases occurring outside the major risk groups are claimed to prove that HIV alone is sufficient to cause AIDS in persons with no other AIDS risks (Blattner *et al.,* 1988; Booth, 1988; Baltimore and Feinberg, 1989; Weiss and Jaffe, 1990). Four examples illustrate this point:

(1) Ryan White, an 18-year-old hemophiliac, was said to have died from AIDS in April 1990. However, information from the National Hemophilia Foundation revealed that White had died from unstoppable internal bleeding and had also been treated for an extended period with the cytotoxic DNA chain terminator AZT prior to his death (Duesberg and Ellison, 1990). It appears that hemophilia and AZT (Section 4) would each be sufficient causes of death, and certainly a combination of both would be more than adequate to explain the death of Ryan White. Thus there is no convincing evidence that White died from HIV.

To prove that HIV played a role in White's death, it would be necessary to compare mortality of matched hemophiliacs with and without HIV. To prove that AZT contributed to his death, matched HIV-positive hemophiliacs with and without AZT must be compared. Without such evidence the HIV-death of White is just a hypothesis. Yet White was generally described as an innocent victim of HIV (practicing no risk behavior), which is why the U.S. Senate approved the Ryan

White Comprehensive AIDS Resources Act for over $550 million in aid to hospitals for AIDS emergencies and treatment of children (Anonymous, 1990).

(2) In 1989 the California tax-reformer Paul Gann was reported to have died from AIDS at the age of 77 after receiving HIV from a blood transfusion. However, a close examination of Gann's case reveals that he had 5-bypass heart surgery for blocked arteries in 1982, when he may have received the blood transfusion with HIV. In 1983 he needed further bypass surgery for blocked intestinal arteries. In 1989, at the age of 77, he was hospitalized again for a broken hip. While recovering from the hip fracture, Gann was immobilized for weeks and developed a pneumonia from which he died (Folkart, 1989). This is a rather typical death for a 77-year-old man in poor health.

To determine whether HIV played any role at all in his death, a controlled study would be necessary showing that the mortality of HIV-positive 77-year-old bypass patients with broken hips is higher than that of HIV-negative counterparts. No such study exists.

(3) Kimberly Bergalis, a 22-year-old woman, developed candidiasis and a transient pneumonia 17 and 24 months, respectively, after the extraction of two molars (Centers for Disease Control, 1990). After her dentist had publicly disclosed that "he had AIDS," she was tested for HIV, although Bergalis was a virgin and did not belong to an AIDS risk group (Breo and Bergalis, 1990). Since she was HIV-antibody-positive the CDC concluded that she had contracted AIDS from her dentist (Centers for Disease Control, 1990), who was a homosexual with Kaposi's sarcoma (Ou *et al.,* 1992).

Clearly prior to the virus-AIDS hypothesis, the story of a doctor transmitting his Kaposi's sarcoma in the form of a yeast infection to his client via a common infectious cause would have hardly made *The New York Times* and certainly not the scientific literature (Lambert, 1991). But since the two entirely unrelated diseases are both labeled AIDS and because of the tremendous popularity of the virus-AIDS hypothesis, the paradoxical story became a case célèbre for AIDS in the general population.

Once diagnosed for AIDS Bergalis was treated with the cytotoxic DNA chain terminator AZT, which is prescribed to inhibit HIV, until

she died in December 1991 with weight loss (15 kg), hair loss, uncontrollable candidiasis, anemia and muscle atrophy (requiring a wheelchair) (Breo and Bergalis, 1990; Anonymous, 1991; Lauritsen, 1991)—the symptoms of chronic AZT toxicity (Section 4). It is not clear whether her AZT therapy started before or after her pneumonia, since it was only mentioned in an edited interview conducted for the American Medical Association (Breo and Bergalis, 1990) and in some newspapers (Anonymous, 1991), but not in a single one of several scientific reports (Centers for Disease Control, 1990; Witte and Wilcox, 1991; Ou *et al.,* 1992; Palca, 1992a,b) and not in *The New York Times* (Lambert, 1991). Since her fatal condition was attributed to HIV, she received $1 million in compensation from her dentist's, rather than from her AZT doctor's (Section 4), malpractice insurance (Palca, 1992a).

In view of the celebrity of the case and the fear it inspired among patients, 1100 further patients of the dentist came forward to be tested for HIV (Ou *et al.,* 1992; Palca, 1992a). Seven of these, including Bergalis, tested positive. Four or 5 of these, including Bergalis and another woman, did not belong to an AIDS risk group, but 2 or 3 did. At least three of those who did not belong to a risk group received $1 million settlements from the dentist's malpractice insurance (Palca, 1992b). However, a plausible mechanism of HIV transmission from the dentist to his 4–5 positive clients without AIDS risks was never identified, and there is no consensus as to whether the viruses of the three carriers studied by the CDC and the insurance companies were sufficiently related to claim a common source (Palca, 1992a,b).

Statistically, it can be shown that the incidence of HIV-infections among the dentist's clients reflects, almost to the decimal point, the national incidence of the virus in the U.S. The national incidence of HIV-positives among all Americans is 0.4% (1 out of 250) (Table 1), the incidence of HIV-positives among 1100 patients of the Florida dentist was 0.4% (4 to 5 out of 1100) and the incidence among 15,795 patients from 32 HIV-positive doctors, determined by the CDC for the Bergalis case, was 0.5% (84 out of 15,795). Thus the incidence of HIV in patients from HIV-positive doctors reflects the national incidence of HIV. This suggests noniatrogenic and, most likely, perinatal infection as the source of HIV in these patients, particularly in the case of the virgin Bergalis

(Section 3.5.2). In addition, it identifies a rich source of insurance income for 0.4% of American patients of HIV-positive doctors!

To determine whether HIV had contributed to Bergalis' death, a controlled study would be necessary comparing the mortality of women with yeast infections, with and without antibodies against HIV, and with and without AZT therapy. Since such a study is not available, the assumption that Bergalis died from HIV is pure speculation.

(4) A doctor, presumably infected with HIV from a needle stick in 1983 (Aoun, 1992), described himself in a letter to the *New England Journal of Medicine* as an AIDS patient (Aoun, 1989). He was diagnosed HIV-positive in 1986 (Aoun, 1992). His only AIDS symptom at that time was a weight loss of 4.5 kg (Aoun, 1989). In 1991, then 8 years after the presumed date of the infection, the doctor described his case again in a speech "From the eye of the storm ..." published in the *Annals of Internal Medicine* (Aoun, 1992). The speech did not describe any current AIDS symptoms. This case has been cited as an example that HIV is sufficient to cause AIDS (Baltimore and Feinberg, 1989).

However, the weight loss diagnosed in 1986 could have been the result of the anxiety that HIV infection causes in believers of the HIV-AIDS hypothesis, rather than the work of HIV. This interpretation is consistent with the fact that since 1985 at least 800,000 Americans (1 million minus the 206,000 AIDS cases recorded by the end of 1991; see Table 1) have not lost weight or developed other AIDS diseases (Duesberg, 1991a). Likewise, 6 million Central Africans (minus the 129,000 with AIDS) have been healthy HIV-carriers since at least 1985 (Table 1).

Thus, there are no convincing anecdotal cases to prove that HIV causes AIDS in persons outside the major risk groups. The use of the above assumptions and anecdotal cases as proof for the virus-AIDS hypothesis is misleading, although they may provide valuable clues for future research.

3.6. Consequences of the Virus-AIDS Hypothesis

Despite the lack of proof and numerous discrepancies with orthodox criteria of infectious disease, the virus-AIDS hypothesis has remained since 1984 the only basis for all efforts in predicting, preventing, investigating and even treating AIDS. AIDS prevention is based entirely on

preventing the spread of HIV. This includes promotion of safe sex (Booth, 1988; Institute of Medicine, 1988; Weiss and Jaffe, 1990; Mann and the Global AIDS Policy Coalition, 1992; Anderson and May, 1992), clean injection equipment for intravenous drugs (National Commission on AIDS, 1991) and the exclusion of HIV antibody-positive blood donations from transfusions (Vermund, 1991; Duesberg and Schwartz, 1992).

The Food and Drug Administration mandated in 1985 that the 12 million plus annual blood donations in the U.S. (Williams *et al.,* 1990) are tested for HIV-1, and as of 1992 also for HIV-2, although there is as yet only one single American AIDS patient infected by HIV-2 (O'Brien *et al.,* 1992). Since 1985 over 2 million tests have also been performed annually by the U.S. Army (Burke *et al.,* 1990). By 1986 already over 20 million "AIDS tests" were performed in the U.S. (Institute of Medicine, 1986), at a minimum cost to the client of $12 to $70 (Irwin Memorial Blood Bank, San Francisco, personal communication) or $45 (U.S. Immigration Service). The former U.S.S.R. conducted 20.2 million "AIDS tests" in 1990 and 29.4 million in 1991 to detect 112 and 66 antibody-positives, respectively (Voevodin, 1992).

The detection of antibodies in healthy persons is interpreted as a 50% certain prognosis for AIDS within 10 years (Section 3.5.12). Therefore, a positive "AIDS test" is psychologically toxic (Grimshaw, 1987; Albonico, 1991b) and often the basis for the physiologically toxic antiviral therapy with AZT (Section 4) (Duesberg, 1992b,d). A negative test for HIV is a condition for admission to the U.S. Army (Burke *et al.,* 1990), for admission to health insurance programs, for residence in many countries and even for travel into the U.S. and China. Currently, over 50 countries restrict one or more classes of entrants based on positive antibody-tests for HIV (Duckett and Orkin, 1989). Antibody-positive Americans who had sex with antibody-negatives have been convicted of "assault with a deadly weapon" (Duesberg, 1991c; McKee, 1992). In communist Cuba about 600 antibody-positive persons are quarantined in the name of the virus-AIDS hypothesis (Scheper-Hughes and Herrick, 1992; Treichler, 1992).

Based on the assumption that HIV had either originated recently or spread recently from isolation to its current levels, at the same rates as AIDS had spread in the risk groups in the U.S. and Europe, and on the

assumption that AIDS would follow the presumed spread of HIV with a hiatus of 10 years, epidemiologists have made apocalyptic predictions about an AIDS epidemic that has raised fears and funding to unprecedented levels (Heyward and Curran, 1988; Mann *et al.,* 1988; Mann and the Global AIDS Policy Coalition, 1992; Anderson and May, 1992).

Above all, over 180,000 antibody-positives, with and without AIDS, are currently treated indefinitely with the cytotoxic DNA chain terminator AZT in an effort to inhibit HIV (Section 4.4).

4. The Drug-AIDS Hypothesis

After the global acceptance of the virus-AIDS hypothesis, several investigators have recently revived the original hypothesis that AIDS is not infectious (Section 2.2). In view of (1) the almost complete restriction (97%) of American AIDS to groups with severely compromised health, (2) the predetermination for certain AIDS diseases by prior health risks, and (3) the many links between AIDS and drug consumption (Sections 2.1.3 and 3.4, Table 2), it has been proposed that recreational drugs and AZT may cause AIDS (Lauritsen and Wilson, 1986; Haverkos, 1988a, 1990; Holub, 1988; Papadopulos-Eleopulos, 1988; Rappoport, 1988; Duesberg, 1990a, 1991a, 1992c,f; Lauritsen, 1990; Albonico, 1991a,b; Pillai *et al.,* 1991; Cramer, 1992; Leonhard, 1992). Here the hypothesis is investigated that all American and European AIDS diseases, above the normal background of hemophilia and transfusion-related diseases, are the result of the long-term consumption of recreational and anti-HIV drugs.

4.1. Chronological Coincidence Between the Drug and AIDS Epidemics

The appearance of AIDS in America in 1981 followed a massive escalation in the consumption of psychoactive drugs that started after the Vietnam War (Newell *et al.,* 1985b; Kozel and Adams, 1986; National Institute on Drug Abuse, 1987; Bureau of Justice Statistics, 1988; Haverkos, 1988b; Office of National Drug Control Policy, 1988; Flanagan and Maguire, 1989; Lerner, 1989; Shanon *et al.,* 1990). The Bureau of Justice Statistics reports that the number of drug arrests in the U.S.

has increased from about 450,000 in 1980 to 1.4 million in 1989 (Bureau of Justice Statistics, 1988; Shannon *et al.,* 1990). About 500 kg of cocaine were confiscated by the Drug Enforcement Administration in 1980, about 9000 kg in 1983, 80,000 kg in 1989, and 100,000 kg in 1990 (Bureau of Justice Statistics, 1988, 1991; Flanagan and Maguire, 1989). In 1974, 5.4 million Americans had used cocaine at some point in their lives and in 1985 that number had gone up to 22.2 million (Kozel and Adams, 1986). Currently about 8 million Americans are estimated to use cocaine regularly (Weiss, S.H., 1989; Finnegan *et al.,* 1992). The number of dosage units of domestic stimulants confiscated, such as amphetamines, increased from 2 million in 1981 to 97 million in 1989 (Flanagan and Maguire, 1989).

Several arguments indicate that these increases reflect increased drug consumption rather than just improved drug control, as has been suggested (Maddox, 1992a):

(1) The Bureau of Justice Statistics estimates that at most 20% of the cocaine smuggled into the U.S. was confiscated each year (Anderson, 1987).

(2) The National Institute on Drug Abuse reports that between 1981 and 1990 cocaine-related hospital emergencies increased 24-fold from 3296 to 80,355 and deaths from 195 to 2483 (Kozel and Adams, 1986; National Institute on Drug Abuse, 1990a,b). Thus cocaine-related hospital emergencies had increased 24-fold during 9 of the 10 years in which cocaine seizures had increased 100-fold.

(3) It is highly improbable that, before the jet-age, the U.S. would have imported annually as much cocaine as it did in 1990 plus the 100,000 kg that were confiscated in that year.

Further, the recreational use of psychoactive and aphrodisiac nitrite inhalants began in the 1960s and reached epidemic proportions in the mid-1970s, a few years before AIDS appeared (Newell *et al.,* 1985b, 1988). The National Institute on Drug Abuse reports that in 1979–1980 over 5 million people used nitrite inhalants in the U.S. at least once a week (Newell *et al.,* 1988), a total of 250 million doses per year (Wood, 1988). In 1976 the sales of nitrite inhalants in one American city alone amounted to $50 million annually (Newell *et al.,* 1985b, 1988) at $5 per 12 mL dose (Schwartz, 1988).

Since 1987 the cytocidal DNA chain terminator AZT has been prescribed as an anti-HIV drug to AIDS patients (Kolata, 1987; Yarchoan and Broder, 1987b) and since 1990 to asymptomatic carriers of HIV (Editorial, 1990). Currently about 120,000 Americans and 180,000 HIV-positive persons worldwide, with and without AIDS, take AZT in efforts to inhibit HIV. This estimate is based on the annual AZT sales of $364 million and a wholesale price of $2000 per year for a daily dose of 500 mg AZT per person (Burroughs Wellcome Public Relations, 3 April 1992). In addition, an unknown number take other DNA chain terminators like ddI and ddC (Smothers, 1991; Yarchoan *et al.,* 1991).

4.2. Overlap Between Drug-Use and AIDS Statistics

Drugs and AIDS appear to claim their victims from the same risk groups. For instance, the CDC reports that the annual mortality of 25- to 44-year-old American males increased from 0.21% in 1983 to 0.23% in 1987, corresponding to about 10,000 deaths among about 50 million in this group (Buehler *et al.,* 1990). Since the annual AIDS deaths had also reached 10,000 by 1987, HIV was assumed to be the cause (Institute of Medicine, 1986; Centers for Disease Control, 1987, 1992b). Further, HIV infection was blamed for a new epidemic of immunological and neurological deficiencies, including mental retardation, in American children (Blattner *et al.,* 1988; Institute of Medicine, 1988; Centers for Disease Control, 1992b).

However, mortality in 25- to 44-year-old males from septicemia, considered an indicator of intravenous drug use, rose almost 4-fold from 0.46 per 100,000 in 1980 to 1.65 in 1987, and direct mortality from drug use doubled (National Center for Health Statistics, 1989; Buehler *et al.,* 1990), indicating that drugs played a significant role in the increased mortality of this group (Buehler *et al.,* 1990). In addition, deaths from AIDS diseases and nonAIDS pneumonia and septicemia per 1000 intravenous drug users in New York increased at exactly the same rates, from 3.6 in 1984 to 14.7 and 13.6, respectively, in 1987 (Selwyn *et al.,* 1989). Indeed, the cocaine-related hospital emergencies alone could more than account for the 32% of American AIDS patients that are intravenous drug users (Section 2.1.3). The emergencies had increased from "a negligible number of people" in 1973 to 9946 non-fatal and 580

fatal cases in 1985 (Kozel and Adams, 1986), when a total of 10,489 AIDS cases were recorded and to 80,355 nonfatal and 2483 fatal cases in 1990 (National Institute on Drug Abuse, 1990a,b), when a total of 41,416 AIDS cases were recorded by the CDC (Centers for Disease Control, 1992a). Moreover 82% of the cocaine-related and 75% of the morphine-related hospital emergencies were 20–39 years old (National Institute on Drug Abuse, 1990a), the age distribution typical of AIDS patients (Section 2.1.1).

Another striking coincidence is that over 72% of all American AIDS patients (Centers for Disease Control, 1992b) and about 75% of all Americans who consume "hard" psychoactive drugs such as cocaine, amphetamines and inhalants (National Institute on Drug Abuse, 1987, 1990a,b; Ginzburg, 1988) or get arrested for possession of such drugs (Bureau of Justice Statistics, 1988) or are treated for such drugs (National Institute on Drug Abuse, 1990a) are 20- to 44-year-old males. Thus there is substantial epidemiological overlap between the two epidemics (Lerner, 1989), reported as "The twin epidemics of substance use and HIV" by the National AIDS Commission (National Commission on AIDS, 1991).

Moreover, maternal drug consumption was blamed by some for the new epidemic of immunological and neurological deficiencies, including dementias, of American children (Toufexis, 1991). In view of this, the CDC acknowledges, "We cannot discern, however, to what extent the upward trend in death rates from drug abuse reflects trends in illicit drug use independent of the HIV epidemic" (Buehler *et al.,* 1990).

4.3. Drug Use in AIDS Risk Groups

4.3.1. *Intravenous Drug Users Generate a Third of All AIDS Patients*

Currently 32% of the American (National Commission on AIDS, 1991; Centers for Disease Control, 1992b) and 33% of the European (Brenner *et al.,* 1990; World Health Organization, 1992a) AIDS patients are intravenous or intrauterine users of heroin, cocaine, and other drugs (Section 2.1.3). These include:

(1) 75% of all heterosexual AIDS cases in America and about 70% of those in Europe,

(2) 71% of the American and 57% of the European females with AIDS,

(3) over 10% of the American and 5% of the European male homosexuals,

(4) 10% of the American hemophiliacs with AIDS,

(5) 70% of American children with AIDS including 50% born to mothers who are confirmed intravenous drug users and another 20% to mothers who had "sex with intravenous drug users" and are thus likely users themselves (Amaro *et al.,* 1989),

(6) 80–85% of the European children with AIDS who were born to drug-addicted mothers (Mok *et al.,* 1987; European Collaborative Study, 1991).

In an article entitled "AIDS and intravenous drug use: the real heterosexual epidemic" the AIDS researcher Moss points out that "90% of infected prostitutes reported in Florida, Seattle, New York and San Francisco have been intravenous drug users ... Drug use is also the source of most neonatal AIDS, with 70% of cases occurring in children of intravenous drug users ..." (Moss, 1987). Indeed, all studies of American and European prostitutes indicate that HIV infection is almost exclusively restricted to drug users (Rosenberg and Weiner, 1988), although all prostitutes should have the same risks of HIV infection, if HIV were sexually transmitted. Surprisingly, all of these studies only mention the incidence of HIV, rather than of AIDS, in prostitutes.

4.3.2. *Homosexual Users of Aphrodisiac Drugs Generate about 60% of AIDS Patients*

Approximately 60% of American AIDS patients are male homosexuals over the age of 20 (Table 1). They are generated by risk groups that have sex with large numbers of partners (Centers for Disease Control, 1982; Jaffe *et al.,* 1983b; Darrow *et al.,* 1987; Oppenheimer, 1992) that often average over 100 per year and have exceeded 1000 over a period of several years (Mathur-Wagh *et al.,* 1984; Newell *et al.,* 1985a; Turner *et al.,* 1989; Callen, 1990). The following evidence indicates that these sexual activities and the corresponding conventional venereal diseases are directly proportional to the consumption of toxic sexual stimulants, which include nitrite- and ethylchloride inhalants, cocaine, ampheta-

mines, methaqualone, lysergic acid, phenylcyclidine, and more (Blattner *et al.,* 1985; Shilts, 1987; Lauritsen and Wilson, 1986; Darrow *et al.,* 1987; Haverkos, 1988a; Rappoport, 1988; Raymond, 1988; Adams, 1989; Turner *et al.,* 1989; Weiss, S.H., 1989; Ostrow *et al.,* 1990; Lesbian and Gay Substance Abuse Planning Group, 1991a).

An early CDC study of 420 homosexual men attending clinics for sexually transmitted diseases in New York, Atlanta and San Francisco reported that 86.4% had frequently used amyl- and butylnitrites as sexual stimulants. The frequency of nitrite use was proportional to the number of sexual partners (Centers for Disease Control, 1982).

In 1983 Jaffe *et al.* investigated AIDS risk factors of 170 male homosexuals from sexual disease clinics, including 50 with Kaposi's sarcoma and pneumonia and 120 without AIDS. In this group, 96% were regular users of nitrite inhalants and 35–50% of ethylchloride inhalants. In addition, 50–60% had used cocaine, 50–70% amphetamines, 40% phenylcyclidine, 40–50% lysergic acid, 40–60% methaqualone, 25% barbiturates, 90% marijuana and 10% heroin (Jaffe *et al.,* 1983b). Over 50% had also used prescription drugs. About 80% of these men had past or current gonorrhea, 40–70% had syphilis, 15% mononucleosis, 50% hepatitis and 30% parasitic diarrhea. Those with Kaposi's sarcoma had a median of 61 sex partners per year and those without AIDS about 26. The study points out that "lifetime exposure to nitrites ... (and) use of various 'street' drugs ... was greater for cases than controls." The lifetime drug dose of "cases" was reported to be two times higher than of asymptomatic HIV carriers (Jaffe *et al.,* 1983b).

A study of a group of 359 homosexual men in San Francisco reported in 1987 that 84% had used cocaine, 82% alkylnitrites, 64% amphetamines, 51% methaqualone, 41% barbiturates, 20% injected drugs and 13% shared needles (Darrow *et al.,* 1987). About 74% had past or current infection by gonococcus, 73% by hepatitis B virus, 67% by HIV, 30% by amoebae and 20% by treponema (Darrow *et al.,* 1987). This group had been randomly selected from a list of homosexuals who had volunteered to be investigated for hepatitis B virus infection and to donate antisera to hepatitis B virus between 1978 and 1980. For the same group the 50% "progression rate" from HIV to AIDS was calculated to be 8–11 years (Table 2) (Moss *et al.,* 1988; Lemp *et al.,* 1990)—

and reported to be relevant for "the (HIV-infected) population as a whole" (Moss *et al.,* 1988)!

A study investigating AIDS risk factors among French homosexuals reported that 31% of those with AIDS, but only 12% of those without AIDS, had achieved "over 100 nitrite inhalations" (Messiah *et al.,* 1988). The study included 53, or 45%, of all homosexual AIDS patients recorded in France by 1987.

The staggering oral drug use among male homosexuals at risk for AIDS was confirmed in 1990 by the largest survey of its kind. It reports that 83% of 3916 self-identified American homosexual men had used one, and about 60% two or more drugs with sexual activities during the previous six months (Ostrow *et al.,* 1990). Similar drug use has been reported for European homosexuals at risk for AIDS (van Griensven *et al.,* 1987).

A survey of homosexual men from Boston, conducted between 1985 and 1988, documented that among 206 HIV-positives 92% had used nitrite inhalants, 73% cocaine, 39% amphetamines, 29% lysergic acid in addition to six other psychoactive drugs as sexual stimulants; among 275 HIV-negative controls 71% had used nitrites, 57% cocaine, 21% amphetamines, 17% lysergic acid again in addition to six other psychoactive drugs (Seage *et al.,* 1992). A similar survey of 364 HIV-positive homosexual men in Berlin conducted between 1983 and 1987 stated that 194 (53.3%) had used nitrite inhalants (Deininger *et al.,* 1990).

According to Newell *et al.* (1985b), volatile nitrites had penetrated "every corner of gay life" by 1976. Surveys studying the use of nitrite inhalants found that in San Francisco 58% of homosexual men were users in 1984 and 27% in 1991, compared to less than 1% of heterosexuals and lesbians of the same age group (Lesbian and Gay Substance Abuse Planning Group, 1991b).

Several investigators have pointed out that nitrite inhalants, and possibly other drugs, are preferred by male homosexuals as aphrodisiacs because they facilitate anal intercourse by relaxing smooth muscles (Section 4.4.1) (Mirvish and Haverkos, 1987; Newell *et al.,* 1985b; Ostrow *et al.,* 1990; Lesbian and Gay Substance Abuse Planning Group, 1991a; Seage *et al.,* 1992). "Nitrites were used primarily for heightened sexual stimulation during sexual activity by reducing social and sexual inhi-

bitions, prolonging duration, heightening sexual arousal, relaxing the anal sphincter during anal intercourse, and prolonging orgasm" (Newell *et al.,* 1985b).

4.3.3. *Asymptomatic AZT Users Generate an Unknown Percentage of AIDS Patients*

The DNA chain terminator AZT has been licensed in the U.S. since 1987 as a treatment for AIDS patients (Chernov, 1986; Kolata, 1987; Lauritsen, 1990; Yarchoan *et al.,* 1991) based on a placebo controlled study sponsored by Burroughs Wellcome, the manufacturer of AZT (Section 4.4.2) (Fischl *et al.,* 1987; Richman *et al.,* 1987). In 1990 AZT was also licensed as AIDS prophylaxis for healthy HIV carriers (Section 4.4.2) (Volberding *et al.,* 1990; Yarchoan *et al.,* 1991).

The choice of this drug as anti-AIDS treatment is based entirely on the virus-AIDS hypothesis. According to Broder *et al.,* "The rationale for anti-retroviral therapy for AIDS is ... that HIV is the etiologic agent of AIDS" and that HIV RNA-dependent DNA synthesis is inhibited by AZT (Yarchoan *et al.,* 1991). In view of this and their faith in the virus-AIDS hypothesis, about 120,000 American HIV carriers, with and without AIDS, and 180,000 worldwide currently take AZT every day (Section 4.1). It follows that probably a high percentage of the 40,000 Americans and 15,000 Europeans that currently develop AIDS per year (Table 1) have used AZT and other DNA chain terminators prior to AIDS.

The drug is now recommended as AIDS prophylaxis for all AIDS-free persons with less than 500 T-cells per microliter by the director of AIDS research at the NIH (Kolata, 1992) and with some reservations also by the National Hemophilia Association of New York (personal communication), despite recent doubts about its usefulness (Kolata, 1992). For instance, AZT has been used indefinitely by over 1200 AIDS-free, but presumably HIV-infected, homosexual men from the Multicenter AIDS Cohort Study referenced above (Ostrow *et al.,* 1990), including 7% of 3670 with over 500 T-cells per microliter, 16% of 1921 with 350–499 T-cells, 26% of 1374 with 200–349 T-cells and 51% of 685 with fewer than 200 T-cells (Graham *et al.,* 1991). Yet the large study acknowledges finding "... no effects (of AZT) on rates of progression

to lower CD4+ lymphocyte counts in any of the transition intervals" (Graham *et al.,* 1991). In San Francisco 3.3% of 151 AIDS-free male homosexuals with over 500 T-cells, 11% of 128 with 200–500 T-cells and 36% of 42 with less than 200 T-cells were on AZT in 1989 (Lang *et al.,* 1991). Another study reports that, in 1989, 26 out of 322 HIV-positive but AIDS-free homosexuals from San Francisco, Chicago and Denver had taken AZT for less than 6 months and 101 for over 6 months (Holmberg *et al.,* 1992).

To distinguish between HIV and drugs as causes of AIDS, it is necessary to identify either HIV-carriers that develop AIDS only when they use drugs (Section 4.4) or to identify HIV-free drug users that develop AIDS indicator diseases (Section 4.5) and to demonstrate drug toxicity (Section 4.6).

4.4. Drug Use Necessary for AIDS in HIV-Positives

Studies demonstrating that drugs are necessary for AIDS among HIV-positives fall into two subgroups: (1) those demonstrating that AIDS among HIV-positives depends on the long-term use of recreational drugs and (2) those demonstrating that HIV-positive AIDS-free persons and AIDS patients on the antiviral drug AZT develop new AIDS diseases or AZT-specific diseases. Since the health of AIDS-free persons selected for AZT prophylaxis is compromised by prior AIDS risks, e.g. less than 500 T-cells, and since nearly all American and European AIDS patients have used recreational drugs or have been immunosuppressed by long-term transfusions, evaluating the role of AZT in the progression of AIDS is complicated by these confounding risk factors (Sections 3.4.4 and 4.3.3).

4.4.1. *AIDS From Recreational Drugs*

(1) A study of 65 HIV-infected drug users from New York showed that their T-cell count dropped over nine months in proportion with drug injection, on average 35%, compared to controls who had stopped (Des Jarlais *et al.,* 1987).

(2) The incidence of AIDS diseases and death among HIV-positive, asymptomatic intravenous drug users over 16 months were 19% (23/124)

among those who persisted in injecting psychoactive drugs, 5% (5/93) among those who had stopped injecting drugs and 6% (5/80) among those on methadone treatment (Weber *et al.,* 1990).

(3) Among male homosexuals, receptive anal intercourse carries a 2.75 times (Warren Winkelstein, personal communication) to 4.4 times (Haverkos, 1988b) higher AIDS risk than insertive intercourse, presumably reflecting a higher risk of infection by HIV (Moss *et al.,* 1987; van Griensven *et al.,* 1987; Winkelstein *et al.,* 1987; Seage *et al.,* 1992). However, if HIV were the cause of AIDS, the donors should have the same AIDS risk as the recipients, because recipients can only be infected by HIV donors. No microbe can survive that is only unidirectionally transmitted. All venereal microbes are therefore bitransitive. Indeed, Haverkos found no differences in sexually transmitted diseases between those practicing receptive and insertive intercourse (Haverkos, 1988b). The probable reason for the higher AIDS risk associated with receptive anal intercourse is that this sexual practice directly correlates with a 2-fold (van Griensven *et al.,* 1987; Seage *et al.,* 1992) to an 8-fold (Moss *et al.,* 1987; Haverkos, 1988b) enhanced use of nitrite inhalants and other aphrodisiac drugs that facilitate anal intercourse (Sections 4.3.2 and 4.6).

(4) A Canadian study reports that every one of 87 HIV-positive male homosexual AIDS patients had used nitrite inhalants. Those who had used over 20 "hits" per month were more likely to have Kaposi's sarcoma and sarcoma plus pneumonia than those who had used less than 20 hits per month. HIV-free controls, described in a previous report of the same cohort (Section 4.5) (Marion *et al.,* 1989), were not mentioned in this study (Archibald *et al.,* 1992). The authors concluded that a "sexually transmitted agent," which is even more difficult to transmit than HIV(!) (Section 3.5.1), would explain the Kaposi's sarcomas among the AIDS patients. The nitrites were proposed to be a cofactor of this cofactor of HIV (Archibald *et al.,* 1992). Thus nitrites were necessary for AIDS in HIV-positives.

To determine whether HIV was indeed necessary for these AIDS cases, the incidence of AIDS-defining diseases in HIV-positive and negative homosexuals who are matched for the duration and extent of drug consumption must be compared. This is what the Canadian team has

recently attempted to do in a study termed "HIV causes AIDS: a controlled study" (Craib *et al.,* 1992). The study asserts to meet the challenge of "Duesberg [who] wrote in 1988 (*Science,* 1988; 242: 997–998) and repeated in public addresses in 1991 that the necessary comparisons in controlled cohorts were not available. . . ."

However the study failed to match the HIV-free control group with the HIV-positives for the extent and duration of drug consumption. It mentions that 49% of the HIV-negatives had used "psychoactive drugs," but fails to mention the percentage of drug users among the HIV-positives. In their previous study 100% of the HIV-positive AIDS patients had used such drugs (Archibald *et al.,* 1992). In addition the authors failed to recognize that HIV-infection is a marker for the duration of drug consumption. Since an average of 1000 sexual contacts is required for sexual transmission of HIV (Section 3.5.2), HIV is a marker for the dosage of sexual stimulants that is used for 1000 contacts. Thus HIV-positives would have used more sexual stimulants, the equivalent for 1000 contacts, than HIV-negatives. Indeed the authors acknowledge problems with "claims that AIDS is caused by other exposures and not by HIV . . . the problem may be semantics. No one has ever disputed that cofactors play a very important role . . ." (Craib *et al.,* 1992). Moreover the authors failed to mention whether AZT was prescribed to the HIV-positives.

(5) A survey of 99, including 92 "gay or bisexual," AIDS patients from an "HIV clinic" at St. Mary's Hospital in London reports that 78% used "poppers" (nitrite inhalants), 78% cannabis, 76% cigarettes, 68% alcohol, and 48% "ecstasy" (amphetamines). In addition, the patients received an average of three unspecified medications, probably including AZT (Valentine *et al.,* 1992). HIV-tests were not reported, but are assumed to be positive because the patients were in an "HIV clinic." Clearly, the multiplicity of drugs consumed by these patients could be relevant to their pathogenesis.

(6) A European survey of HIV-positive infants with AIDS found that "nearly all children were born to intravenous-drug-abusing mothers" and that AIDS was 9.4 times more likely in children whose mothers had AIDS symptoms before delivery than in those who had no symptoms (Mok *et al.,* 1987). "Children with drug withdrawal symp-

toms" were most likely to develop diseases, those with no withdrawal symptoms but "whose mothers had used recreational drugs in the final 6 months of pregnancy were intermediate on all indices, whereas children of former drug users did not significantly differ from those born to women who had no history of i.v. drug use" (European Collaborative Study, 1991). An American survey reported that 63 of 68 infants "with symptomatic HIV infections" had "at least one parent who had AIDS or was in an AIDS high-risk group" (Belman *et al.,* 1988). Since the risk of infants to develop AIDS increased with maternal drug consumption and increased 10-fold with maternal AIDS symptoms, it would appear that disease or subclinical deficiencies during pregnancy rather than perinatal infection by HIV are responsible for pediatric AIDS.

4.4.2. *AIDS from AZT and AZT Plus Confounding Recreational Drug Use*

(1) A placebo-controlled study, sponsored by Burroughs Wellcome the manufacturer of AZT, investigated 289 patients with "unexplained" weight loss, fever, oral candidiasis, night sweats, herpes zoster and diarrhea for the licensing of the drug as AIDS therapy in the U.S. (Fischl *et al.,* 1987; Richman *et al.,* 1987). All but 13 of these patients were males. The study was planned for 6 months, but it was interrupted after 4 months, because by then the therapeutic benefits of AZT seemed too obvious to continue the placebo control:

(a) after 4 months on AZT 1 out of 145 in the AZT group but 19 out of 137 in the placebo group had died. Therefore the study claimed that AZT can "decrease mortality";

(b) T-cell counts first increased from 4–8 weeks and then declined to pretreatment levels within 4 months;

(c) the lymphocyte count decreased over 50% in 34% of the AZT recipients but in only 6% of the control group;

(d) 66 in the AZT group suffered from severe nausea, compared to only 25 in the control group;

(e) muscle atrophy was observed in 11 AZT recipients but in only 3 from the control group. Yet, the primary claim of the study, "decreased mortality" from AZT is not realistic if one considers that 30 out of the 145 in the AZT-group depended on multiple transfusions to survive

anemia, compared to only 5 out of the 137 in the placebo group. Thus the number of subjects in the AZT-group who would have died from severe anemia if untreated was larger, i.e. 30, than the AIDS deaths and anemias of the control group combined, namely 19+ 5. The "decreased mortality"-claim is further compromised by numerous "concomitant medications" other than transfusions for AZT-specific diseases and failure to match the AZT and placebo groups for the cumulative effects of prior and parallel recreational drug use. In addition some of the AZT-specific AIDS diseases observed in the placebo group appear to be due to patient-initiated "drug sharing" between AZT and placebo recipients (Lauritsen, 1990; Duesberg, 1992d; Freestone, 1992) and falsification of the case report forms (Lauritsen, 1992).

Moreover the low mortality of 0.7% (1/145) claimed by the licensing study for the first 4 months on AZT could not be extended in a follow-up study which found the "survival benefits" of AZT rapidly declining after the original 4 month period. By 18 months 32% of the original AZT group had died and 35% of the former control group, which by then had also received AZT for 12 months (Fischl *et al.,* 1989).

Since the original study considered AZT effective in decreasing AIDS mortality, subsequent placebo-controlled studies were deemed unethical. But the low mortality claimed by the licensing study has not been confirmed by later studies, which observed mortalities of 12–72% within 9–18 months (see items (3) to (6) below). In addition, a CDC study has recently reported a mortality of 82% in a cohort of 55 AIDS patients that had been on AZT for up to 4 years (Centers for Disease Control, 1991)—hardly recommending AZT as an AIDS therapy.

The brief transient gains of T-cells observed upon AZT treatment by the licensing study may reflect compensatory hemopoiesis, random killing of pathogenic parasites (Elwell *et al.,* 1987) and the influence of concomitant medication, including multiple transfusions (Richman *et al.,* 1989). Indeed the study concluded, based on the "hematological toxicity" described above, that "... the initial beneficial immunological effects of AZT may not be sustained" (Richman *et al.,* 1987). A French study confirms "... the decrease of cell counts below the initial value after a few months of AZT suggests that this drug might be toxic to cells" (see item (3) below) (Dournon *et al.,* 1988). And a recent Amer-

ican study also confirms "... no effects on rates of progression to lower CD4 + lymphocyte counts in (6 month) transition intervals" (Section 4.3.3) (Graham et a]., 1991). Moreover, the manufacturer states, "A modest increase in mean CD4 (T4) counts was seen in the zidovudine group but the significance of this finding is unclear as the CD4 (T4) counts declined again in some patients" (Medical Economics Data, 1992).

(2) In view of the reported success of AZT as AIDS therapy, the drug was also tested for licensing as AIDS prophylaxis by much of the same team, including Fischl, Richman and Volberding, and again with support from the manufacturer Burroughs Wellcome (Volberding *et al.,* 1990). The study treated AIDS-free, HIV-positive 25- to 45-year-old male homosexuals and intravenous drug users with "fewer than 500 T-cells" for one year either with AZT or with a placebo. The expected annual AIDS risk for intravenous drug users and male homosexual risk groups is about 4–6% per year without AZT (Section 3.4.4.4).

The study reports AIDS diseases in: (1) 11 out of 453 on 500 mg AZT per day, (2) 14 out of 457 on 1500 mg AZT per day and (3) 33 out of 428 on a placebo (Volberding et a]., 1990). Thus the AZT-groups appeared to do better than expected and the placebo group did as expected. Therefore it was claimed that AZT prevents AIDS.

However, the price for the presumed savings of 22 (33–11) and 19 (33–14) AIDS cases with AZT, compared to the placebo group, was high because 19 AZT-specific cases of potentially fatal anemia, neutropenia and severe nausea appeared in the 500 mg AZT-group, and 72 such cases, including 29 anemias requiring life-saving blood transfusions, appeared in the 1500 mg AZT-group. This indicates cytocidal effects of AZT on hemopoiesis and on the intestines. Although the AZT-specific diseases were not diagnosed as AIDS, neutropenia generates immunodeficiency (Walton *et al.,* 1986) and thus AIDS. If these AZT-specific cases were included in the calculation of benefits from AZT compared to the placebo group, the 500 mg-group no longer benefited and the 1500 mg-group tripled its disease risk.

The study was further compromised by its failure to match the treatment groups for their cumulative recreational drug use prior to and during the study and for the many compensatory treatments for the

AZT-specific diseases of the subjects analyzed. The fact that 8 cases in the control group but only 3 and 1 in the 500 mg and 1500 mg-AZT groups developed AIDS cancers suggests that the control group could have been exposed to higher recreational drug doses.

Since the licensing study considered AZT effective in preventing AIDS, subsequent controlled trials were deemed unethical. However, several subsequent studies cast further doubt on the claim that AZT is a useful AIDS prophylactic. One study reported that persons with "early" AIDS, i.e. AIDS-free persons at risk for AIDS, died at the same rate of 12–14% as AIDS controls and that 82% developed leukopenia within less than a year (see item 6 below) (Hamilton *et al.,* 1992). Another study described "no effects on rates of progression to lower CD4+ lymphocytes . . ." recorded within 6 month periods in over 1200 AIDS-free men on AZT (Section 4.3.3) (Graham *et al.,* 1991). A third study reported that 26 out of 127 HIV-positive, AIDS-free homosexuals had discontinued an unreported dose of AZT within less than 6 months, most because of severe toxicity (Section 4.3.3) (Holmberg *et al.,* 1992). In view of these and other data, it is surprising that a loss of T-cells was not noted in the licensing study (Kolata, 1987).

(3) A French study investigated the effects of AZT on 365 AIDS patients. The patients included 72% male homosexuals and 11% intravenous drug users with a median age of 36 years and with opportunistic infections and Kaposi's sarcoma. The study, the largest of its kind, observed new AIDS diseases, including leukopenia, in over 40% and death in 20% within 9 months on AZT (Dournon *et al.,* 1988). The AIDS diseases of 30% worsened during AZT treatment. The study reported no therapeutic benefits 6 months after initiating AZT therapy. The authors concluded: "... the rationale for adhering to high-dose regimens of AZT, which in many instances leads to toxicity and interruption of treatment, seems questionable."

(4) A Dutch study treating 91 male AIDS patients, averaging 39 years, after 67 weeks on AZT, observed mortality in 72% and AZT-specific myelotoxicity, requiring on average 5 blood transfusions, in 57%. About 34% of the myelotoxicity manifested in anemia and 20% in leukopenia. The authors concluded that "the majority of patients ... cannot be maintained on these (AZT) regimens, most commonly due

to the development of hematological toxicity" (van Leeuwen *et al.*, 1990).

(5) An Australian study involving 308 homosexual and bisexual men with Kaposi's sarcoma, lymphoma and opportunistic infections and a median age of 36 years, reported 30% mortality within 1–1.5 years on AZT. In addition one or more new AIDS diseases, including pneumonia, candidiasis, fever, night sweats and diarrhea were observed in 172 (56%) within one year (Swanson *et al.*, 1990). Moreover, 50% needed at least one blood transfusion and 29% needed multiple blood transfusions to survive AZT treatment. Yet the authors concluded that the "risk:benefit ratio (is) advantageous to AIDS patients" (Swanson *et al.*, 1990).

(6) A comparison of the effects of indefinite AZT treatment on 170 HIV-positive AIDS-free persons with "early" AIDS to 168 with "late" AIDS indicated that the mortality was the same in both groups, i.e. 12–14% per 1–1.5 years (Hamilton *et al.*, 1992). The median age of the AZT recipients was 40 years; 63% were male homosexuals and 25% were intravenous drug users. AZT-specific diseases were observed in most "early AIDS" cases, i.e. leukopenia in 82%, severe leukopenia in 14%, anemia in 20%, severe anemia requiring transfusions in 5%, nausea in 40% and skin rashes in 47%. This indicates directly that AZT is toxic for AIDS-free HIV carriers, and that AZT toxicity is sufficiently dominant over other AIDS causes that it accelerates the progression to death of AIDS-free HIV carriers to the same rate that is observed in late AIDS patients (Duesberg, 1992d). The authors concluded that AZT, contrary to the Wellcome-sponsored study from 1987 conducted for licensing AZT, does not extend life.

(7) The annual lymphoma incidence of AZT-treated AIDS patients, with Kaposi's sarcoma, pneumonia and wasting disease, was reported to be 9% by the National Cancer Institute and was calculated to be 50% over three years (Pluda *et al.*, 1990). The estimate of the 3-year incidence of lymphoma from this study was recently revised down to 31% (Yarchoan *et al.*, 1991). An independent study observed in a group of 346 AIDS patients in London, most of whom were on AZT, "during the past three years a progressive increase in the number of patients dying from lymphoma, ..." to a current total of 16% in 1991 (Peters

et al., 1991). And a CDC study reported a 15% lymphoma incidence during 24 months on AZT (Centers for Disease Control, 1991).

The lymphoma incidence of untreated, HIV-positive AIDS risk groups is 0.3% per year, derived from the putative average progression rate of 10 years from HIV to AIDS (Moss *et al.,* 1988; Lemp *et al.,* 1990; Duesberg, 1991a) and the 3% incidence of lymphoma in AIDS patients (Centers for Disease Control, 1992b). Therefore, the annual lymphoma risk of AZT recipients is about 30 times higher than that of untreated HIV-positive counterparts. It appears that the chronic levels of the mutagenic AZT, at 20–60 μM (500–1500 mg/person/day), were responsible for the lymphomas (Section 4.6.2).

An alternative interpretation suggests that AZT had prolonged life sufficiently to allow HIV to induce the lymphomas directly or via immunodeficiency (Pluda *et al.,* 1990; Centers for Disease Control, 1991). However, this interpretation is flawed for several reasons: (1) Cancers, including malignant lymphomas, are not consequences of a defective immune system (Section 3.5.8). (2) There is as yet only a model for how HIV, the presumed killer of T-lymphocytes, could also cause cancer (Section 3.5.14) (Gallo, 1990). (3) AZT-induced lymphomas lack HIV-specific markers (McDunn *et al.,* 1991). (4) Several studies indicate that AZT does not prolong life (see above) (Dournon *et al.,* 1988; van Leeuwen *et al.,* 1990; Hamilton *et al.,* 1992; Kolata, 1992).

(8) Ten out of 11 HIV antibody-positive, AZT-treated AIDS patients recovered cellular immunity after discontinuing AZT in favor of an experimental HIV vaccine (Scolaro *et al.,* 1991). The vaccine consisted of an HIV strain that was presumed to be harmless, because it had been isolated from a healthy carrier who had been infected by the virus for at least 10 years. Since there was no evidence that the hypothetical vaccine strain differed from that by which the patients were already naturally vaccinated, the only relevant difference between the patients before and during the vaccine trial was the termination of their AZT treatment. It follows that AZT treatment is at least a necessary, if not a sufficient, cause of immunodeficiency in HIV-positives.

(9) Four out of 5 AZT-treated AIDS patients recovered from myopathy two weeks after discontinuing AZT; two redeveloped myopathy on

renewed AZT treatment (Till and MacDonnell, 1990), indicating that AZT is at least necessary for myopathy in HIV-positives.

(10) Four patients with pneumonia developed severe pancytopenia and bone marrow aplasia 12 weeks after the initiation of AZT therapy. Three out of 4 recovered within 4–5 weeks after AZT was discontinued (Gill *et al.,* 1987), indicating that AZT is necessary for pancytopenia in HIV-positives.

4.5. Drug Use Sufficient for AIDS Indicator Diseases in the Absence of HIV

Studies demonstrating AIDS-defining diseases in drug users in the absence of HIV are chronologically and geographically censored by the virus-AIDS hypothesis. Before the general acceptance of this hypothesis in the U.S., there were numerous American studies blaming AIDS on recreational drugs, but afterwards there was but one American report describing HIV-free Kaposi's sarcomas in homosexuals who had used such drugs, and only a few American and some European studies describing AIDS-defining diseases in HIV-free intravenous drug users (see below).

If HIV were necessary for AIDS among drug users, only HIV-positive drug users should develop AIDS. However, there is not even one controlled study showing that among matched drug users only HIV-positives get AIDS. On the contrary, such studies all indicate that drugs are sufficient to cause AIDS.

4.5.1. *Drugs Used for Sexual Activities Sufficient for AIDS Diseases*

(1) The first five AIDS cases, diagnosed in 1981 before HIV was known, were male homosexuals who had all consumed nitrite inhalants and presented with *Pneumocystis* pneumonia and cytomegalovirus infection (Gottlieb *et al.,* 1981).

(2) In 1985 and again in 1988 Haverkos analyzed the AIDS risks of 87 male homosexual AIDS patients with Kaposi's sarcoma (47), Kaposi's sarcoma plus pneumonia (20) and pneumonia only (20) (Haverkos *et al.,* 1985; Haverkos, 1988b). All men had used several sexual stimulants, 98% had used nitrites. Those with Kaposi's sarcomas reported double

the amount of sexual partners and 4.4-times more receptive anal intercourse than those with only pneumonia. The median number of sexual partners in the year prior to the illness was 120 for those with Kaposi's and 22 for those with pneumonia only. The Kaposi's cases reported 6-times more amylnitrite and ethylchloride use, 4-times more barbiturate use, and twice the methaqualone, lysergic acid and cocaine use than those with pneumonia only. Since no statistically significant differences were found for sexually transmitted diseases among the patients, the authors concluded that the drugs had caused Kaposi's sarcoma.

Although the data for Haverkos' analysis had been collected before HIV was declared the cause of AIDS, Haverkos' conclusion is valid. This is because (1) all patients had AIDS but only the heavy drug users had Kaposi's sarcoma in addition to immunodeficiency and because (2) not all can be assumed to be infected by HIV because transmission depends on an average of 1000 contacts (Section 3.5.2). Indeed, HIV was found in only 24% (Deininger *et al.,* 1990), 31% (van Griensven *et al.,* 1990), 43% (Graham *et al.,* 1991; Seage *et al.,* 1992), 48% (Winkelstein *et al.,* 1987), 49% (Lemp *et al.,* 1990), 56% (Marion *et al.,* 1989) and 67% (Darrow *et al.,* 1987) of cohorts of homosexuals at risk for AIDS in Berlin, Amsterdam, Chicago-Washington DC-Los Angeles-Pittsburgh, Boston, San Francisco and Canada that were similar to those described by Haverkos.

(3) A 4.5 year tracking study of 42 homosexual men with lymphadenopathy but not AIDS reported that 8 had developed AIDS within 2.5 years (Mathur-Wagh *et al.,* 1984) and 12 within 4.5 years of observation (Mathur-Wagh *et al.,* 1985). All of these men had used nitrite inhalants and other recreational drugs including amphetamines and cocaine, but they were not tested for HIV. The authors concluded that "a history of heavy or moderate use of nitrite inhalant before study entry was predictive of ultimate progression to AIDS" (Mathur-Wagh *et al.,* 1984).

(4) Before HIV was known, three controlled studies compared 20 homosexual AIDS patients to 40 AIDS-free controls (Marmor *et al.,* 1982), 50 patients to 120 controls (Jaffe *et al.,* 1983b) and 31 patients to 29 controls (Newell *et al.,* 1985a) to determine AIDS risk factors. Each study reported that multiple "street drugs" were used as sexual stimu-

lants. And each study concluded that the "lifetime use of nitrites" (Jaffe *et al.*, 1983b) were 94% to 100%-consistent risk factors for AIDS (Newell *et al.*, 1985a).

(5) Early CDC data indicate that 86% of male homosexuals with AIDS had used oral drugs at least once a week and 97% occasionally (Centers for Disease Control, 1982; Haverkos, 1988b). The National Institute on Drug Abuse reports correlations from 69% (Lange *et al.*, 1988) to virtually 100% (Haverkos, 1988a; Newell *et al.*, 1988) between nitrite inhalants and other drugs and subsequent Kaposi's sarcoma and pneumonia.

(6) A 27- to 58-fold higher consumption of nitrites by male homosexuals compared to heterosexuals and lesbians (Lesbian and Gay Substance Abuse Planning Group, 1991 a,b) correlates with a 20-fold higher incidence of Kaposi's sarcoma (Selik *et al.*, 1987; Beral *et al.*, 1990) and a higher incidence of all other AIDS diseases in male homosexuals compared to most other risk groups (Tables 1 and 2).

(7) During the last 6–8 years the use of nitrite inhalants among male homosexuals decreased, e.g. from 58% in 1984 to 27% in 1991 in San Francisco (Lesbian and Gay Substance Abuse Planning Group, 1991b). In parallel, the incidence of Kaposi's sarcoma among American AIDS patients decreased from a high of 50% in 1981 (Haverkos, 1988b), to 37% in 1983 (Jaffe *et al.*, 1983a), to a low of 10% in 1991 (Centers for Disease Control, 1992b). It follows that the incidence of Kaposi's sarcoma is proportional to the number of nitrite users.

(8) After the discovery of HIV, 5 out of 6 HIV-free male homosexuals from New York with Kaposi's sarcoma have reported the use of nitrite inhalants (Friedman-Kien *et al.*, 1990). Some of these men had no immunodeficiency. Soon after another six cases of HIV-free Kaposi's sarcoma were reported in a "high risk population" from New York (Safai *et al.*, 1991). This indicates directly that HIV is not necessary and suggests that drugs are sufficient for AIDS.

(9) A 44-year-old, HIV-free homosexual man from Germany developed Kaposi's sarcoma and had a T4 to T8-cell ratio of only 1.2. The man "had used nitrite inhalants for about 10 years," but had no apparent immunodeficiency (Marquart *et al.*, 1991). Likewise, Kaposi's sarcoma was diagnosed in a 40-year-old, promiscuous HIV-free homosexual

from England who admitted "frequent use of amyl nitrite." The patient was otherwise symptom-free with a normal T4/T8 cell ratio (Archer *et al.,* 1989). In 1981 an English male homosexual with a "history of amyl-nitrite inhalation," hepatitis B, gonorrhea and syphilis was also diagnosed with Kaposi's sarcoma. In 1984 he was found to be free of HIV, but in 1986 he became antibody-positive (Lowdell and Glaser, 1989).

(10) A prospective study from Canada identified immunodeficiency in 33 out of 166 HIV-free homosexual men (Marion *et al.,* 1989). The study did not mention drug consumption, but a later report on homosexual men with AIDS from the same cohort documented that all had been using either more or less than 20 "hits" of nitrites per month (Section 4.4) (Archibald *et al.,* 1992). Thus nitrites and possibly other drugs were sufficient for immunodeficiency.

Likewise, Lang, *et al.* (1989) described a steady decline of T4-cells in 37 homosexual men in San Francisco from 1200 per μL prior to HIV infection to 600 or less at the time of infection. Although recreational drug use and AZT were not mentioned, other studies of the same cohort of homosexual men from San Francisco described extensive use of recreational drugs (Section 4.3.2) (Darrow *et al.,* 1987; Moss, 1987) and AZT (Lang *et al.,* 1991).

4.5.2. *Long-term Intravenous Drug Use Sufficient for AIDS-defining Diseases*

(1) Among intravenous drug users in New York representing a "spectrum of HIV-related diseases," HIV was observed in only 22 out of 50 pneumonia deaths, 7 out of 22 endocarditis deaths, and 11 out of 16 tuberculosis deaths (Stoneburner *et al.,* 1988).

(2) Pneumonia was diagnosed in 6 out of 289 HIV-free and in 14 out of 144 HIV-positive intravenous drug users in New York (Selwyn *et al.,* 1988).

(3) Among 54 prisoners with tuberculosis in New York state, 47 were street-drug users, but only 24 were infected with HIV (Braun *et al.,* 1989).

(4) In a group of 21 long-term heroin addicts, the ratio of helper to suppressor T-cells declined during 13 years from a normal of 2 to less

than 1, which is typical of AIDS (Centers for Disease Control, 1987; Institute of Medicine, 1988), but only 2 of the 21 were infected by HIV (Donahoe *et al.,* 1987).

(5) Thrombocytopenia and immunodeficiency were diagnosed in 15 intravenous drug users on average 10 years after they became addicted, but 2 were not infected with HIV (Savona *et al.,* 1985).

(6) The annual mortality of 108 HIV-free Swedish heroin addicts was similar to that of 39 HIV-positive addicts, i.e. 3–5%, over several years (Annell *et al.,* 1991).

(7) A survey of over a thousand intravenous drug addicts from Germany reported that the percentage of HIV-positives among drug deaths (10%) was exactly the same as that of HIV-positives among living intravenous drug users (Puschel and Mohsenian, 1991). Another study from Berlin also reported that the percentage of HIV-positives among intravenous drug deaths was essentially the same as that among living intravenous drug users, i.e. 20–30% (Bschor *et al.,* 1991). This indicates that drugs are sufficient for and that HIV does not contribute to AIDS-defining diseases and deaths of drug addicts.

(8) In 1989, the annual mortality of 197 HIV-positive, parenteral drug users from Amsterdam with an average age of 29 years was 4% and that of 193 age-matched HIV-negatives was 3% (Mientjes *et al.,* 1992). The annual incidence of pneumonia was 29% in the HIV-positives and 9% in the negatives. Clearly, a 3-fold higher morbidity is intrinsically inconsistent with a near identical mortality. However, the slightly higher mortality of HIV-positives is compatible with the fact that the positives had injected more drugs for a longer time, e.g. 84% of the positives vs 64% of the negatives had injected over the last 5 years, 85% vs 72% over the last 6 months and 59% vs 50% had injected heroin and cocaine.

(9) Lymphocyte reactivity and abundance were depressed by the absolute number of injections of drugs not only in 111 HIV-positive, but also in 210 HIV-free drug users from Holland (Mientjes *et al.,* 1991).

(10) The same lymphadenopathy, weight loss, fever, night sweats, diarrhea and mouth infections were observed in 49 out of 82 HIV-free, and in 89 out of 136 HIV-positive, long-term intravenous drug users in New York (Des Jarlais *et al.,* 1988).

(11) Among intravenous drug users in France, lymphadenopathy was observed in 41 and an over 10% weight loss in 15 out of 69 HIV-positives, and in 12 and 8, respectively, out of 44 HIV-negatives (Espinoza *et al.,* 1987). The French group had used drugs for an average of 5 years, but the HIV-positives had injected drugs about 50% longer than the negatives.

(12) In a group of 510 HIV-positive intravenous drug users in Baltimore, 29% reported one and 19% reported two or more AIDS-defining diseases. In a control group of 160 HIV-negative intravenous drug users matched with the HIV-positives for "current drug use," again 29% reported one and 13% reported two or more AIDS-defining diseases (Munoz *et al.,* 1992).

Nevertheless, the average T-cell count of HIV-negatives was about 2-times higher than that of HIV-positives (Munoz *et al.,* 1992). As in the above French study (Espinoza *et al.,* 1987), this appears to reflect a higher lifetime dose of drugs, because HIV is a marker for the duration and extent of drug consumption (Sections 3.4.3, 4.4 and 5).

(13) Among 97 intravenous drug users in New York with active tuberculosis, 88 were HIV-positive and 9 were HIV-negative; and among 6 "crack" (cocaine) smokers with tuberculosis, 3 were HIV-negative and 3 were positive (Brudney and Dobkin, 1991).

(14) The mental development and psychomotor indices of 8 HIV-infected and 6 uninfected infants were observed from 6–21 months of age. The mothers of each group were HIV-positive and had used intravenous drugs and alcohol during pregnancy (Koch, 1990; Koch *et al.,* 1990; T. Koch, R. Jeremy, E. Lewis, P. Weintrub, C. Rumsey and M. Cowan, unpublished data). The median indices of both groups were significantly below average, e.g. 80/100 mental development and 85/100 psychomotor units. The uninfected infants remained on average about 5/100 units higher. A control group of 5 infants, born to HIV-negative mothers who had also used intravenous drugs and alcohol during pregnancy, also had subnormal indices averaging about 95/100 for both criteria.

The degree of neurological retardation of the infants correlated directly with maternal drug consumption: 80% of the mothers of infected infants were "heavy" and 10% occasional parenteral cocaine users and

33% were "heavy" and 33% occasional alcohol users during pregnancy; 45% of the mothers of uninfected infants were "heavy" and 30% occasional parenteral cocaine users and 35% were "heavy" and 30% occasional alcohol users; and 21% of the HIV-free mothers were "heavy' and 58% occasional parenteral cocaine users and 12% were "heavy" and 44% occasional alcohol users. In addition 66% of the HIV-positive and 63% of the negative mothers reported the use of opiates during pregnancy (T. Koch, R. Jeremy, E. Lewis, P. Weintrub, C. Rumsey and M. Cowan, unpublished data).

(15) The psychomotor indices of infants "exposed to substance abuse in utero" were "significantly" lower than those of controls, "independent of HIV status." Their mothers were all drug users but differed with regard to drug use during pregnancy. The mean indices of 70 children exposed during pregnancy were 99 and those of 25 controls were 109. Thus maternal drug use during pregnancy impairs children independent of HIV (Aylward *et al.,* 1992).

The same study also reports a "significant difference" based on the HIV status of these children. The mean scores of 12 HIV-positives was 88 and that of 75 negatives was 102. But the study did not break down the scores of the HIV-positive infants based on "exposure to substance abuse in utero." Indeed, the scores of 4 of the 12 HIV-infected infants were "above average," i.e. 100–114, and 4 of the 12 mothers did not inject drugs during pregnancy.

(16) Ten HIV-free infants born to intravenous drug-addicted mothers had the following AIDS-defining diseases, "failure to thrive, persistent generalized lymphadenopathy, persistent oral candidiasis, and developmental delay . . ." (Rogers *et al.,* 1989).

(17) One HIV-positive and 18 HIV-free infants born to intravenous drug-addicted mothers had only half as many leukocytes at birth than normal controls. At 12 months after birth, the capacity of their lymphocytes to proliferate was 50–70% lower than that of lymphocytes from normal controls (Culver *et al.,* 1987).

(18) Two studies to test the role of HIV on neurological function confirm the drug-AIDS hypothesis indirectly and directly. The first of these, which excluded users of psychoactive drugs, found that neuropsychometric functions of 50 HIV-negative homosexuals were the

same as those of 33 HIV-positives (Clifford *et al.,* 1990). Another study of intravenous drug users on methadone found that neither the drug-impaired neuropsychological functions of 137 HIV-negatives nor those of 83 HIV-positives were deteriorating over 7.4 months (McKegney *et al.,* 1990). However, the study notes that the functions of HIV-positives were lower than those of HIV-negatives because "a greater number of injections per month, more frequent use of cocaine ... were strongly associated with HIV seropositivity."

Thus, a critical lifetime dosage of drugs appears necessary in HIV-positives and sufficient in HIV-negatives to induce AIDS-indicator and other diseases.

4.6. Toxic Effects of Drugs Used By AIDS Patients

4.6.1. *Toxicity of Recreational Drugs*

From as early as 1909 (Achard *et al.,* 1909) evidence has accumulated that long-term consumption of psychoactive drugs leads to immune suppression and clinical abnormalities similar to AIDS, including lymphopenia, lymphadenopathy, fever, weight loss, septicemia, increased susceptibility to infections and profound neurological disorders (Terry and Pellens, 1928; Briggs *et al.,* 1967; Dismukes *et al.,* 1968; Sapira, 1968; Harris and Garret, 1972; Geller and Stimmel, 1973; Brown *et al.,* 1974; Louria, 1974; McDonough *et al.,* 1980; Cox *et al.,* 1983; Kozel and Adams, 1986; Selwyn *et al.,* 1989; Turner *et al.,* 1989; Kreek, 1991; Pillai *et al.,* 1991; Bryant *et al.,* 1992). Since the early 1980s, when T-cell ratios became measureable, low T4 to T8-cell ratios averaging 1 or less were reported in addicts who had injected drugs for an average of 10 years (Layon *et al.,* 1984).

Intravenous drugs can be toxic directly and indirectly. Indirect toxicity can be due to malnutrition, because of the enormous expense of illicit drugs, or to septicemia because most illicit drugs are not sterile (Cox *et al.,* 1983; Stoneburner *et al.,* 1988; Lerner, 1989; Buehler *et al.,* 1990; Pillai *et al.,* 1991; Luca-Moretti, 1992). Typically, intravenous drug users develop pneumonia, tuberculosis, endocarditis and wasting disease (Layon *et al.,* 1984; Stoneburner *et al.,* 1988; Braun *et al.,* 1989; Brudney and Dobkin, 1991). Oral consumption of cocaine and other psychoactive drugs has been reported to cause pneumonitis, bronchi-

tis, edema (Ettinger and Albin, 1989) and tuberculosis (Brudney and Dobkin, 1991). Physiological and neurological deficiencies, including mental retardation, are observed in children born to mothers addicted to cocaine and other narcotic drugs (Fricker and Segal, 1978; Lifschitz *et al.,* 1983; Alroomi *et al.,* 1988; Blanche *et al.,* 1989; Root-Bernstein, 1990a; Toufexis, 1991; Finnegan *et al.,* 1992; Luca-Moretti, 1992). According to the National Institute on Drug Abuse, "Cocaine is currently the drug of greatest national concern, from a public health point of view . . ." (Schuster, 1984).

Because inhalation of alkylnitrites relaxes smooth muscles, it has been prescribed since 1867 against angina pectoris and heart pain at doses of 0.2 mL (Cox *et al.,* 1983; Newell *et al.,* 1985b; Shorter, 1987; Seage *et al.,* 1992). No AIDS defining diseases have been reported at these doses in patients with those relatively severe, terminal cardiovascular diseases (Cox *et al.,* 1983; Shorter, 1987), possibly because they did not live long enough to develop them. However, immediate and late toxicities have been observed in recreational users who have inhaled millilitres of nitrite inhalants (Newell *et al.,* 1985b; Schwartz, 1988). Alkylnitrites are directly toxic as they are rapidly hydrolyzed *in vivo* to yield nitrite ions, which react with all biological macromolecules (Osterloh and Olson, 1986; Maikel, 1988). Addicts with 0.5 mM nitrite derivatives and 70% methemoglobin in blood have been recorded (Osterloh and Olson, 1986). Toxicity for the immune system, the central nervous system, the hematologic system and pulmonary organs has been observed after short exposure to nitrites in humans and in animals (Newell *et al.,* 1985b, 1988; Wood, 1988). In 1982, Goedert *et al.* found that the helper to suppressor T-cell ratio was lower in homosexual men who had used volatile nitrite inhalants than among nonusers. Further, alkylnitrites were shown to be both mutagenic and carcinogenic in animals (Jorgensen and Lawesson, 1982; Hersh *et al.,* 1983; Mirvish *et al.,* 1988; Newell *et al.,* 1985b, 1988).

By comparing the AIDS risk factors of 31 homosexual men with AIDS to 29 without, Newell *et al.* and others determined a direct "dose-response gradient": the higher the nitrite usage the greater the risk for AIDS (Marmor *et al.,* 1982; Newell *et al.,* 1985a; Haverkos and Dougherty, 1988) and deduced a 7–10 year lag time between chronic

consumption and Kaposi's sarcoma (Newell *et al.,* 1985b). Likewise, a French study of homosexual men with and without AIDS who had inhaled nitrites documents that "cases were significantly older (approximately 10 years) than controls" (Section 4.3.2) (Messiah *et al.,* 1988). Also, a German study observed Kaposi's sarcoma in an HIV-free man after he had inhaled nitrites for 10 years (Section 4.5.1) (Marquart *et al.,* 1991). These studies indicate that about 10 years of nitrite inhalation are necessary to convert "controls" to "cases."

In view of this several investigators have proposed that nitrite inhalants cause pulmonary and skin Kaposi's sarcoma and pneumonia by direct toxicity on the skin and oral mucosa (Centers for Disease Control, 1982; Marmor *et al.,* 1982; Haverkos *et al.,* 1985; Mathur-Wagh *et al.,* 1985; Newell *et al.,* 1985a; Lauritsen and Wilson, 1986; Haverkos, 1990). Because of their toxicity a prescription requirement was instated for the sale of nitrite inhalants by the Food and Drug Administration in 1969 (Newell *et al.,* 1985b) and because of an "AIDS link" (Cox, 1986) the sale of nitrites was banned by the U.S. Congress in 1988 (Public Law 100–690) (Haverkos, 1990) and by the "Crime Control Act of 1990" (January 23, 1990).

Although a necessary role of HIV in HIV-positive AIDS patients cannot be excluded, this role would be stoichiometrically insignificant compared to that of the drugs. This is because drug molecules exceed HIV molecules by over 13 orders of magnitude. Given about 10^{10} leukocytes per human, of which at most 1 in 10^4 are actively infected (Section 3.5.1), and that each actively infected cell makes about 100 viral RNAs per day, there are only 10^6 T-cells with 10^2 HIV RNAs in an HIV-positive person. By contrast, 1 mL (or 0.01 mol) of amyl nitrite with a molecular weight of 120 contains 6×10^{21} molecules, or 6×10^7 nitrite molecules, for every one of the 10^{14} cells in the human body. Thus, based on molecular representation, HIV's role in AIDS, if it existed, would have to be catalytic in comparison with that of drugs.

Pillai, Nair and Watson conclude from a recent review on the role of recreational drugs in AIDS: "Circumstantial and direct evidence suggesting a possible role for drug ... induced immunosuppression appears overwhelming. What is required now is better and more accurate detection of substance abuse, a direct elucidation of the immune and related

mechanisms involved, and appropriate techniques to analyze it" (Pillai *et al.,* 1991).

4.6.2. *Toxicity of AZT*

Since 1987 AZT has been used as an anti-HIV agent (Section 4.3.3) based on two placebo-controlled studies reporting therapeutic and prophylactic benefits (Section 4.4.2). However, AZT was originally developed in the 1960s for cancer chemotherapy to kill human cells via termination of DNA synthesis (Cohen, 1987; Yarchoan and Broder, 1987a; Yarchoan *et al.,* 1991). The primary AZT metabolites are 3'-termini of DNA which are cell-killing, 3'-amino-dT which is more toxic than AZT, and 5'-O-glucuronide which is excreted (Cretton *et al.,* 1991). As a chain terminator of DNA synthesis, AZT is toxic to all cells engaged in DNA synthesis. AZT toxicity varies a great deal with the subject treated due to differences in its uptake and in its cellular metabolism (Chernov, 1986; Elwell *et al.,* 1987; Yarchoan and Broder, 1987b; Smothers, 1991; Yarchoan *et al.,* 1991).

AZT is prescribed as AIDS prophylaxis or therapy at 500–1500 mg per day, corresponding to a concentration of 20-60 μmol/L in the patient. Prior to the licensing of AZT, Burroughs Wellcome, the manufacturer of the drug, and the NIH have jointly claimed selective inhibition of HIV by AZT *in vitro* because human lymphoblasts and fibroblasts appeared over 1000-fold more resistant to AZT (inhibited only at 1–3 mM) than was replication of HIV (inhibited at 50–500 nM) (Furman *et al.,* 1986). On this basis they calculated an *in vitro* antiviral therapeutic index of 10^4. This "selective" sensitivity of HIV to AZT was explained in terms of a "selective interaction of AZT with HIV reverse transcriptase" (Furman *et al.,* 1986). Accordingly the manufacturer informs AZT recipients: "The cytotoxicity of zidovudine [AZT] for various cell lines was determined using a cell growth assay ... ID50 values for several human cell lines showed little growth inhibition by zidovudine except at concentrations > 50 μg/mL (≥200 μM) or less." (Medical Economics Data, 1992). Further, it informs them that enterobacteria including *E. coli* are inhibited "by low concentrations of zidovudine [AZT]," between 0.02 and 2 μM AZT, just like HIV (Medical Economics Data, 1992).

However, an independent study showed in 1989 that AZT is about

1000-times (!) more toxic for human T-cells in culture, i.e. at about 1 μM than the study conducted by its manufacturer and the NIH (Avramis *et al.,* 1989). Other studies have also found that AZT inhibits T-cells and other hemopoietic cells *in vitro* at 1–8 μM (Balzarini *et al.,* 1989; Mansuri *et al.,* 1990; Hitchcock, 1991). Since normal deoxynucleotide triphosphates are present in the cell at micromolar concentrations, toxicity of AZT should be expected in the micromolar range. Indeed, when AZT is added at a micromolar concentration to the culture medium, it and its phosphorylated derivatives quickly reach an equivalent or higher concentration in the cell, and thus effectively compete with their natural thymidine counterparts (Avramis *et al.,* 1989; Balzarini *et al.,* 1989; Ho and Hitchcock, 1989; Hitchcock, 1991).

Thus the low cellular toxicity reported by the manufacturer and the NIH for human cells appears erroneous—possibly because "the clinical development of AZT was exceedingly rapid; it was approved for clinical use in the U.S. about 2 years after the first *in vitro* observation of its activity against HIV" (Yarchoan *et al.,* 1991). It follows that AZT does not selectively inhibit viral DNA synthesis and is prescribed at concentrations that exceed 20- to 60-fold the lethal dose for human cells in culture.

In view of its inevitable toxicity, the rationale of using AZT as an anti-HIV drug must be reconsidered and its potential antiviral effect must be weighed against its toxicity.

4.6.2.1. *AZT not a rational anti-HIV drug.* A rational antiviral therapy depends on proof that the targeted virus is the cause of the disease to be treated and that toxicity for the virus outweighs that for the host cell. Such proof cannot be supplied for AZT for the following reasons:

(1) There is no proof that HIV causes AIDS (Section 3.3).

(2) Even if the hypothesis that HIV causes AIDS by killing T-cells were correct, it would be irrational to kill the same infected cells twice, once presumably with HIV and once more with AZT.

(3) Since many healthy persons with antibodies against HIV have equal or even higher percentages of infected T-cells than AIDS patients (Section 3.3), there is no reverse transcription of HIV during progres-

sion to AIDS that could be targeted with AZT. Even if some reverse transcription occurred in antibody-positive persons, AZT could not differentially inhibit viral DNA, because HIV DNA comprises only 9 kb but cell DNA comprises 10^6 kb. Thus cell DNA is a 100,000-fold bigger target for AZT than HIV. And even if AZT showed a 100-fold preference for reverse transcriptase of HIV over cellular DNA polymerase, as has been claimed by the study conducted by Burroughs Wellcome and the NIH (Furman *et al.,* 1986), cell DNA would still be a 1000-fold bigger target for AZT than viral DNA. It follows that cell DNA is the only realistic target of AZT in antibody-positive persons.

(4) Since AZT cannot distinguish infected from uninfected leukocytes and on average less than 1 in 1000 is infected (Section 3.3), AZT must kill at least 1000 leukocytes in AIDS patients and in asymptomatic HIV-carriers to kill just 1 infected cell—a very high toxicity index, even if HIV were the cause of AIDS.

It follows that there is no rational basis for AZT therapy or prophylaxis for AIDS (Duesberg, 1992d).

4.6.2.2. *Toxicity of AZT in AIDS Patients and AIDS-free Persons.* The following AZT-specific diseases have been recorded in AIDS patients, in AIDS-free persons and animals treated with AZT, based on studies listed here (Section 4.4.2) and reviewed elsewhere (Smothers, 1991; Medical Economics Data, 1992):

(1) anemia, neutropenia and leukopenia in 20–80%, with about 30–57% requiring transfusions within several weeks (Gill *et al.,* 1987; Kolata, 1987; Richman *et al.,* 1987; Dournon *et al.,* 1988; Walker *et al.,* 1988; Swanson *et al.,* 1990; van Leeuwen *et al.,* 1990; Smothers, 1991; Hamilton *et al.,* 1992),

(2) severe nausea from intestinal intoxication in up to 45% (Richman *et al.,* 1987; Volberding *et al.,* 1990; Smothers, 1991),

(3) muscle atrophy and polymyositis, due to inhibition of mitochondrial DNA synthesis in 6–8% (Richman *et al.,* 1987; Bessen *et al.,* 1988; Gorard and Guilodd, 1988; Helbert *et al.,* 1988; Dalakas *et al.,* 1990; Till and MacDonnell, 1990; Yarchoan *et al.,* 1991; Hitchcock, 1991),

(4) lymphomas in about 9% within 1 year on AZT (Section 4.4.2),

(5) acute (nonviral) hepatitis (Dubin and Braffman, 1989; Smothers, 1991),

(6) nail dyschromia (Don *et al.,* 1990; Smothers, 1991),

(7) neurological diseases including insomnia, headaches, dementia, mania, Wernicke's encephalopathy, ataxia and seizures (Smothers, 1991), probably due to inhibition of mitochondrial DNA (Hitchcock, 1991),

(8) 12 out of 12 men reported impotence after 1 year on AZT (Callen, 1990),

(9) in addition AZT is carcinogenic in mice, causing vaginal squamous carcinomas (Cohen, 1987; Yarchoan and Broder, 1987a), and it transforms mouse cells *in vitro* as effectively as methylcholanthrene (Chernov, 1986).

Overall AZT is not a rational prophylaxis or a therapy for AIDS and is capable of causing potentially fatal diseases, such as anemia, leukopenia and muscle atrophy. Yet, despite its predictable toxicity, AZT is thought to have serendipitous therapeutic and prophylactic benefits according to those investigators who have studied its effects together with the manufacturer for licensing of the drug (Section 4.4.2) (Fischl *et al.,* 1987; Richman *et al.,* 1987; Volberding *et al.,* 1990). Confronted with the difficulties in rationalizing anti-HIV prophylaxis and therapy with AZT, the Wellcome researcher Freestone cites the Burroughs Wellcome study analyzed above (Section 4.4.2, item 1): "the primary endpoint for the study was death (1 in 145 zidovudine recipients, 19 in 137 placebo recipients . . .)—an end-point little subject to observer error or bias" (Freestone, 1992).

The popularity of AZT as an anti-HIV drug can only be explained by the widespread acceptance of the virus-AIDS hypothesis, the failure to consider the enormous difference between the viral and cellular DNA targets and a general disregard for the long-term toxicity of drugs (Section 6). In the words of the retrovirologist Temin "but the drug generally becomes less effective after six months to a year . . ." (Nelson *et al.,* 1991)—a euphemism for its fatal toxicity by that time. This is a probable reason that AZT was licensed without long-term studies in

animals compatible with human applications and that the need for such studies is neither mentioned nor called for in reviews of its toxic effects in humans (Chernov, 1986; Yarchoan and Broder, 1987b; Smothers, 1991; Yarchoan *et al.,* 1991), although AZT must be the most toxic drug ever approved for indefinite therapy in America. Even the manufacturer acknowledges that "... the drug has been studied for limited periods of time and long term safety and efficacy are not known" (Shenton, 1992) and recommends that "patients should be informed ... that the long-term effects of zidovudine are unknown at this time" (Medical Economics Data, 1992). And after prescribing it for five years, even AIDS "experts" have recently expressed doubts about the "survival benefit" of AZT (Kolata, 1992).

4.7. Drug-AIDS Hypothesis Correctly Predicts the Epidemiology and Heterogeneous Pathology of AIDS

(1) The long-term consumption of drugs, but not the hosting of a latent virus, predicts drug-specific pathogenicity after "long latent periods." These long latent periods of HIV are in reality the lag periods that recreational drugs (Schuster, 1984; Newell *et al.,* 1985b) and frequent transfusions of foreign proteins take to cause AIDS-defining diseases (Section 3.4.4.5). Drugs are molecularly abundant (Section 4.6.1) and biochemically active as long as they are administered and thus cumulatively toxic over time. It is for this reason that it typically takes 5–10 years for recreational drugs, and months for AZT, to cause AIDS-defining and other diseases (Sections 3.1 and 5). But HIV, after a brief period of immunogenicity (Clark *et al.,* 1991; Daar *et al.,* 1991), is chronically dormant and thus molecularly and biochemically irrelevant for the rest of the host's life.

(2) Drugs and other noninfectious agents also exactly predict the epidemiology of AIDS. About 32% of American AIDS patients are confirmed intravenous drug users, 60% appear to use recreational drugs orally, and an unknown but large percentage of people in both behavioral and clinical AIDS risk groups use AZT. Moreover, the consumption of recreational drugs by AIDS patients is probably under-reported because the drugs are illicit, and because medical scientists and support for research are currently heavily biased in favor of viral-AIDS

(Section 6) (Ettinger and Albin, 1989; Lerner, 1989; Duesberg, 1991b). In sum, more than 90% of American AIDS is correlated with drugs. The remainder would reflect the natural background of AIDS-defining diseases in the U.S. (Duesberg, 1992). Indeed, only drug users do not benefit from the ever improving health parameters and increasing life spans of the Western World (Hoffman, 1992; The Software Toolworks World Atlas™, 1992). The widespread use of AZT in hemophiliacs (Section 4.3.3) unfortunately predicts a new increase in their mortality.

The dramatic increase in America in the consumption of all sorts of recreational drugs since the Vietnam War also explains the simultaneous increase of AIDS in intravenous drug users and male homosexuals (Centers for Disease Control, 1992b). AIDS of both risk groups followed closely the above listed drug-use statistics during the last 15 years, with increases in 1987 that corresponded to the expanded AIDS definition (Centers for Disease Control, 1987) and the introduction of AZT treatment. By contrast a sexually transmitted AIDS would have spread much faster among homosexuals than among intravenous drug users (Weyer and Eggers, 1990; Eggers and Weyer, 1991). The apparent exponential spread of AIDS during the period from 1984 to 1987 (Heyward and Curran, 1988; Mann *et al.,* 1988; Weyer and Eggers, 1990) probably reflected an exponential spread of "AIDS testing," which resulted in an exponential spread of AIDS diagnoses for drug diseases (Section 4.2). AIDS testing had increased from 0 in 1984 to 20 million tests per year in 1986 in the U.S. alone (Section 3.6).

(3) The drug hypothesis further predicts that the 50–70% of American and 50–80% of European intravenous drug users who are HIV-free (Stoneburner *et al.,* 1988; Turner *et al.,* 1989; Brenner *et al.,* 1990; U.S. Department of Health and Human Services, 1990; National Commission on AIDS, 1991), and the HIV-free male homosexuals who use sexual stimulants will develop the same diseases as their HIV-positive counterparts—except that their diseases will be diagnosed by their old names. This has been amply confirmed for intravenous drug users (Section 4.5). But since AIDS research became dominated by the virus-hypothesis, only a few studies have published HIV-free homosexual immunodeficiencies and "AIDS cases" (Section 4.5, Note added in proof). Yet more such cases must exist because the CDC allows "pre-

sumptive diagnosis" of HIV disease and only about 50% of all American AIDS cases are confirmed positives (Sections 2.2 and 3.4.1) and because only about 50% of homosexuals from many different cohorts at risk for AIDS are confirmed HIV-positive (Section 4.5.1).

(4) The drug hypothesis also correctly predicts drug-specific AIDS diseases in distinct risk groups due to distinct drugs (Sections 2.1.3, 3.4.5 and 5, Table 2).

4.8. Consequences of the Drug-AIDS Hypothesis: Risk-Specific Preventions and Therapies, but Resentment by the Virus-AIDS Establishment

The drug-AIDS hypothesis predicts that the AIDS diseases of the behavioral AIDS risk groups in the U.S. and Europe can be prevented by stopping the consumption of recreational and anti-HIV drugs, but not by "safe sex" (Institute of Medicine, 1988; Weiss and Jaffe, 1990; Maddox, 1991b) and "clean needles," i.e. sterile injection equipment (National Commission on AIDS, 1991) for toxic and unsterile street drugs. Indeed AIDS has continued to increase in all countries that have promoted safe sex to prevent AIDS for over 5 years now (Centers for Disease Control, 1992b; World Health Organization, 1992a; Anderson and May, 1992). Further, the hypothesis raises the hopes for risk-specific therapies.

According to the drug-AIDS hypothesis, AZT is AIDS by prescription. Screening of blood for antibodies to HIV is superfluous, if not harmful, in view of the anxiety that a positive test generates among the many believers in the virus-AIDS hypothesis (Grimshaw, 1987) and the toxic AZT prophylaxis prescribed to many who test "positive." Eliminating the test would also reduce the cost of the approximately 12 million annual blood donations in the U.S. (Williams *et al.*, 1990) and of examining annually 200,000 recruits and 2 million servicemen for the U.S. Army (Burke *et al.*, 1990) by $12 to $70 each (Irwin Memorial Blood Bank, San Francisco, personal communication).

Further, it would lift travel restrictions for antibody-positives to many countries including the U.S. and China, and would lift quarantine for HIV-positive Cubans, and would acquit all those antibody-positive Americans who are currently imprisoned for having had sex with antibody-negatives, and would grant to HIV "antibody-positives" the same

chances to be admitted to a health insurance program as to those who have only antibodies to other viruses.

Despite its many potential blessings, the drug hypothesis is currently highly unpopular—not because it would be difficult to verify, but because of its consequences for the virus-AIDS establishment (Section 6). The drug hypothesis is very testable epidemiologically and experimentally by studying the effects of the drugs consumed by AIDS patients in animals. Indeed most tests have already been done (Section 4). To disprove this hypothesis it would be necessary to document that an infectious agent exists which—in the absence of AZT (!) causes AIDS diseases above their normal background in the nondrug using population. The medical, ethical and legal consequences of the drug-AIDS hypothesis, should it prevail, have recently been summarized under the title "Duesberg: An enemy of the people?" (Ratner, 1992). Ratner points out that, "The loss of confidence of Americans in their scientists and perhaps, by extension, their physicians, could rival their current disillusionment with politicians" and wonders, "What would happen to the reservoir of good will painstakingly built up for the victims of AIDS?"

5. Drugs and Other Noncontagious Risk Factors Resolve All Paradoxes of the Virus-AIDS Hypothesis

A direct application of the hypothesis that drugs and other noncontagious risk factors cause AIDS proves that it can resolve all paradoxes of the virus-AIDS hypothesis:

(1) It is paradoxical to assume that AIDS is new because HIV is new. HIV is a long-established, perinatally transmitted retrovirus. It just appears new because, being a chronically latent virus, it only became detectable with recently developed technology (Section 3.5.1). Instead drugs are the only new health risks in this era of ever improving health parameters. Thus AIDS is new because the drug epidemic is new.

(2) According to the virus-AIDS hypothesis it is paradoxical that AIDS did not "explode" into the general population as predicted (Institute of Medicine, 1986; Shorter, 1987; Fineberg, 1988; Heyward and Curran, 1988; Blattner, 1991; Mann and the Global AIDS Policy Coali-

tion, 1992). AIDS has remained restricted for over 10 years to only 15,000 annual cases (0.015%) of the over 100 million sexually active heterosexual Americans, and to only 25,000 (0.3%) of the 8 million homosexuals (Centers for Disease Control, 1992b), although venereal diseases (Aral and Holmes, 1991), unwanted pregnancies and births (Hoffman, 1992; The Software Toolworks World Atlas™, 1992) are on the increase in America. (The homosexuals represent about 10% of the adult male population (Turner *et al.,* 1989; Lesbian and Gay Substance Abuse Planning Group, 1991a).) This is because psychoactive drugs and AZT, not HIV, are the causes of AIDS.

(3) The paradox of a virus causing risk group-specific and country-specific AIDS diseases is resolved by distinct nonviral AIDS causes including drugs and other noncontagious pathogens like long-term transfusions and malnutrition (Sections 2.1.3 and 3.4.5, Tables 1 and 2).

(4) The paradox of a male-specific AIDS virus (i.e. 90% of all American and 86% of all European AIDS cases are males), although no AIDS disease is male-specific, is resolved by male-specific behavior and by male genetic disorders. In America and Europe males consume over 75% of all "hard" injected psychoactive drugs (Section 4.3.1), homosexual males are almost exclusive users of oral aphrodisiacs like nitrites (Section 4.3.2) and nearly all hemophiliacs are males.

(5) The paradox of a 10-year-slow AIDS virus, i.e. AIDS occurs only after "latent (!) periods" of HIV that average 10 years in adults and 2 years in babies (Section 2.2), is resolved by the cumulative toxicity of long-term drug use. According to the CDC the "lifetime use" of drugs determines the AIDS risk (Jaffe *et al.,* 1983b). On average 5–10 years elapse in adult drug addicts between the first use of drugs and "acquiring" drug-induced AIDS diseases (Layon *et al.,* 1984; Schuster, 1984; Savona *et al.,* 1985; Donahoe *et al.,* 1987; Espinoza *et al.,* 1987; Weber *et al.,* 1990). The time lag from a nitrite habit to Kaposi's sarcoma has been determined to be 7–10 years (Newell *et al.,* 1985b). Severe T-cell depletion and immunodeficiency is also "acquired" by hemophiliacs on average only after 14–15 years of treatment with blood concentrates (Section 3.4.4.5).

In babies of drug-addicted mothers AIDS appears much sooner than

in adults because of a much lower threshold of the fetus for drug-pathogenicity. This also resolves the secondary paradox of a discrepancy of 8 years between the "latent periods" of HIV in babies and in adults.

(6) It is paradoxical that American teenagers do not get AIDS, although over 70% are sexually active and about 50% are promiscuous (Turner *et al.,* 1989; Burke *et al.,* 1990; Congressional Panel, 1992) and 0.03% to 0.3% carry HIV (Section 3.5.2). The paradox that a sexually transmitted "AIDS virus" would spare American and European teenagers is resolved by the fact that only years of drug consumption, and years of transfusions for hemophilia (Section 3.4.4.5) will cause AIDS—by which time these teenagers are in their twenties.

(7) The apparent paradox that the same virus would at the same time cause two entirely different AIDS epidemics, one in Africa and the other in America and Europe is an artifact of the AIDS definition. Because of the HIV-based AIDS definition, a new drug epidemic in America and Europe and an epidemic of old Africa-specific diseases like fever, diarrhea and tuberculosis (Section 3.4.4.4) were both called AIDS when HIV became detectable. Since HIV is endemic in over 10% of Central Africans, over 10% of their AIDS-defining diseases are now called AIDS (Section 2.2).

6. Why Did AIDS Science Go Wrong?

6.1. The Legacy of the Successful Germ Theory: A Bias Against Noninfectious Pathogens

Unlike any other scientific hypothesis, the virus-AIDS hypothesis became national American dogma before it could be reviewed by the scientific community. It had been announced by the Secretary of Health and Human Services in 1984 before it had been published in the scientific literature. Unlike any other medical hypothesis it captured the world without ever bearing any fruits in terms of public health benefits. From the beginning the hypothesis has absorbed the critical potential of its many followers with the question, whether Montagnier from France or Gallo from the U.S. had won the race in isolating the "AIDS virus" and who owned the lucrative patent rights for the "AIDS test." This

question was so consuming that the presidents of the two countries were called to sign a settlement, and a revisionist paper was published by the opponents describing their fierce controversy as an entente cordiale against the real enemy, the "deadly" AIDS virus (Gallo and Montagnier, 1987). During the 1980s press accounts consistently called HIV "the deadly virus" (Duesberg, 1989c).

Clearly, the enthusiastic acceptance of the virus-AIDS hypothesis was not based on its scientific rigor or its fruits. It was instead grounded on the universal admiration and respect for the germ theory. The germ theory of the late 19th century ended the era of infectious diseases, which now account for less than 1% of all mortality in the Western World (Cairns, 1978). It celebrated its last triumph in the 1950s with the elimination of the polio epidemic by antiviral vaccines.

But the germ theory continues to inspire both scientists and the public to believe that a "good" body can be protected against "evil" microbes. Accordingly, even the greatly feared and highly stigmatizing "AIDS test" for a presumably new, sexually transmitted "AIDS virus" was readily sold to all governments, medical associations and even to the AIDS risk-groups (Section 6.2), despite the absence of convincing evidence for transmissibility. In the words of one observer, "The rationale for such programs is often the historical precedent of syphilis screening," which "never proved to be effective" and led to "toxic treatments with arsenical drugs, assuming the tests were correct . . ." and "deep stigma and disrupted relationships . . . ." "Patients required a painful regimen of injections, sometimes for as long as two years" (Brandt, 1988). Even epidemiologists failed to recognize that AIDS and HIV were only spreading in newly-established behavioral and clinical risk groups and that HIV was a long-established virus in the general populations of many countries (Section 3.5.1). Instead of considering noninfectious causes, they simulated "coagents" (Eggers and Weyer, 1991) and "assortative scenarios" (Anderson and May, 1992) to hide the growing discrepancies between HIV and AIDS and intimidated skeptics with apocalyptic predictions of AIDS pandemics in the general populations of many countries that have raised fears and funds to unprecedented levels (Section 1) (Heyward and Curran, 1988; Mann *et al.,* 1988; Mann and the Global AIDS Policy Coalition, 1992; Anderson and May, 1992).

Even now, in an era free of infectious diseases but full of man-made chemicals, scientists and the public share an unthinking preference for infectious over noninfectious pathogens. Both groups share an obsolete microbophobia but tolerate the use or even indulge in the consumption of numerous recreational and medical drugs. Moreover, progressive scientists and policy makers are not interested in recreational and medical drugs and man-made environmental toxins as causes of diseases, because the mechanisms of pathogenesis are predictable. Further, prevention of drug diseases is scientifically trivial and commercially unattractive.

By contrast, microbial and particularly viral pathogens are scientifically and commercially attractive to scientists. Beginning with Peyton Rous, at least 10 Nobel prizes have been given to virologists in the last 25 years. And many virologists have become successful biotechnologists. For example, a blood test for a virus is good business if the test becomes mandatory for the 12 million annual blood donations in the U.S., e.g. the "AIDS test." The same is true for a vaccine or an antiviral drug that is approved by the Food and Drug Administration.

Thousands of lives have been sacrificed to this bias for infectious theories of disease, even before AIDS appeared. For example, the U.S. Public Health Service insisted for over 10 years in the 1920s that pellagra was infectious, rather than a vitamin B deficiency as had been proposed by Joseph Goldberger (Bailey, 1968). Tertiary syphillis is commonly blamed on treponemes, but is probably due to a combination of treponemes and long-term mercury and arsenic treatments used prior to penicillin, or merely to these treatments alone (Brandt, 1988; Fry, 1989). "Unconventional" viruses were blamed for neurological diseases like Kreutzfeld-Jacob's disease, Alzheimer's disease and kuru (Gajdusek, 1977). The now extinct kuru was probably a genetic disorder that affected just one tribe of natives from New Guinea (Duesberg and Schwartz, 1992). Although a Nobel Prize was given for this theory, the viruses never materialized and an unconventional protein, termed "prion," is now blamed for some of these diseases (Evans, 1989c; Duesberg and Schwartz, 1992). Shortly after this incident, a virus was also blamed for a fatal epidemic of neuropathy, including blinding, that started in the 1960s in Japan, but it turned out later to be caused by the

prescription drug clioquinol (Enteroviofoform, Ciba-Geigy) (Kono, 1975; Shigematsu *et al.,* 1975). In 1976 the CDC blamed an outbreak of pneumonia at a convention of Legionnaires on a "new" microbe, without giving consideration to toxins. Since the "Legionnaire's disease" did not spread after the convention and the "Legionnaires bacillus" proved to be ubiquitous, it was later concluded that "CDC epidemiologists must in the future take toxins into account from the start" (Culliton, 1976). The Legionnaire's disease fiasco is in fact the probable reason that the CDC initially took toxins into account as the cause of AIDS (Oppenheimer, 1992).

The pursuit of harmless viruses as causes of human cancer, supported since 1971 by the Virus-Cancer Program of the National Cancer Institute's War On Cancer, was also inspired by indiscouragable faith in the germ theory (Greenberg, 1986; Duesberg, 1987; Shorter, 1987; Anderson, 1991; Editorial, 1991; Duesberg and Schwartz, 1992). For example, it was claimed in the 1960s that the rare Burkitt's lymphoma was caused by the ubiquitous Epstein-Barr virus, 15 years after infection (Evans, 1989c). But the lymphoma is now accepted to be nonviral and attributed to a chromosome rearrangement (Duesberg and Schwartz, 1992). Further, it was claimed that noncontagious cervical cancer is caused by the widespread herpes virus in the 1970s, and by the widespread papilloma virus in the 1980s—but in each case cancer would occur only 30 to 40 years after infection (Evans, 1989c). Noninfectious causes like chromosome abnormalities, possibly induced by smoking, have since been considered or reconsidered (Duesberg and Schwartz, 1992). Further, ubiquitous hepatitis virus was proposed in the 1960s to cause regional adult hepatomas 50 years (!) after infection (Evans, 1989c). In the 1980s the rare, but widely distributed, human retrovirus HTLV-I was claimed to cause regional adult T-cell leukemias (Blattner, 1990). Yet the leukemias would only appear at advanced age, after "latent periods" of up to 55 years, the age when these "adult" leukemias appear spontaneously (Evans, 1989c; Blattner, 1990; Duesberg and Schwartz, 1992). Although the Virus-Cancer program has generated such academic triumphs as retroviral oncogenes (Duesberg and Vogt, 1970) and reverse transcriptase (Temin and Mitzutani, 1970), it has been a total failure in terms of clinical relevance. Indeed, the pride

of retrovirologists in retrovirus-specific reverse transcription is the probable reason that inhibition of DNA synthesis with AZT is perceived, even now, as a "specific" antiretroviral therapy (Section 4.3.3).

The wishful thinking that viruses cause "slow" diseases and cancers faces four common problems: (1) the diseases or tumors occur on average only decades after infection; (2) the viruses are all inactive, if not defective, during fatal disease or cancer; (3) the "viral" tumors are all clonal, derived from a single cell (with a tumor-specific chromosome abnormality) that had emerged out of billions of identically infected cells of a given carrier; and (4) above all, no human cancers and none of the "slow viral diseases" are contagious (Rowe, 1973; Duesberg and Schwartz, 1992).

Therefore these viruses all fail Koch's postulates, the acid test of the germ theory. And therefore these viruses are all assumed to be very "slow," causing diseases only after long "latent periods" that exceed by decades the short periods of days or weeks that these viruses need to replicate and to become immunogenic. Because of their consistent scarcity, defectiveness and even complete absence from some tumors and slow diseases (Duesberg and Schwartz, 1992), the search for the presumably pathogenic latent viruses has been directed either at antiviral antibodies, i.e. "seroepidemiological evidence" (Blattner *et al.,* 1988), or at artificially amplified viral DNA and RNA (Section 3.3) or at the "activation" of latent viruses, euphemistically called "virus isolation" (Section 2.2).

Accordingly cancer-, AIDS- and other slow-virologists try to discredit Koch's postulates in favor of "modern concepts of causation." For example, Evans states that, "... Koch's postulates, great as they were for years, should be replaced with criteria reflecting modern concepts of causation, epidemiology, and pathogenesis and technical advances" (Evans, 1992). And Blattner, Gallo and Temin point out that Koch's postulates are just a "useful historical reference point" (Blattner *et al.,* 1988), and Weiss and Jaffe find it "bizarre that anyone should demand strict adherence to these unreconstructed postulates 100 years after their proposition" (Weiss and Jaffe, 1990)—but they all fail to identify a statute of limitation for adherence to the virus-AIDS hypothesis. In addition, "cofactors" are assumed (a) to make up for the typi-

cal inertia of the viral pathogens or carcinogens, (b) to account for the clonality of the cancers via a clonal cellular cofactor, and (c) to help to close the enormous gaps between the very common infections and the very rare incidences of "slow" disease or cancer, that even the long "latent periods" could not close (Duesberg and Schwartz, 1992). The tumor virologist Rowe "recognized that the latent period may cover much of the life span of the animal and that the virus did not act alone but that the tumor response might require . . . treatment with a chemical carcinogen" (Rowe, 1973).

Despite the total lack of public health benefits and even negative consequences of these theories, such as the psychologically toxic prognoses that antibodies against HTLV-I or against papilloma virus signal future cancers (Duesberg and Schwartz, 1992), or that antibodies against HIV signal future AIDS and the need for AZT prophylaxis, the public and the majority of scientists have held on to them much longer than was justified in terms of scientific evidence. The irresistible appeal of the germ theory was the basis for each of these unproductive theories of the past, as it is the basis now for the universal and enthusiastic approval of the virus-AIDS hypothesis.

But unlike the mistaken germ theories of the past, the virus-AIDS hypothesis was a windfall not only for (1) the virologists and epidemiologists, but also for (2) the biotechnology companies who could develop virus-tests and antiviral drugs, (3) the AIDS patients who were relieved that a God-given, egalitarian virus rather than behavioral factors were to blame for their diseases, and (4) the politicians who had to confront the public and the gay (homosexual) lobby requesting action against AIDS. Indeed, a thoroughly intimidated public was happy, once more, to be offered protection by its scientists against another "deadly" virus, albeit for the highest price-tag ever.

6.2. Big Funding and Limited Expertise Paralyze AIDS Research

Ironically, AIDS research suffers not only from being tied to an unproductive hypothesis, it also suffers from the staggering funds it receives from governments (Section 1) and from conceptually matched private sources. Intended to buy a fast solution for AIDS, these funds have instead paralyzed AIDS research by creating an instant orthodoxy of retrovirol-

ogists that fiercely protects its narrowly focused scientific expertise and global commercial interests (Booth, 1988; Rappoport, 1988; Nussbaum, 1990; Duesberg, 1991b, 1992b; Savitz, 1991; Connor, 1991, 1992).

The leaders of the AIDS orthodoxy are all veterans from the wars on "slow" and cancer viruses. Naturally they were highly qualified to fill the growing gaps in the virus-AIDS hypothesis with their "modern concepts of causation" (Evans, 1992), including long "latent periods," "cofactors" and "seroepidemiological" arguments of causation (Sections 3.3, 3.4 and 3.5). When it became apparent that the first order mechanism of viral pathogenesis, postulating direct killing of T-cells, failed to explain immunodeficiency, the bewildering diversity of AIDS diseases, the many asymptomatic HIV infections, and HIV-free AIDS cases, the scientific method would have called for a new hypothesis. Instead the virus hunters have shifted the virus-AIDS hypothesis from a failed first order mechanism to a multiplicity of hypothetical second order mechanisms, including cofactors and latent periods, to fill the ever growing discrepancies between HIV and AIDS. By conjugating these second order mechanisms with a multiplicity of unrelated diseases, the virus-AIDS hypothesis has become by far the most mercurial hypothesis in biology. It predicts either diarrhea or dementia or Kaposi's sarcoma or no disease, 1, 5, 10 or 20 years after 1 or 2000 sexual contacts with an antibody-HIV-positive person with or without an AIDS disease.

But the coup to rename dozens of unrelated diseases with the common name AIDS, proved to be the most effective weapon of the AIDS establishment in winning unsuspecting followers from all constituencies. By making AIDS a synonym for Kaposi's sarcoma and candidiasis and dementia and diarrhea and lymphoma and lymphadenopathy, the road was paved for a common cause. Who would have accepted, prior to AIDS, that a dental patient caught candidiasis from her doctor's Kaposi's sarcoma? Or which scientist would accept it even now knowing the original data rather than just the corresponding press release? According to the sociologist David Phillips "researchers use newspapers as a 'filter' to help them decide which scientific article is worth reading" (Briefings, 1991) or more often which article is worth knowing about.

The control of AIDS research by the nationally and internationally funded AIDS orthodoxy via the popular and scientific press is almost total. It instructs science writers that faithfully report every "breakthrough" in HIV research and every "explosion" of the epidemic. It feeds scientific journals with over 10,000 HIV-AIDS papers annually and with advertisements for HIV tests and antiviral drugs (Schwitzer, 1992). The AIDS doctors are controlled by the companies created, consulted or owned by the AIDS establishment (Barinaga, 1992; Schwitzer, 1992). For example, the Physician's Desk Reference 1992 instructs AIDS doctors about AZT with an exact copy of Burroughs Wellcome's instructions. *Science* writers are warned against reporting minority views. For example, Fauci states: "Journalists who make too many mistakes, or who are sloppy, are going to find that their access to scientists may diminish" (Fauci, 1989). And Ludlam points out, "Whilst I support, and encourage the reporting of, minority views ... If the belief that AIDS is not due to HIV becomes prevalent ... (it) could lead directly to the deaths of countless misinformed individuals" (Ludlam, 1992). Any challengers are automatically outnumbered and readily marginalized by the sheer volume of the AIDS establishment. For example, the 12,000 scientists attending the annual international AIDS conference held in San Francisco in 1990 were only a fraction of the many who study the information encoded in the 9000 nucleotides of HIV. Says the HIV virologist Gallo when asked about a dissenter: "Why does the Institute of Medicine, WHO, CDC, National Academy of Sciences, NIH, Pasteur Institute and the whole body of world science 100 percent agree that HIV is the cause of AIDS?" (Liversidge, 1989).

Consequently there is no "peer-reviewed" funding for researchers who challenge the virus-AIDS hypothesis (Duesberg, 1991b; Maddox, 1991a; Bethell, 1992; Farber, 1992; Hodgkinson, 1992). Since HIV became the dominant focus of the billion-dollar AIDS-research (Coffin *et al.,* 1986; Institute of Medicine, 1988), there has not been even one follow-up of the many previous studies blaming sexual stimulants and psychoactive drugs for homosexual AIDS (Sections 4.4 and 4.5). None of the former "lifestyle" advocates (Section 2.2) have investigated whether drugs might cause AIDS without HIV. Instead drugs, if mentioned at all, were since described as risk factors for infection by HIV (Darrow

et al., 1987; Moss *et al.,* 1987; van Griensven *et al.,* 1987; Chaisson *et al.,* 1989; Weiss, S.H., 1989; Goudsmit, 1992; Seage *et al.,* 1992)—as if HIV could discriminate between hosts on the basis of their drug habits (Duesberg, 1992a). For example, Friedman-Kien concluded in 1982 and 1983 with Marmor *et al.* (1982) and Jaffe *et al.* (1983b) that the "lifetime exposure to nitrites . . ." was responsible for AIDS (Section 4.3.2). In 1990 he and his collaborators just mentioned nitrite use in HIV-free Kaposi's sarcoma cases (Friedman-Kien *et al.,* 1990) and in 1992 they blamed viruses other than HIV for HIV-free AIDS cases, and drug use was no longer mentioned (Huang *et al.,* 1992).

Likewise all studies investigating transfusion-mediated immunodeficiency in hemophiliacs were frozen around 1987 (Table 3), once the virus-AIDS hypothesis had monopolized AIDS research. The question whether immunodeficient (!) HIV-free hemophiliacs would ever develop AIDS defining diseases was left unanswered and even became unaskable.

Fascinated by the past triumphs of the germ theory, the public, science journalists and even scientists from other fields never question the authority of their medical experts, even if they fail to produce useful results (Adams, 1989; Schwitzer, 1992). Medical scientists are typically credited for the virtual elimination of infectious diseases with vaccines and antibiotics, although most of the credit for eliminating infectious diseases is actually owed to vastly improved nutrition and sanitation (Stewart, 1968; McKeown, 1979; Moberg and Cohn, 1991; Oppenheimer, 1992). Indeed, the belief in the infallibility of modern science is the only ideology that unifies the 20th century. For example, in the name of the virus-AIDS hypothesis of the American Government and the American researcher Gallo, antibody-positive Americans have been convicted for "assault with a deadly weapon" because they had sex with antibody-negatives, Central Africa dedicates its limited resources to "AIDS testing," the former U.S.S.R. conducted 20.2 million AIDS tests in 1990 and 29.4 million in 1991 to identify a total of 178 antibody-positive Soviets and communist Cuba even quarantines its own citizens if they are antibody-positive (Section 3.6).

Predictably the AIDS virus hunters, on their last crusade for the germ theory, have no regard for the current drug-use epidemic and its

many overlaps with American and European AIDS. Even direct evidence for the role of drugs in AIDS is fiercely rejected by the virus-AIDS orthodoxy (Booth, 1988; Moss *et al.,* 1988; Kaslow *et al.,* 1989; Baltimore and Feinberg, 1990; Ostrow *et al.,* 1990). Merely questioning the therapeutic or prophylactic benefits of AZT is protested by the AIDS establishment (Baltimore and Feinberg, 1990; Weiss and Jaffe, 1990; Anonymous, 1992; Freestone, 1992; Tedder *et al.,* 1992). The prejudice against noninfectious pathogens is so popular, that the virus-AIDS establishment uses it regularly to intimidate those who propose noninfectious alternatives, to censor their papers (Duesberg, 1992e) and even to question their integrity.

For example, an editorial in *Science* called me a "rebel without a cause for AIDS," because denying HIV was to deny a cause altogether. The editorial quoted Baltimore as saying I was "irresponsible and pernicious" (Booth, 1988). An article in *Nature* called my drug hypothesis a "perilous message" that would "belittle 'safe sex,' would have us abandon AIDS screening ... and curtail research into anti-HIV drugs." "Arguments that AIDS (is) the result of evil vapors (poppers (!)), mal'aria ... (are from) the last century." "We ... regard the critics as 'flat-earthers' bogged down in molecular minutiae and miasmal theories of disease, while HIV continues to spread" (Weiss and Jaffe, 1990). This is said even though the article agrees that, "Duesberg is right to draw attention to our ignorance of how HIV causes disease ..." (Weiss and Jaffe, 1990). Others declare "All attempts by epidemiologists to link AIDS to the use of amyl nitrite or other drugs as a direct cause of disease have failed ... Duesberg's continued attempts to persuade the public to doubt the role of HIV in AIDS are not based on facts" (Baltimore and Feinberg, 1990). Gallo called the author of the article, "Experts mount startling challenge to AIDS orthodoxy" in *The Sunday Times* (London) (Hodgkinson, 1992), "irresponsible both to myself (Gallo) and to HIV as the cause of AIDS" (Gallo, 1992). Further, Vandenbrouke and Pardoel argue, "If one is allowed to compare the evolution of scientific theories with the evolution of biologic nature in general, the poppers (nitrite inhalants) episode is the Neanderthal of modern epidemiology" (Vandenbroucke and Pardoel, 1989).

As a consequence there are no studies that investigate the long-term

effects of psychoactive drugs (Lerner, 1989; Pillai *et al.,* 1991; Bryant *et al.,* 1992). The toxicologist Lerner points out that "fewer than 60 are currently enrolled in fellowship programs on alcoholism and drug abuse in the entire country" (Lerner, 1989), although about 8 million Americans alone are estimated to use cocaine (Weiss, S.H., 1989; Finnegan *et al.,* 1992) and many more use other psychoactive drugs regularly (Section 4). This stands in contrast to the 40,000 annual AIDS cases that are studied by at least 40,000 AIDS researchers of which just 12,000 attended the annual International AIDS Conference in San Francisco in 1990.

Instead of warning against drugs, the AIDS establishment "educates" the public with its "clean needle" campaigns that drugs (albeit illegal) are safe, but bugs are not. For example, AIDS researcher Moss, citing Napoleon's line "On s'engage et puis on voit," recommends "clean needles" for "harm reduction" (Moss, 1987). Mindful of its educators, the public is unaware and even disinformed about the health risks of recreational drugs. A popular joke in point is the response of two "junkies" (drug addicts) sharing a syringe filled with an intravenous drug to a concerned colleague: "We are safe, because we use a clean needle and condoms." The long "latent periods" between the gratification from recreational drugs, such as tobacco, alcohol, cocaine and nitrite inhalants, to their irreversible health effects unfortunately give credence to the "perilous message" that drugs are safe but bugs are not.

Particularly the victims of drug consumption prefer egalitarian infectious causes over noninfectious behavioral ones that imply personal responsibility (Shilts, 1985; Lauritsen and Wilson, 1986; Rappoport, 1988; Callen, 1990). For example, the executive director of the San Francisco based national "Project Inform," an organization operated mainly for and by male homosexuals, Martin Delaney, informs its clients about a study documenting a "level of sexual contact and drug use which was shocking to the general public" as follows: "It (the study) might just as well have noted that most wore Levi's (jeans) for all this told us about the cause of AIDS" (Project Inform, 1992). The organization collaborates with the NIH and is supported by grants from pharmaceutical companies including Burroughs Wellcome, the manufacturer of AZT (Project Inform, 1992).

In 1987, before AZT, Delaney advised gay men in his book *Strate-*

gies for Survival: A Gay Men's Health Manual for the Age of AIDS about the health effects of nitrite inhalants: "Possible heart damage; fibrillation (compulsive, erratic heart rhythms); possible stroke and resulting brain damage. Conducive to high-risk sexual behavior; distortion of judgement and senses. Statistical link to Kaposi's sarcoma (KS, an AIDS-related cancer); suspected immuno-suppression" (Delaney and Goldblum, 1987). Delaney's advice about amphetamines reads as follows: "Liver and heart damage; neuropathy (nerve damage); possible brain damage; weight loss; nutritional and vitamin depletion; adrenal depletion (uses up the body's energy reserves). Distorted judgment, values, senses, delusions of strength, anxiety, paranoia, rebound depression, financial strain, powerful addiction, conducive to high-risk sexual activity. Likely immunosuppression (not currently measured), potential for unknown and risky drug interactions, complication in treatment of brain disorders." Delaney also warns about the effects of cocaine: "Heart and lung damage, stroke, cardiovascular irregularities, possible physical addiction. Distortion of judgment, values, and senses, dangerous delusions of grandeur and strength, intense anxiety, paranoia, financial strain, leads to poor judgment about high-risk sexual activity. Likely immunosuppression (not currently measured); increased stress, if smoked, complicates treatment of pneumonia." The book also gives the basis for Delaney's intimate knowledge of drug toxicity: "He ... has done work for the National Institute on Drug Abuse" (Delaney and Goldblum, 1987).

Clearly big science is not always good science, particularly if it is conceptually paralyzed by an unproductive hypothesis. I hope that the scientific evidence collected for this article will focus attention on the noninfectious causes of AIDS and prove that it is not "too late to correct" (Red Queen) the spell of the virus-AIDS hypothesis by the scientific method. Considering noninfectious causes may prove to be as beneficial to the challenge of AIDS as it was, for example, to the challenge of pellagra. Indeed, a few investigators have recently smuggled recreational drugs as "cofactors" of HIV (Haverkos and Dougherty, 1988; Haverkos, 1990) or even more cautiously as cofactors of cofactors of HIV (Archibald *et al.,* 1992) into the highly fundable virus-AIDS hypothesis. One investigator even dared to document that drugs are

sufficient for pediatric AIDS, if only in preliminary reports (Koch, 1990; Koch *et al.,* 1990). A complete report of the data (Section 4.5) was not published for political reasons (Thomas Koch, personal communication). And the "100 percent" consensus on HIV claimed by Gallo in 1989 (Liversidge, 1989) is eroding just a bit in the face of a growing group of dissenters, some of which united in the "Group for the Scientific Reappraisal of the HIV/AIDS Hypothesis" (DeLoughry, 1991; Bethell, 1992; Bialy and Farber, 1992; Farber, 1992; Hodgkinson, 1992; Project Inform, 1992; Nicholson, 1992; Ratner, 1992; Schoch, 1992).

Note Added in Proof

Sparked by an article in *Newsweek* (Cowley, 1992), numerous HIV-free AIDS cases were unexpectedly reported by many independent (!) investigators at the VIII International Conference on AIDS/III STD World Congress in Amsterdam in July 1992 (now a joint meeting with sexually transmitted diseases, STDs). Surprisingly, some of the recently announced HIV-free AIDS cases had been studied for years (Altman, 1992a; Cohen, 1992a,b; Laurence *et al.,* 1992), even by the CDC (Spira and Jones, 1992). As a result the CDC had to alter its long-held position that HIV causes all AIDS to "HIV causes the vast majority of AIDS cases ..." (Nicholson, 1992). In its monthly *HIV/AIDS Surveillance Reports* the CDC still states that "AIDS is a specific group of diseases which are indicative of severe immunosuppression related to infection with the human immunodeficiency virus (HIV)" (Centers for Disease Control, 1992b). The AIDS risk factors of most of these HIV-free "AIDS patients" were reported to be "intravenous drugs, unprotected sex and transfusions" and the corresponding diseases were Kaposi's sarcoma and pneumonia (Cowley, 1992).

AIDS-virus matchmakers soon reached the consensus that an as yet undiscovered "new AIDS virus," that "doesn't appear any more contagious than HIV" (Cowley, 1992), was to be blamed for HIV-negative AIDS (Bowden *et al.,* 1991; Castro *et al.,* 1992; Huang *et al.,* 1992; Altman, 1992a,b; Cohen, 1992a,b; Laurence *et al.,* 1992). And the director for AIDS research at the NIH reassured the public, "If there is something, scientists will find it" (News Report, 1992). States *The New York Times,* "Arguably, the greatest thrills for a scientist are in discov-

ering a new microbe, a new disease, cure and prevention ... Many ... know how quickly the exhilaration that comes from believing they are on the verge of making such a discovery vanishes when the initial findings cannot be confirmed" (Altman, 1992b).

However, the new HIV-free AIDS cases are entirely consistent with those listed above that were caused by drug consumption and other noncontagious risk factors (Section 4.5). Although public recognition of HIV-free AIDS cases is new, the new cases just complement the over 1200 cases of "acquired" immunodeficiency and AIDS-defining diseases described above including 334 hemophiliacs (Section 3.4.4.5, Table 3), 265 male homosexuals (Sections 3.4.4.3 and 4.5), 444 intravenous drug users (Section 4.5) and 183 mostly male tuberculosis patients from Florida (Pitchenik *et al.,* 1987, 1990). If the 2466 HIV-free AIDS cases from Africa were included (Section 3.4.4.8), the number of documented HIV-free AIDS cases would exceed 3000!

Moreover healthy HIV carriers who have been infected for over 10 years and have transmitted their HIV to at least 5 healthy persons via blood transfusions over 7–10 years ago have now received public recognition (Altman, 1992c; Learmont *et al.,* 1992). These cases supplement the 1 million Americans, 0.5 million Europeans, 0.3 million Thais and 6 million Africans who are healthy, although most had been infected by 1985 (Section 3.5.1).

Thus both predictions of the hypothesis that AIDS is noncontagious are now generally accepted: (1) HIV-free AIDS and (2) AIDS-free transmission of HIV. Asks John Maddox, editor of *Nature,* "Does that mean Duesberg has been right all along, and that HIV plays no part in the causation of AIDS?" (Maddox, 1992b). Indeed, it would be an evolutionary miracle if the last decade had generated three different AIDS viruses, HIV-1, HIV-2 and the "new AIDS virus," when no such virus has ever emerged before in the history of medicine.

Acknowledgements

Dedicated to: (1) all intravenous drug users, oral users of recreational drugs and AZT recipients who were never told that drugs cause AIDS diseases; (2) all "antibody-positives" who were never told that the virus-AIDS hypothesis is unproven.

I thank Janie Stone (Berkeley) for numerous corrections of the manuscript, David Shugar (Associate Editor of *Pharmacology and Therapeutics,* Warsaw, Poland) for his courage to take up the AIDS controversy and for playing the devil's advocate of HIV, Annette Gwardyak (Managing Editor) for accommodating many "final" revisions, Hansueli Albonico (Langrau, Switzerland), Harvey Bialy (New York), Julie Castiglia (San Diego), Robert Cramer (Montlhery/Paris), Bryan Ellison (Berkeley), Celia Farber (New York), Harry Haverkos (Rockville, Maryland), Robert Hoffman (San Diego), Geoff Hoffmann (Vancouver, Canada), Phillip E. Johnson (Berkeley), Bill Jordan (Los Angeles), John Lauritsen (New York), Nathaniel Lehrman (New York), Anthony Liversidge (New York), Claus Pierach (Minneapolis), Paul Rabinow (Berkeley), Robert Root-Bernstein (East Lansing, Michigan), Harry Rubin (Berkeley), Frank Rothschild (Berkeley), Russell Schoch (Berkeley), Craig Schoonmaker (New York), Jody Schwartz (Berkeley), Joan Shenton (London), Gordon Stewart (Bristol, U.K.), Richard Strohman (Berkeley), Charles Thomas, Jr (San Diego), Fritz Ulmer (Wuppertal, Germany), Michael Verney-Elliott (London), Warren Winkelstein (Berkeley) and Yue Wu (Berkeley) for critical and catalytic information, Gedge Rosson (Berkeley) for Fig. 1, Brian Davis for fact-checking and typing, Osias Stutman for suggesting the Lewis Carroll quotation, Ted Gardner (Santa Barbara) for a generous donation and encouragement, and the librarians of UC-Berkeley, particularly Chris Campbell, Ingrid Radkey, Pat Stewart and Norma Kobzina, for AIDS references that were not even cited in the daily American newspapers. I am still supported by Outstanding Investigator Grant 5-R35-CA39915-07 from the National Cancer Institute.

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Note added in proof:

Ten years after designating AIDS infectious based on clusters of cases, the CDC published in 1995: "Such clusters may be difficult to identify because most persons with AIDS have had contact with many different people. In particular, drug users and homosexual and bisexual men may have had contact with hundreds of partners that they did not know very well." (Drotman, Peterman and Friedman-Kien, 1995).

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Chapter Seven

The HIV Gap in National AIDS Statistics

Bio/Technology, Vol. 11, pp. 955–956, August 1993

The HIV-AIDS hypothesis rests on the assertion that all AIDS cases are associated with HIV (*Confronting AIDS-Update 1988,* Natl. Acad. Sci. Press, Wash., D.C.; Blattner, W., *et al.,* 1988, *Science* 241, 514–515; Weiss, R. and Jaffe, H., 1990, *Nature* 345, 659–660; Duesberg, P.H., 1992, *Pharmacol. Ther.* 55, 201–277). Therefore, the Centers for Disease Control (CDC) groups American AIDS cases in its *HIV/AIDS Surveillance* into "exposure (to HIV) categories." However, there are no national AIDS statistics that document the natural coincidence between AIDS diseases and HIV. Contrary to its title, the *HIV/AIDS Surveillance* of the CDC does not report HIV tests. Correlations between HIV and AIDS can only be determined from individual studies and from those CDC AIDS case report forms that include HIV tests.

But most "HIV tests" measure antibodies against HIV rather than the virus itself. And antibodies are not unambiguous evidence for the presence of a virus, nor are they rational predictors for viral disease. Instead antibodies neutralize HIV and restrict the virus to latency. This is the reason that leading AIDS researchers have had notorious difficulties in isolating HIV, even in people dying from AIDS (Weiss, R., 1991, *Nature* 349, 374; Cohen, J., 1993, *Science* 259, 168–170).

Editorial Note:

Peter H. Duesberg is a professor in the department of Molecular & Cell Biology at the University of California at Berkeley, Berkeley, CA 94720. The views expressed here are the author's own, and not necessarily those of *Bio/Technology.*

Moreover, antibody tests generate false-positive results if an epitope is shared between different organisms. According to a recent review entitled "HIV testing: State of the Art," "depending on the population tested, 20 to 70% of . . . two successive positive ELISAs (enzyme-linked immunosorbent assay) are confirmed by Western blot (an alternative antibody assay)." (Sloand, E.M., *et al.,* 1991, *JAMA* 266, 2861–2866).

In a population with a low probability of infection, the false-positive rate is high. According to the widely cited study of applicants to the U.S. Army by Burke *et al.,* 83% of all initially positive ELISAs (10,000/12,000) were false-positives (*New Eng. J. Med.* 319, 961–964, 1988).

In a population with a high incidence of infection, however, the false-positive rate is expected to be low. Therefore the CDC assumes that "the tiny proportion of possibly false-positive screening tests in persons with AIDS-indicative diseases is of little consequence" (*Confronting AIDS-Update 1988*). But this is not observed.

For example, one study documented 131 repeatedly ELISA-positive homosexual men with negative Western blots in a cohort of 4,994 homosexuals of which 37% were HIV-positive (Phair, J., *et al.,* 1992, *J. AIDS* 5, 988–992). Another study "found HIV-1 infection in only 4 (12.5%) of 32 high-risk cases" with repeatedly positive ELISAs (Celum, C.L., *et al.,* 1991, *J. Infect. Dis.* 164, 656–664). HIV infection was negative by Western blot, provirus amplification with the polymerase chain reaction (PCR), and virus isolation tests. Another study identified 33 ELISA-positive and even Western blot-positive subjects who were HIV-negative based on the PCR test for HIV DNA (Schechter, M., *et al.,* 1991, *AIDS* 5, 373–379). These subjects were from a group of 316 homosexuals of which 158 (50%) were PCR-positive.

The relatively high incidence of false-positive HIV antibody tests in these HIV risk groups probably reflects the presence of antibodies to other viruses and microbes that may cross-react with HIV. For example, 7 out of 10 blood donors treated with an influenza virus vaccine in 1991 became HIV ELISA-positive. Each of these proved to be false-positives upon confirmation with a Western blot (Mac Kenzie, W.R., *et al.,* 1992, *JAMA* 268, 1015–1017). Since the CDC " . . . accepts a reactive screening test for HIV antibody without confirmation by a sup-

plemental test . . ." (*Confronting AIDS-Update 1988*) and does not request a repeatedly positive antibody test in its "AIDS adult confidential case report" forms, it includes false-positives in its *HIV/AIDS Surveillance.*

In fact, the CDC even includes AIDS cases in its *HIV/AIDS Surveillance* "without laboratory evidence regarding HIV infection" (*Confronting AIDS-Update 1988*). Upon request, the CDC's director of the HIV/AIDS division, Harold Jaffe, stated that the HIV status of 43,606 out of the 253,448 American AIDS cases recorded by the end of 1992 was "not tested" (per. com., 1993). However this figure seems to be an understatement. Obviously, all 10,360 American AIDS cases diagnosed before the HIV antibody test, i.e., before 1985, were not tested (*HIV/AIDS Surveillance,* February 1993). In addition, the CDC published that "Approximately one third of AIDS patients in the United States have been from New York and San Francisco, where, since 1985, <7 % have been reported with HIV-antibody test results, compared with >60 % in other areas." (*Confronting AIDS-Update 1988*). Thus, between 1985 and 1987, 58% (93% x 1/3 + 40% x 2/3) of the 56,807 AIDS cases recorded in that period, or 32,948, have not been tested. For 1988, the CDC reported that 27% or 9,039 of the 33,480 AIDS cases recorded for that year were not tested for HIV (Selik, R. M., *et al.,* 1990, *J. AIDS* 3, 73–82). According to the CDC's Technical Information Activity, 3682 AIDS cases without an HIV-test were recorded in 1989, 2888 in 1990, 1960 in 1991, and 1395 in 1992 (per. com., 1993). Thus, at least 62,272, or 18,666 more than Jaffe reports, were not tested.

Determination of the HIV-AIDS correlation is further obscured because HIV-free AIDS cases are not recorded in the CDC's *HIV/AIDS Surveillance.* By 1993, at least 4621 HIV-free AIDS cases had been documented in the U.S., Europe, and Africa with the clinical AIDS definition (Table 1). Even Jaffe, again upon request, reported 89 HIV-free AIDS cases (per. com., 1993). The cases recorded in Table 1 suffered from one or more of the over 25 heterogeneous AIDS-defining diseases and from AIDS-defining immunodeficiencies without diseases. Some of these proved to be HIV-free even by PCR amplification of viral RNA and DNA.

Table 1 includes some American and European immunodeficiencies that may not exactly fit the current definition of AIDS-defining

Table 1
HIV-free AIDS defining diseases and immunodeficiencies

Risk Group	U.S./Canada	Europe	Africa	References*
Homosexuals	722	37		1–22/23–26, 74
Intravenous (IV) drug users	251	335		18–20, 27–35, 75/36–39, 74
Infants of IV drug users	55	11		40–43/44, 45
Hemophiliacs	256	78		46–56/57–61
None/ unreported	307	14	2555	16–21, 62–67/ 21, 68/26, 69–73
Totals	**1591**	**475**	**2555**	
Sum total	**4621**			

*References for risk group categories from each continent are separated by slashes.

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immmunodeficiency without disease, which is <200 T-cells per microliter (CDC, 1992, *MMWR* 41, RR 17, 1–19), as for example, HIV-free male homosexuals on various recreational drugs with "<600 T-cells per cubic millimeter" (Table 1, ref. 14) or HIV-negative hemophiliacs with T4/T8 cell ratios of about 1 or <1 (Table 1, refs. 46–61). But even if not all of these cases fit the current definition of AIDS-defining immunodeficiency exactly, they do so prospectively. This is because their T-cells typically continue to decline either because of risk behavior, such as the consumption of recreational drugs, or because of clinical AIDS risks, such as chronic transfusion of foreign proteins as prophylaxis against hemophilia (Duesberg, P.H. 1992, op, cit.).

Since a clinical definition is used in Africa, statistics from this continent are not biased against HIV-free AIDS. For example, 2215 out of 4383 (50.5%) African AIDS patients from Abidjan, Ivory Coast, Lusaka, Zambia, and Kinshasa, Zaire, were HIV-antibody negative (Table 1, ref. 70, 71). Another study using antibody tests and supplementary PCR tests for HIV reports 135 (59%) HIV-free AIDS patients from Ghana out of 227 suffering from weight loss, diarrhea, chronic fever, tuberculosis, and neurological diseases (Table 1, ref. 72). Only 37 (30%) of a group of 122 African tuberculosis patients were HIV-positive, accord-

ing to a study published in 1993 (Table 1, ref. 73). An earlier study documents 116 HIV-negatives among 424 African patients, and Montagnier *et al.,* diagnosed HIV in four out of eight (Table 1, ref. 26, 69). It follows that about 50% of the African AIDS cases, or 65,000 of the 129,000 diagnosed by 1992 (Duesberg, P.H, 1992, op. cit.), maybe HIV-free and thus not caused by HIV.

Instead of considering the potential usefulness of HIV-free AIDS cases in the search for the cause of AIDS, the CDC and the NIH's director for AIDS research hid in 1992 the then rapidly growing numbers of HIV-free AIDS cases (Duesberg, P.H., 1992, op. cit.) under a new name, "idiopathic CD4 lymphocytopenia" or ICL. Indeed, the new name has sent HIV-free AIDS cases into obscurity. But efforts to set apart HIV-free from HIV-positive AIDS cases by the new term are not based on clinical or scientific arguments. According to an editorial by Anthony Fauci, HIV-free AIDS or ICL cases are unlike the HIV-positive cases because (1) "Given the heterogeneity of the [ICL] syndrome, it is highly likely that there is no common cause," and because (2) "Approximately one-third of the patients are women, as compared with 11% among those with HIV ... [in America]" (Fauci, A., 1993, *New Eng. J. Med.* 328, 429–431). Yet proponents of the HIV hypothesis, including Fauci, insist that HIV is the common cause of the more than 25 heterogeneous AIDS diseases and that HIV causes African AIDS, although about 50% of the African patients are women (Duesberg, P.H., 1992, op. cit.).

In view of the above, I submit that the natural coincidence between HIV and AIDS in America and Europe remains unknown, and is certainly less than perfect. Thus arguments for the etiological role of HIV in AIDS, which assume a perfect correlation, are fundamentally flawed.

Chapter Eight

Can Epidemiology Determine Whether Drugs or HIV Cause AIDS?

AIDS-Forschung (AIFO),* 12, pp. 627–635, December 1993

Summary

Two recent longitudinal surveys of homosexual men, one from San Francisco, the other from Vancouver, have reinvestigated the question whether AIDS is caused by HIV or drugs. During 8-year observation periods the San Francisco survey observed that 215 out of 445 HIV-positive drug users developed AIDS and the Vancouver survey that 136 out of 365 HIV antibody-positive drug users developed AIDS. On the basis of these correlations both surveys have concluded that HIV causes AIDS, and have rejected my hypothesis that recreational drugs and anti-HIV drugs, like AZT, cause AIDS. However, these conclu-

*Viewpoint

With Viewpoint, *AIFO (AIDS-Forschung)* has created a forum for scientific controversies. To date Viewpoint has covered diverse topics including measures to control AIDS—on which no consensus has been reached.

The drug-AIDS hypothesis (in contrast to the HIV-AIDS hypothesis) of Duesberg has been a source of several controversies over the last year. *AIFO* has contributed several articles of Duesberg to this controversy (*AIFO* 4, 115–126; 507–515; 517–521 [1989]; *AIFO* 6, 299–306 [1991]; *AIFO* 7, 619–641 [1992]).

Early in 1993 several articles appeared in the international press that appeared to refute Duesberg's theses (Ascher *et al.*, *Nature* 362, 103; Schechter et al., *Lancet* 341, 658; Piatak *et al.*, *Science* 259, 1749; Pantaleo *et al.*, *Nature* 362, 355; Embretson, *Nature* 362, 359). Therefore *AIFO* has invited Duesberg to critically review and discuss his theses in view of these challenges.

—The editor of AIDS-Forschung

sions are worthless because the authors failed to recognize that: i) even a perfect correlation with HIV (Koch's first postulate) does not prove causation without functional tests; ii) positive antibody tests do not prove HIV infection due to false-positives, e.g. 17% in the Vancouver group; iii) they lacked the only absolute epidemiological argument against the drug-AIDS hypothesis, drug-free AIDS cases; iv) drug toxicity is dosage dependent, i.e. "the dose is the poison." Since short-term drug users were not distinguished from long-term users, no drug dose-AIDS response relationships emerged; v) AZT, prescribed as an anti-HIV drug to HIV-positives, is immunotoxic and lymphomagenic. Contrary to the authors' conclusion, data of both surveys confirm the drug-AIDS hypothesis with consistent drug AIDS correlations, drug-AIDS dose-response relationships, and even drug-specific diseases. A definitive test to distinguish between HIV and drugs as causes of AIDS would: i) define all AIDS diseases clinically, independent of HIV; ii) test clinically defined AIDS cases (a) for HIV, not antibodies against HIV, and (b) for their lifetime dosage of recreational drugs and AZT; iii) conduct functional tests with drugs or HIV, if no drug-free or HIV-free AIDS cases can be found.

Key words: recreational drugs—AZT—clinical AIDS definition—drug-dose AIDS dependence—drug-specific AIDS diseases.

Introduction

What is observed will always depend on the hypothesis held by the observer.

—David Horrobin (1)

Two longitudinal surveys, one of 812 homosexual men and 215 heterosexual controls from San Francisco (2), the other of 715 homosexual men from Vancouver (3), have recently reinvestigated the question whether recreational and aphrodisiac drugs or HIV cause AIDS. Both surveys took aim at my hypothesis that recreational drugs and AZT cause AIDS (4, 5). But the Vancouver team also credited me erroneously with the hypothesis that "chronic promiscuous male homosexual activity" causes AIDS (3). After an 8-year observation period the San Francisco survey had observed 215 AIDS cases out of 445 HIV-positive drug

users (Table 1). The Vancouver survey had observed 136 AIDS cases out of 365 HIV-positive drug users after an observation period of 8.6 years (Table 1).

Table 1
Drug use, AIDS and health among HIV positives reported by the San Francisco and Vancouver surveys (2, 3).

	HIV-positives	Drug use*	AIDS	Healthy
San Francisco	445	100 %	215	230
Vancouver	365	>98 %	136	229

*Drug use among HIV-positives is documented below.

Thus both surveys report perfect correlations between drug use and AIDS (see below), but claim to have refuted my hypothesis that injected and orally consumed recreational drugs and AZT cause AIDS (4, 5).

The epidemiologists from San Francisco state that "substance abuse as a main cause of AIDS has ... no basis in fact," and the epidemiologists from Vancouver state that "the hypothesis that AIDS in homosexual men is caused ... by drugs ... is rejected by these data," and that "HIV has an integral role in the pathogenesis of AIDS" but it "does not rule out a role for cofactors ..." (3). The Vancouver survey even warns that my drug hypothesis is "a hindrance to public health initiatives" (3), and the San Francisco survey advises "The energies of Duesberg and his followers could better be applied to unraveling the enigmatic mechanism of the HIV pathogenesis of AIDS."

Although my name was cited 13 times by the authors of the San Francisco survey in their 2-page *Nature* Commentary, the editor of *Nature* denied me the right of reply because I had asked "unanswerable rhetorical questions" (78). Two HIV researchers have seconded this decision and have even submitted procedures how I "should be stopped" (79).

Here I will demonstrate that inherent limitations of the epidemiological method, biases due to the HIV-based AIDS definition and the

failures of both surveys to recognize the dosage dependence of drug toxicity and of drug-specific AIDS diseases invalidate their conclusions. Indeed, data of both teams confirm the drug hypothesis with consistent correlations, drug-AIDS dose-response relationships and drug-specific AIDS diseases.

1. Limits of the Epidemiological Method

i) *Epidemiology not sufficient to prove that a microbe causes disease.* Because a microbe can be pathogenic when it is active and abundant, and is harmless when it is inactive and rare, documenting the presence of a microbe is not sufficient to prove causation. The necessary tests to prove causation have been defined by Robert Koch and since termed Koch's postulates. According to these postulates i) the agent must be present in every case of the disease in amounts sufficient to cause disease; ii) it must be isolated in pure form; and iii) it must cause the disease if inoculated into a suitable host.

Because of its descriptive nature, epidemiological search for an infectious pathogen is restricted to correlations and thus only relevant for an appraisal of Koch's first postulate. Epidemiology can at best confirm Koch's first postulate and hence never prove that an infectious agent causes a disease.

ii) *Epidemiology sufficient to prove that drugs cause disease, if dosage is determined.* Clearly if drugs were to cause AIDS, the risk of a short-term user would be much lower than that of a long-term user. The toxicity of drugs depends on the dose that is consumed over a lifetime because "the dose is the poison." One year of smoking or drinking does not cause lung cancer or liver cirrhosis, but 10 to 20 years may do so (6). Thus, a drug dose-response relationship must be established to distinguish a toxic drug from other non-toxic agents. For this purpose groups controlled for the dosage of drug use must be compared to otherwise matched non-drug users. Final proof of causation is obtained by causing toxin-specific disease in animals. Thus, demonstrating unquantified drug use by AIDS patients is not sufficient to prove causation.

iii) *Epidemiology can exclude possible causes of a disease.* Epidemiology can exclude both an infectious and a noninfectious agent as a cause, if

the disease occurs in its absence. Thus, drug-free AIDS cases must be identified to exclude drugs, or HIV-free AIDS cases to exclude HIV as causes of AIDS.

iv) *Disease must be definable independent of a putative cause.* In studies designed to find the cause of a disease, the disease must be clinically definable, independent of its putative cause. If A and B are investigated as possible causes, it must be possible to define the disease independent of A and B. The disease cannot be defined as A-disease, because such a definition would exclude all A-negative cases, and would bias the investigation in favour of a 100% correlation with A. Thus, AIDS cases must be first diagnosed clinically and only then analysed for the presence of drugs or HIV in order to study the roles of drugs and HIV in AIDS.

2. Correlation between HIV and AIDS Does Not Prove Causation

The surveys from San Francisco and Vancouver have stated that HIV causes AIDS because all of their AIDS cases were HIV antibody-positive (Table 1). However, this conclusion is flawed for three reasons.

i) Even a perfect correlation with HIV does not prove causation without functional evidence. It confirms only the first but not the third of Koch's postulates. Indeed, other microbes have been proposed as causes of AIDS on the basis of high or perfect correlations, as for example human T-cell leukemia virus I (7) and cytomegalovirus (8–12). Thus, it was arbitrary to single out HIV as the cause of AIDS, because other microbes also correlate with AIDS.

Since both surveys report perfect correlations not only between AIDS and HIV but also between AIDS and drugs (see below), the choice of HIV as the causative correlate was even more arbitrary than if it had been the only known AIDS correlate. This is because the epidemiological method cannot by itself distinguish between three consistent alternatives: HIV alone, drugs and HIV, and drugs alone.

ii) A positive HIV antibody test is not a rational prognosis for a viral disease, because antibodies are the classical indicator for a virus that has been rejected by the immune system. In response to antibodies,

which of necessity include cellular immunity, the virus is either eliminated or restricted to latency—the reason why HIV is exceedingly difficult to isolate from antibody-positive carriers with and without AIDS (13–16). Thus, a positive antibody test is in general a counter-indication for future viral pathogenicity.

Moreover, a positive antibody test is not a reliable indicator for the presence of a virus (17, 18). According to a recent review entitled "HIV Testing: State of the Art," "depending on the population tested, 20 to 70% of . . . two successive ELISAs are confirmed by Western blot [two variant antibody tests]," i.e. 30 to 80% are false positives (19). But even in groups with a high probability of infection, such as the San Francisco and Vancouver groups, significant numbers of false positive Western blots have been recorded (18). For example, Schechter et al. reported in 1991, that 33 out of 158 (17%) of Western blot-confirmed, antibody-positives in their Vancouver cohort were HIV-free, based on HIV DNA testing with the polymerase chain reaction (20). Two of these 33 had AIDS, the remainder had various degrees of immunodeficiency and lymphadenopathy, but not sufficient for a diagnosis for AIDS. The report also cites further studies documenting that 14 to 17% of antibody-positive homosexuals are HIV-provirus free.

Since a 100% correlation with antibody-positivity does not mean 100 % infection, it is probable that the AIDS cases from the San Francisco survey, and certain that the cases from the Vancouver survey included HIV-free AIDS.

iii) At least 4621 HIV-free AIDS cases have been documented in the literature, indicating that HIV is not necessary to cause AIDS (18).

Thus the conclusion of both surveys that HIV causes AIDS, because all AIDS cases appeared antibody-positive, is not valid.

3. Failure to Identify Drug-Free AIDS, the Absolute Argument against the Drug-AIDS Hypothesis

The most critical argument against the drug-AIDS hypothesis would be a group of drug-free AIDS patients. However neither the Vancouver nor the San Francisco survey provided drug-free AIDS cases.

All 136 AIDS patients from Vancouver belonged to a group of 365

HIV-positive drug users (Table 1). This is documented as follows: Among the 365 HIV-positive men surveyed, 88% reported consumption of nitrites and 80% the use of other "illicit" recreational drugs including cocaine, heroin, amphetamines, methylene amphetamines, lysergic acid, and diethylamide (3). Thus, assuming no specific linkages between the use of these different drugs, 98% have used at least one drug, because only 2% (12% x 20%) reported no use of recreational drugs. And 70% (88 x 80) have used at least two drugs. Even this high drug use may be an underestimate because illicit drug use is known to be underreported and because the Vancouver survey did not ever verify self-reported drug use by any tests. Indeed, a recent article by the Vancouver team reports that 100% of 87 AIDS patients had used nitrites (21). I followed their suggestion to "reread" their article for a statement that this group "includes some whose use was zero" (22), but I failed to find that statement. In addition the Vancouver survey failed to consider AZT use by HIV-positives (see below), but acknowledged it upon request (22) and in previous publications (20). Thus, the Vancouver survey lacks the most critical epidemiological argument to refute the drug-AIDS hypothesis—a group of verified non-drug users who developed AIDS.

In response to this critique (23), the Vancouver team has recently claimed that 19, or 5%, of the 365 HIV-positive men surveyed "... reported no recreational drug use ..." and that " ... their CD4 counts fell a mean of 138/microliter per year ..." (22). However there was no verification that these men were indeed recreational drug-free and no mention whether they were on AZT. Moreover, no claim was made that these presumably drug-free men ever developed AIDS.

Despite a claim to the contrary, the San Francisco survey also lacked drug-free AIDS. The survey reported that 100% of their 215 AIDS cases had used nitrites in its table 2 (2). Additional undetermined percentages of these cases had also used other illicit recreational drugs, such as cocaine and amphetamines (2). Moreover, since the introduction of AZT in 1987, 132 (84%) of the 157 AIDS cases observed by the San Francisco survey were on AZT (Ascher et al., personal communication, 9 April 1993). AZT is generally prescribed before AIDS, once T-cell counts drop below 500 per microliter (24). Thus, it is safe to conclude that all 215 AIDS patients from San Francisco were on multiple drugs

including nitrites, one or more other recreational drugs and AZT (Table 1).

Yet the San Francisco survey claims a "group" of "seropositive no-drug" users who lost T-cells, although there are no data for such a group in their paper. This is documented as follows. According to the paper's table 1, all AIDS patients were HIV-positive homosexuals, and all HIV-positives were homosexuals (2). All heterosexuals were HIV-negative, except one who was a drug addict (Ascher, personal communication). According to Table 2, 100% of the homosexual men were either "heavy" or "light" nitrite users, namely 144 plus 668 out of 812 (text) (2). Thus, all AIDS patients and all HIV-positives in this study had used at least nitrites. In addition they had used cocaine, amphetamines, other recreational drugs and AZT. However, the corresponding figure purports, in color (!), to give data on "average adjusted" T-cell losses of three seropositive groups, with "no drug use," with "moderate drug use" and "heavy drug use," respectively. Three curves in that figure correspond to these three groups. Yet based on tables 1 and 2 the category "seropositive—no drug use" is an empty set representing nobody. Clearly the curve labeled "seropositive—no drug use" needs to be "adjusted" to reality.

In response to this critique (23), the San Francisco epidemiologists "acknowledge that it might have been clearer ... if we had labeled the latter group as 'none/light' in the table ..." (25).

Thus, neither the San Francisco nor the Vancouver survey provided the absolute epidemiological argument to exclude drugs as causes of AIDS, i.e. drug-free AIDS cases.

4. Failure to Quantitate Drug Dosage—the Key to Drug Toxicity

The San Francisco team relied for drug use information on statements "for the 24-month period before entry into the study" (2), and the Vancouver team on "ever versus never" statements. Thus the epidemiologists from San Francisco and Vancouver failed to quantitate drug consumption in three ways: i) They did not determine the cumulative lifetime drug dose of their subjects; ii) They did not verify self-reported

drug use by any tests, although they acknowledged that illicit drug use is generally underreported (22); iii) They ignored AZT use altogether.

Indeed, the failure to quantitate drug consumption did not reflect a lack of suitable data, but a genuine disregard for drug toxicity. For example, the San Francisco survey stated "We examined the cohort at 6-month intervals for 96 months ..." But for correlations with AIDS over the 8-year study period "We compared heavy drug use for the 24-month period before entry into the study ..." (2). The Vancouver survey asked study subjects for drug use on an "ever versus never" basis, "once every six months" according to their 1993 study (3), and "on an annual basis" according to an earlier study (20). Clearly such efforts shed little light on the lifetime drug dosage of study subjects.

If one were to correlate lung cancer with information on smoking for only 24 months or on an "ever versus never" smoking statement the results would be as inconclusive as the results on drugs and AIDS described by the San Francisco and Vancouver teams. Drug use would indeed be as "casually [sic] associated with AIDS" as the San Francisco team writes in its paper (2). By not quantifying and by not verifying drug use, both teams missed the most relevant parameter of drug toxicity, the lifetime dosage.

Other epidemiological studies aimed at distinguishing between drugs and HIV as causes of AIDS in homosexuals from San Francisco (26) have likewise been invalidated by the failure to quantitate and verify drug consumption (27).

The casual disregard for drug toxicity by the San Francisco and Vancouver surveys is hard to reconcile with the solid documentation of drug toxicity in the literature. Toxicity has been documented empirically for all and mechanistically for many psychoactive drugs (4). For example, alkylnitrites are directly toxic as they are rapidly hydrolyzed in vivo to yield nitrite ions which react with all biological macromolecules (28). Toxicity for the immune system, the central nervous system, the hematological system and pulmonary organs has been observed after short exposure to nitrites in humans and animals (28–33). In addition, nitrites were among the first known mutagens and carcinogens, the reason they are considered health hazards in food (34, 35). The toxicity of the long-term use of cocaine, amphetamines and other illicit

neurotropic, psychoactive drugs has been documented since 1909. It includes nearly all AIDS-defining diseases such as lymphopenia, lymphadenopathy, fever, weight loss, septicemia, increased susceptibility to infections, low T4 to T8 cell ratios and profound neurological disorders (4, 36–49). These drugs are neurotoxic directly and immunotoxic indirectly via malnutrition, insomnia and poor sanitation (4).

Unlike the toxicity of psychoactive drugs consumed by AIDS patients, the toxicity of the DNA chain terminator AZT is not a side effect, but a design. AZT was designed for chemotherapy over 30 years ago to kill all growing cells in cancer patients by terminating DNA synthesis (50). Since this is its only known function, its cytotoxic effects on the fast growing cells of the bone marrow (50–55), the source of T-cells, are equivalent to "AIDS by prescription" (4, 5).

Moreover, recreational drugs and AZT are used in sufficient quantities to explain fatal AIDS diseases. An approximate daily psychoactive dose of amyl nitrite is 1 ml (or 0.01 mol) (55, 56). This represents about 6×10^{21} molecules and corresponds to 6×10^{7} molecules for every one of the 10^{14} cells of the human body, enough for abundant toxicity. The daily prescription of 500–1500 mg AZT also corresponds to $2–6 \times 10^{21}$ molecules or $2–6 \times 10^{7}$ for every cell in the human body, more than enough to kill every cell that takes it up (4).

In response to this critique (23), the San Francisco and the Vancouver team now claim in letters to *The Lancet* that drugs do not cause AIDS because 39 (25) and 78 (22) HIV-free drug users did not develop AIDS. Again the self-reported drug use of these subjects was not quantitated and is likely to have been lower than in HIV-positives because HIV is a marker for drug use (see below). Another clear reason why they might not have developed AIDS diseases is that HIV-negatives are not prescribed the immunotoxic AZT (see above).

However, a negative representing a limited number of cases does not disprove any scientific hypothesis, including the drug-AIDS hypothesis. For example, subjects who have smoked for 20 years and not developed lung cancer do not disprove the smoke-cancer hypothesis, and subjects who have been drinking for 20 years and have no cirrhosis do not disprove the alcohol-cirrhosis hypothesis.

Likewise the absence of AIDS in 1 million healthy HIV-positive

Americans and in 0.5 million healthy HIV-positive Europeans and in 8 million healthy HIV-positive Africans (57) does not disprove the HIV-AIDS hypothesis. The San Francisco survey even reported 230 healthy subjects, and the Vancouver survey reported 229 healthy subjects who were drug users and were HIV-positive but did not develop AIDS (Table 1). Indeed, the majority of the HIV-positive drug users remained healthy for 8 years (Table 1). Again these negatives neither disprove the drug nor the HIV-AIDS hypothesis.

5. Censoring HIV-Free AIDS with the HIV-Based AIDS Definition?

By adhering to the HIV-based AIDS definition AIDS researches bias against HIV-free AIDS. Indeed, American AIDS statistics from the Centers for Disease Control do not list the incidence of HIV-free AIDS cases (18).

Adherence to the HIV-based AIDS definition appears to be the reason why the survey from San Francisco did not distinguish between the 30 AIDS-defining diseases including dementia, diarrhea, lymphoma and pneumonia, except for Kaposi's sarcoma. In an effort to provide HIV-independent diagnoses of AIDS both surveys report T-cell depletion (3), as "a more objective and, indeed, the primary pathognomonic feature of AIDS" (2). However, both surveys fail to indicate how T-cell depletion relates to the incidence of AIDS in their cohorts, e.g. whether any of their AIDS cases was just diagnosed by a low T-cell count.

Furthermore both surveys fail to recognize that not all AIDS diseases are based on immunodeficiency (4). For example, in 1992, 39% of all American AIDS patients developed such non-immunodeficiency AIDS diseases as Kaposi's sarcoma (10%), wasting (20%), dementia (6%), and lymphoma (3%) (58). These diseases are not caused by and often not associated with immunodeficiency (4). This may be the reason why the San Francisco survey has listed AIDS and Kaposi's sarcoma as separate items in its table 2 (2).

The following examples suggest that the HIV-based AIDS definition (59, 60) has biased AIDS diagnoses from San Francisco and Vancouver against HIV-free AIDS. The Vancouver survey reports no AIDS

in 350 HIV-negative homosexual men in 8.6 years ("no AIDS illnesses occurred in men who remained persistently negative for HIV-1 antibody") (3) and the San Francisco survey reports "0" cases of AIDS in 367 HIV-negative men in 8 years (2).

However, it is improbable that no AIDS-defining disease—e.g. diarrhea, pneumonia, candidiasis, herpes infection, dementia, >10% weight loss, fever for several weeks, toxoplasmosis, cryptococcosis, cryptosporidiosis, cytomegalovirus infection, mycobacterial infection and "other illnesses" (3)—would have occurred in 717 male drug users in over 8 years, since the very same diseases have been described in drug addicts since 1909 (see above). According to table 2 of the San Francisco survey, 100% of HIV-negative homosexual men had used nitrites and an unknown percentage had also used cocaine, amphetamines and other recreational drugs (2), and according to the Vancouver survey, 56% had used nitrites, and 58% had also used cocaine, amphetamines, heroin, lysergic acid, diethylamide and other illicit drugs (3). Thus, it appears that the reported absence of AIDS in these HIV-free groups reflects the bias of either not diagnosing or not reporting AIDS-defining diseases in HIV-negatives.

6. Drug Data from San Francisco and Vancouver Confirm the Drug-AIDS Hypothesis

Data from the San Francisco and Vancouver surveys confirm the drug hypothesis not only with perfect correlations but also with (i) quantitative and (ii) qualitative arguments for the drug hypothesis—despite the authors conclusions—on several grounds.

i) *Dose response relationships* (a-c). (a) The HIV-AIDS hypothesis and the authors of the surveys from San Francisco and Vancouver assume that AIDS follows HIV infection with an average lag of currently 10 years (20, 60). This lag is termed the latent period of HIV. According to this hypothesis healthy HIV carriers are those who have not accumulated sufficient HIV lag time to experience HIV-mediated AIDS.

However, since HIV is not active during this lag period and rarely even active during AIDS (4, 61–64), while the HIV carriers, as for example those from AIDS risk groups in San Francisco and Vancouver, are

actively using recreational drugs and also AZT, this lag period in fact appears to be a quantitative measure for 10 years of drug use.

Indeed, studies that have measured toxicity of recreational drugs over time, have documented that about 10 years of nitrite use are necessary to cause Kaposi's sarcoma or pneumonia (29), even in persons without HIV (65). Likewise other recreational drugs cause in 10 years immunodeficiency diseases in persons with and without HIV (37, 47, 66–69). This toxicity threshold provides a rational explanation for the 10-year "enigmatic mechanism of the HIV pathogenesis of AIDS." (2).

(b) The claims that HIV-negatives from San Francisco and Vancouver did not develop AIDS diseases can also be illuminated in the light of the dosage argument. Drug use and HIV infection are linked via sexual activity. Recreational drugs are used by homosexuals at risk for AIDS as psychological and physiological aphrodisiacs. They generate euphoria and facilitate anal intercourse, particularly the nitrites which have been prescribed as vasodilators against angina since the 19th century (28, 29, 70). Since it takes about 1000 sexual contacts to pick up HIV (4), and since these contacts are frequently drug-promoted, HIV antibody-positives have consumed the drug the equivalent of 1000 contacts more than HIV-negatives.

Indeed, the Vancouver team acknowledges that "risk behaviors are known to correlate to HIV-1 infection . . ." (3). And the San Francisco team reports that 72.9 % of the heavy drug users but only 50.9 % of the light users are HIV positive (see table 2, 2). Thus, HIV-positives are likely to have used more recreational drugs than HIV-negatives. It is for this reason that I have proposed HIV as a marker of AIDS risks, rather than the cause of AIDS: the more drug-mediated sexual contacts the more likely is infection by HIV (4). In addition, HIV-negatives were spared AIDS-diseases resulting from AZT, which is only prescribed to HIV-positives. Therefore in addition to biases due to the HIV-based AIDS definition (see above), a lower dosage of recreational drugs and the absence of AZT shed light on the observation that HIV-negatives were not reportedly developing AIDS diseases.

(c) The San Francisco survey confirms the quantitative aspect of the drug hypothesis even more directly with the observation that "heavy" drug users had 1.6 times as much AIDS and had 2 times as much

Kaposi's sarcoma as "light" users (see table 2, 2). The authors correctly suggest that "this crude association is apparently the basis for Duesberg's hypothesis." The Vancouver team even acknowledged one HIV-positive death from drug overdose "excluding AIDS-related mortality" (3). Thus both teams provide drug-AIDS dose-response relationships—a definitive argument for the drug-AIDS hypothesis.

ii) *Drug-specific diseases.* The surveys from San Francisco and Vancouver also provide qualitative evidence in support of the drug-AIDS hypothesis. The San Francisco epidemiologists report that 43% (92/215) and the Vancouver epidemiologists that 25% (34/136) of their AIDS victims had Kaposi's sarcoma. This is 4.3 and 2.5 times higher than the U.S. national average of 10% (58). This result is compatible with national statistics indicating that Kaposi's sarcoma is about 20-times more common in male homosexuals than in all other risk groups (71).

The fact that Kaposi's sarcoma occurs almost exclusively in homosexuals but not in other risk groups is hard to reconcile with the claims of the San Francisco and Vancouver teams that HIV, contracted by "receptive anal intercourse," causes Kaposi's sarcoma (3, 72). Indeed, a controlled study has just excluded HIV, but not anal intercourse, as the cause of AIDS. The study showed that among two HIV-positive groups of homosexuals those who developed AIDS had practiced receptive anal intercourse more than twice as much as those who remained healthy (73). In view of such discrepancies with the virus hypothesis, its followers, including the Vancouver team (21), have postulated a second, as yet unknown sexually transmitted agent, to explain the restriction of Kaposi's sarcoma to homosexuals (71, 73, 74).

However Kaposi's sarcoma in homosexuals is totally consistent with the hypothesis that nitrites inhaled to facilitate anal intercourse cause pulmonary and epithelial Kaposi's sarcoma irrespective of the presence of HIV (4, 28). Indeed, 100 % of the AIDS patients from San Francisco and 100 % of the Kaposi cases from Vancouver (21) had inhaled nitrites.

Since HIV replicates via a DNA intermediate, DNA chain terminators, like AZT, are considered antiviral drugs and are prescribed as AIDS prophylaxis to healthy HIV-positives (53) and as therapy to HIV-positive AIDS patients (4). Since AZT kills all dividing human cells by DNA chain termination, it is particularly toxic to the rapidly prolifer-

ating bone marrow, the source of T-cells (4, 50–54). Thus, the widespread use of AZT by HIV-positives from the San Francisco and Vancouver groups (see above) explains the decline of T-cells in HIV-positives as AZT-specific disease.

Moreover, the widespread AZT use also sheds light on the 8% incidence of lymphoma among HIV-positive AIDS patients from Vancouver (3). This is high compared to the national average of 3% in the U.S. (58), but is normal for AZT recipients who have an annual lymphoma incidence of 9% (75).

7. Conclusions

The most urgent and growing problem facing the HIV-AIDS hypothesis is its total failure in terms of public health benefits. Despite enormous efforts over the last 10 years, costing the US taxpayer alone $4 billion, no vaccine has been developed, no AIDS patient has been cured, no prevention has slowed the spread of AIDS. These are the hallmarks of a flawed hypothesis.

Ten years of intensive research have failed to demonstrate that HIV causes AIDS or is even toxic to human cells (4, 76). Indeed HIV is mass-produced in indefinitely growing human T-cell lines at titers of up to 106 infectious units per ml (4, 77). Therefore the primary argument for the HIV-AIDS hypothesis is just HIV/AIDS correlations of the kind analysed here (59, 60, 74).

In the face of a 10-year history of scientific and public health failures, the scientific method calls for alternatives to the prevailing HIV-AIDS hypothesis such as the drug-AIDS hypothesis. This hypothesis is based on excellent correlations, e.g. according to the Centers for Disease Control, 30% of all American AIDS patients including nearly all heterosexuals with AIDS are intravenous drug users (58), and about 60% are male homosexuals who have used aphrodisiac drugs as has been demonstrated here and previously (4). Furthermore drug toxicity has been documented and dose-response relationships and drug-specific AIDS diseases have been described here and previously confirming the drug-AIDS hypothesis (4).

If both AIDS-correlates, drugs and HIV, were given unbiased con-

sideration, the choice between drugs and HIV, or antibodies against HIV, would be easy. It would appear more rational to conclude that drug intake "has an integral role in CD_4 depletion ... and AIDS" (3) than HIV or antiviral antibodies.

Therefore, I call for a reinvestigation of whether in the predominant AIDS risk groups in the U.S. and Europe, male homosexuals and intravenous drug users, HIV or drugs cause AIDS based on the following criteria:

i) AIDS must be determined clinically, independent of HIV. All AIDS-defining diseases must be identified in order to detect drug-specific diseases.

ii) HIV must be identified by virus tests, rather than antibody tests. A positive antibody test would be considered tentative until it is confirmed by HIV isolation.

iii) Drug use must be quantitated to determine dose-response relationships. Both recreational drug use and AZT use must be compounded.

iv) If no drug-free AIDS can be found to eliminate drugs, and no HIV-free AIDS to eliminate HIV, functional tests must be developed to identify the causative correlate. HIV toxicity could be tested in susceptible cells in culture, in animals and in accidentally infected humans who lack other risk factors. Drug toxicity could be tested in cells in culture, experimental animals or in HIV-free drug addicts.

Acknowledgments

I thank Lars Chapsky, Bryan Ellison, Phil Johnson, Harry Rubin, Siggi Sachs, Jody Schwartz, Richard Strohman and Yue Wu for critical review and discussions. I am supported by The Council For Tobacco Research-USA, Inc. and by private donations from Bill Bowie (New York), Glenn Braswell (Los Angeles), Dr. Richard Fischer (Annandale, VA), Dr. Fabio Franchi (Trieste, Italy), Dr. Friedrich Luft (Berlin).

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Chapter Nine

Infectious AIDS—Stretching the Germ Theory Beyond Its Limits*

International Archives of Allergy and Immunology, 103: 118–126, 1994

Key Words: Latent viruses not pathogenic; Infectious diseases equal between sexes; HIV fails Koch's postulates; AIDS only after HIV neutralization; HIV-free AIDS; Non-contagious AIDS; Clinical definition of AIDS; Non-immunodeficiency AIDS diseases; Drug-AIDS hypothesis; Drug use epidemic.

Abstract

The hypothesis that human immunodeficiency virus (HIV) causes AIDS was advanced in 1984, based only on circumstantial evidence. To this date, the primary evidence are correlations between the presence of antibody against HIV and AIDS. But these correlations are biased by proponents of the HIV hypothesis in favour of HIV. They ignore HIV-free AIDS and they base correlations on selected studies because there are no national HIV-AIDS statistics. The HIV-AIDS hypothesis has made the following predictions: (1) AIDS would 'explode' from the original risk groups into the general population via sexual transmission of HIV. (2) Health care workers would contract AIDS from their patients, scientists from propagating HIV, and prostitutes from their clients. (3) The 150 chimpanzees that have been experimentally inoculated with HIV, and the 15,000 American hemophiliacs who have been iatro-

*This article is the first of two in "Controversy: HIV and AIDS," sponsored by Georg Wick, editor-in-chief of *International Archives of Allergy and Immunology.*

genically inoculated before 1984, would develop AIDS. (4) immunity and vaccines would protect against AIDS. (5) HIV would cause AIDS by killing T-cells. (6) AIDS would occur only in people infected by HIV. But none of these predictions proved to be correct. Recent studies show that HIV is a passenger virus instead of the cause of AIDS: (1) AIDS occurs at unpredictable intervals after infection; (2) HIV may be active, passive, or totally absent from otherwise identical AIDS cases. Indeed, AIDS does not meet one of the classical criteria of infectious disease: (1) Equal distribution between the sexes; (2) disease following infection within days or weeks, the time microbes take to become either immunogenic or pathogenic or both; (3) the presence of a common active microbe. Therefore it is proposed that American and European AIDS is caused by the long-term consumption of recreational drugs and the anti-HIV drug AZT. This hypothesis is testable and provides a rational basis for AIDS control.

Introduction

In April 1984, the retrovirologist Robert Gallo from the National Institutes of Health in Bethesda and the American Secretary of Health and Human Services announced, at an international press conference in Washington, that the acquired immunodeficiency syndrome (AIDS) was caused by a retrovirus, now termed human immunodeficiency virus (HIV) [1]. The announcement was made before even one American study on HIV had appeared in the scientific literature. Gallo and his collaborators cited antibodies against the virus in "about 85% of patients with AIDS" as the only evidence for their hypothesis [1]. Although AIDS occurred despite antiviral antibodies, the researchers expressed "hope that a vaccine would be ... ready in about two years" [1]. In the scientific papers that followed the next month, HIV was said to cause AIDS by depleting T-cells [2, 3]. The hypothesis proposed that HIV would cause all of the 30 heterogenous AIDS diseases [4], including those that are not consequences of immunodeficiency, such as cancer, weight loss and dementia (Table 1) [5].

Table 1
AIDS-defining diseases in the US in 1992[a]

Imuno-deficiencies	Percentages	Nonimmuno-deficiencies	Percentages
Pneumonia	42	Wasting disease	20
Candidiasis	17	Kaposi's sarcoma	9
Mycobacterial, including 3% tuberculosis	12	Dementia	6
		Lymphoma	4
Cytomegalovirus	8		
Toxoplasmosis	5		
Herpesvirus	5		
Total (>61% due to overlap)	61	Total	39

a. The data are from the Centers for Disease Control [4].

Infectious AIDS: From Hypothesis to Dogma

In 1986, the American Academy of Sciences and the Institute of Medicine assembled a blue ribbon committee of medical scientists to confront the growing AIDS epidemic. The committee, chaired by David Baltimore, concluded that the isolation of HIV by Montagnier et al. [6] and Gallo et al. [2] "led to its definitive identification as the cause of AIDS" [7]. Without mention of dissent [8, 9], a derivative committee declared in 1988: "The committee believes that the evidence that HIV causes AIDS is scientifically conclusive" [boldface in original] and proposed to rename AIDS "HIV disease" [10]. The committees had sealed the hypothesis into national dogma. However, the committee's conclusion was based only on circumstantial evidence including five questionable assumptions:

(1) The primary assumption was that, " ... close to 100 percent of the affected individuals can be found to harbor the virus" and "The probability that this distribution might have occurred by chance is less than one in a million" [10].

However, since no national HIV-AIDS statistics exist [11], the committee had to rely on selected individual studies and unpublished observations. For example, the committee selected a *Science* News & Comment article entitled "A rebel without a cause of AIDS" [9], an unpublished speech of the epidemiologist Winkelstein and the papers of Montagnier and Gallo as the source for the "close to 100%" correlation [10]. But the original paper by Montagnier et al. [6] only reported a single isolation of HIV from the lymph node of a person who did not have AIDS, and Gallo's isolate proved to be Montagnier's virus [12]. And the authenticity of the HIV-AIDS correlations from Gallo's group has since been questioned on several accounts [12].

(2) The committee also believed that "The virus is not found in persons who are not at risk for infection"—assuming that infection was restricted to AIDS risk groups, e.g. male homosexuals, intravenous drug users and recipients of transfusions [7]. However, HIV has since been found in 1 million healthy Americans, 0.5 million healthy Europeans, 1.5 million healthy South Americans, 1.5 million healthy Asians and 8 million healthy Africans [13].

(3) The committee further believed that " ... AIDS is unknown in populations that are free of HIV antibodies," i.e. that there is no HIV-free AIDS [10]. However, many HIV-free AIDS cases had already been reported by 1986 and 1988, when the committees confronted AIDS [11].

(4) The committee accepted without questioning the unique practice of the HIV researchers to present antibodies against HIV as pathogenic powers of HIV. Proponents of the HIV-AIDS hypothesis interpret these antibodies as indicators of current and future HIV disease. However, antibodies against all other microbes are signs of rejection of the microbe and protection against future disease.

(5) The committee accepted uncontrolled statistics as evidence for AIDS from transfusion of HIV [10]. For example, AIDS researchers blame HIV for pneumonia and other opportunistic infections that occur in about 2% of HIV-positive hemophiliacs per year [5, 10]. However, controlled studies have since shown that the incidence of immunodeficiency in matched groups of HIV-positive and negative hemophiliacs is the same [5].

Thus the committee had adopted the virus-AIDS hypothesis on the basis of questionable assumptions, primarily the assumption that all AIDS correlates with HIV.

How Good is the Correlation between HIV and AIDS?

The natural coincidence between HIV and AIDS can only be determined by first diagnosing AIDS clinically and then testing for HIV. However, since the HIV-AIDS hypothesis has been accepted in 1986, the definition of AIDS by clinical criteria alone has been abandoned in America and Europe in favor of an HIV-based definition [10]. Moreover all HIV-AIDS correlations are based on selected individual studies, because to date no national and international AIDS statistics reporting HIV tests exist [11]. As a result, proponents of the HIV-AIDS hypothesis bias HIV-AIDS correlations in several ways:

(1) They cite HIV-AIDS correlations from selected, individual studies which are frequently based on non-standardized and unconfirmed HIV antibody tests [11, 14].

(2) They present antibodies against HIV, instead of activities and titers of HIV, as a rational cause of AIDS.

(3) They exclude clinically diagnosed, HIV-free AIDS defining diseases from their statistics, e.g., the 4,621 cases cited below [11], because the HIV-AIDS hypothesis postulates that HIV causes AIDS. Therefore HIV-free AIDS cases are either diagnosed by their old names, e.g. Kaposi sarcoma, pneumonia, etc., or renamed "idiopathic CD4 lymphocytopenia," or ICL [15].

But the effort to set apart HIV-positive from HIV-negative AIDS cases is not based on any clinical or convincing epidemiological criteria [11, 16]. According to an editorial by Fauci: "Given the heterogeneity of the [ICL] syndrome, it is highly likely that there is no common cause" [15]. Yet at the same time the proponents of the HIV hypothesis, including Fauci, insist that HIV must be the common cause of the 30 heterogenous AIDS diseases.

The editorial also argues that the HIV-free AIDS or ICL cases are unlike the HIV-positive cases because "Approximately one third of the

patients are women, as compared with 11% among those with HIV . . ." (in America). But proponents of the HIV-AIDS hypothesis, including Fauci, insist that HIV also causes African AIDS, despite about 50% of the African patients being women [10].

Indeed, other retroviruses have been proposed as causes of HIV-free AIDS, particularly at the VIII International AIDS Conference in 1992 in Amsterdam [17, 18], because these cases were clinically indistinguishable from HIV-positive AIDS. Following the HIV precedent, these retroviruses were considered "new" AIDS causes simply because of their presence in these cases.

It follows that the primary argument for the HIV-AIDS hypothesis, the HIV-AIDS correlation, is a circular argument. It is in reality an artefact of the HIV-based AIDS definition, which is a restatement of the HIV hypothesis.

To date the virus-AIDS hypothesis has been a complete failure in terms of public health benefits: no vaccine has been developed, AIDS continues to spread despite efforts to stop the spread of HIV, and nobody has ever been cured from AIDS. However the acid test of a hypothesis is not to produce useful results, but to make accurate predictions.

Predictions of the HIV-AIDS Hypothesis

The HIV-AIDS hypothesis makes the following testable predictions, none of which proved to be correct [5, 19]:

Predicted	**Observed**
(1) AIDS in America would "explode" from the original risk groups via sexual transmission into the general population [20]. Like all other sexually transmitted diseases, AIDS would equilibrate between the sexes.	In America, AIDS has remained in the original groups, e.g. male homosexuals, male and female intravenous drugs users, and recipients of transfusions. Since 1981 90% of all American AIDS cases have been males [4].

Predicted	Observed
(2) The spread of AIDS would follow the dissemination of HIV.	Although AIDS increased in America from a few hundred to about 50,000 cases annually in the last 10 years [4], HIV did not spread at all. Ever since HIV became detectable in 1985, an unchanging 1 million Americans have been HIV-positive (fig. 1a) [5, 10, 24–26]. To hide this discrepancy, a latency period was postulated that was initially estimated at less than 1 year and is currently estimated at 10 years [10, 21–23].
(3) Health care workers would contract AIDS from their patients, scientists from propagating virus [27] and prostitutes from their clients, particularly in the absence of an anti-HIV vaccine or drug.	Not a single confirmed case exists in the scientific literature of a health care worker who contracted AIDS from one of the over 250,000 American AIDS patients. None of the ten thousands of HIV researchers have developed AIDS from propagating HIV. And no prostitutes picked up AIDS from their clients—despite the absence of antiviral vaccines or effective drugs [5].
(4) Chimpanzees inoculated with HIV would develop AIDS, and the 15,000 American hemophiliacs, who were iatrogenically infected before 1984, would die from AIDS.	Not one of the 150 chimpanzees inoculated with HIV since 1983 has developed AIDS [5, 19]. Contrary to prediction, the median life of American hemophiliacs has doubled during the last 10–15 years after 75% (15,000) had already been infected by
(5) Natural or vaccine-induced anti-HIV immunity would cure AIDS or protect against future AIDS.	Natural antiviral immunity observed in many AIDS patients does not protect against AIDS [5, 19].

Predicted	Observed
(6) HIV would cause AIDS by killing T-cells [2, 7, 10, 28].	HIV, like all other retroviruses, is not cytocidal [5]. It is mass-produced for the "AIDS test" in immortal T-cell lines at titers of 106 infectious units per milliliter [29–31]. And HIV does not kill primary T-cells in vitro [32–34].
(7) All AIDS diseases are consequences of HIV-mediated T-cell deficiency.	Acquired immunodeficiency only explains about 61% of all American AIDS diseases, e.g. opportunistic infections such as Pneumocystis carinii, Candida, tuberculosis, etc. [4] (table 1). But 39%, including Kaposi sarcoma, lymphoma, >10% weight loss, and dementia (table 1), are neither caused by, nor consistently associated with immunodeficiency [5]. For example, two studies of homosexuals with Kaposi sarcoma report that the immune systems of 20 [35], and 19 [36] were normal when their disease was first diagnosed.
(8) AIDS would be restricted by controlling the spread of HIV via "safe sex" and via programs adopting the use of "clean needles" for the injection of unsterile street drugs.	AIDS continues to increase despite the "safe sex" and "clean needle" programs [4].
(9) AIDS would only occur in HIV-positive people.	At least 4,621 HIV-free AIDS cases have been reported since HIV could be detected in 1984 [11].

The failure to make valid predictions is the hallmark of a flawed hypothesis. It raises two fundamental questions: (1) Is HIV a passenger virus rather than the cause of AIDS? (2) Is AIDS infectious?

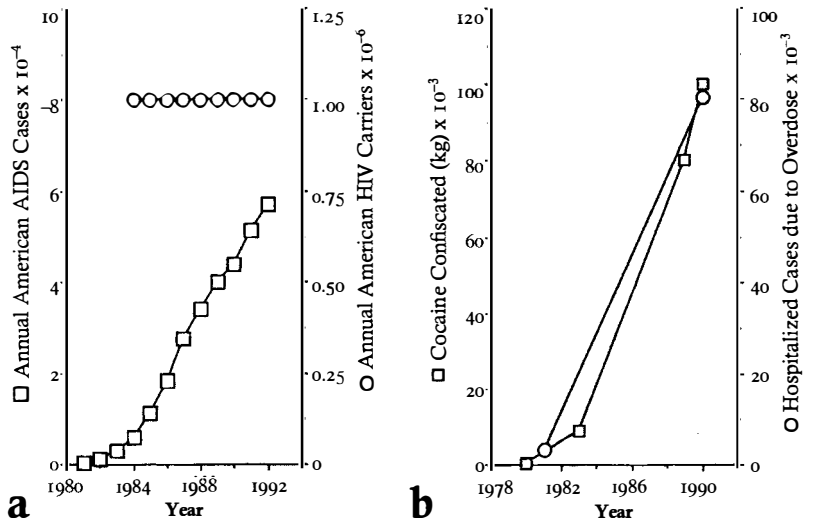

Figure 1 **a** Noncorrelation between the spread of AIDS and the nonspread of HIV in America since 1981 and 1984, respectively. The postulated parallelism between the spread of HIV and AIDS [10] assumes that HIV requires a 10-year latency to AIDS and that HIV increased for 10 years before it became detectable in 1984 and then stabilized completely. It predicts that American AIDS will plateau in 1994.

b Spread of cocaine use and cocaine-related hospital emergencies in the US since 1980 and 1982, respectively. Note the parallelisms between the spread of AIDS, cocaine use and cocaine-related hospital emergencies in contrast with the nonparallelism between the spreads of AIDS and of HIV from 1984 to present.

Is HIV a Passenger Virus Rather than the Cause of AIDS?

The correlation argument assumes that the presence of a virus in a disease is sufficient proof of causation. But the presence of a virus in a disease is by no means proof of causation. Particularly since HIV does not cause AIDS if inoculated into chimpanzees or if iatrogenically introduced into hemophiliacs, it could be just a harmless passenger virus.

Passenger viruses are "widely distributed ... in mammals, causing no obvious disease" [37]. In the absence of functional proof, the distinction between a causative and a passenger virus can be made by the temporal relations between infection and disease, by the consistency of its presence, and by the biochemical activity of the virus during the course of the disease as follows:

Causative	**Passenger virus**
(1) Autonomous viral/microbial pathogens initiate disease within days or weeks after infection. After a primary infection, immunity eliminates most viruses, but some become latent [38, 39]. Latent viruses may be reactivated in response to acquired immunodeficiency to cause disease again [38, 39], as is shown for the example of herpes virus in figure 2.	The time of primary infection by a passenger virus is unrelated to the initiation of disease. Because it is irrelevant to the initiation of a disease, the primary infection may occur decades before the disease or during the course of the disease as is shown for the example of HIV and AIDS in figure 2b.
(2) The presence of the causative microbe is obligatory for disease (Koch's first postulate).	The presence of a passenger is irrelevant for disease.
(3) A causative virus is maximally active just prior to and during disease (fig. 2). This is true even if the virus depended on a co-factor such as a helper virus to cause disease. The virus initiates and determines the course of the disease by its activities, like a pilot initiates and determines the flight of a plane.	During the disease the passenger virus may be either active or latent, because it is irrelevant to the causation of the disease it is associated with (fig. 2).

Causative	**Passenger virus**
(4) Some passenger viruses/microbes can be conditionally pathogenic if activated by an immunodeficiency, e.g. *Pneumocystis carinii,* Candida, herpes virus and cytomegalovirus. Such passengers function as cofactors of a disease. The symptoms of an activated passenger are called "opportunistic infections."	A harmless passenger virus/microbe would cause no specific symptoms, even if it were activated. It is not even a cofactor of a disease, as for example HIV in AIDS.

HIV meets all criteria of a harmless passenger virus in AIDS:

(1) HIV infection precedes AIDS by unpredictable intervals that average about 10 years. This time is referred to as latent period of HIV by proponents of the HIV-AIDS hypothesis, although HIV typically remains latent even when AIDS occurs [5]. Several groups report that HIV may reach high titers during the primary infection [40–42]. According to Piatak et al., these titers range from 10 to 10^4 infectious units per milliliter [42]. Despite these relatively high HIV titers in some people, and despite the absence of antiviral immunity in all, there is no AIDS during the primary infection [40–42]. In addition, the T-cell counts are normal [42, 43].

When the primary infection is terminated by antiviral immunity, no infectious HIV remains, the T-cell are normal and there is also no AIDS [42]. In the face of antiviral immunity, the virus persists as a latent provirus in healthy hosts (fig. 2).

(2) HIV also meets one of the most telling criteria of a passenger virus in relation to a disease: HIV-free AIDS (see above, fig. 2). At least 4,621 AIDS cases have been documented in the literature since 1984 in whom there is no HIV [11]. About a third of these, 1,691, were recorded in the US, 475 in Europe and 2,555 in Africa [11]. Since Africa uses the clinical, rather than the HIV-based AIDS definition, most of these cases were observed in Africa. The US and Europe bias AIDS

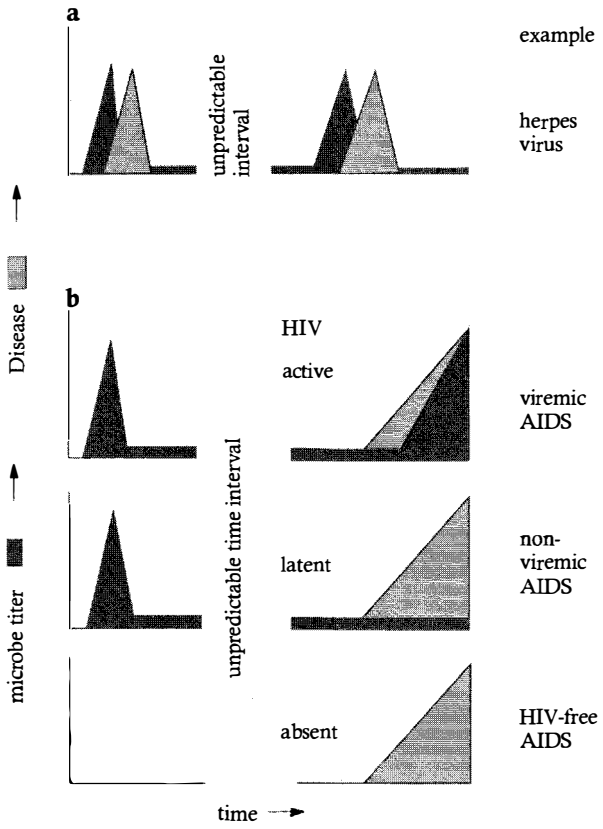

Figure 2 Temporal relations between disease and microbial presence, activity and titer for a causative virus/microbe (**a**), and for a passenger virus/microbe (**b**).

statistics against HIV-free AIDS, because they use the HIV-based AIDS definition (see above).

(3) Several groups have documented that HIV may be either active or passive once immunodeficiency is acquired and AIDS appears [42, 44, 45]: Piatak *et al.* observe either no infectious HIV, e.g. 0 infectious units per milliliter plasma in 5 out of 27 HIV-antibody-positive AIDS cases, or fewer than 25 infectious HIVs per milliliter in 6 out of 27 cases, or 10^2-10^5 in 16 out of 27 otherwise identical AIDS cases [42, 43]. Others have reported similar noncorrelations between virus titers and AIDS [44–46].

Likewise, there is no correlation between AIDS and the number of HIV-infected cells. Simmonds *et al.* report that there are from 1 to 700 to 1 in 83,000 HIV-infected leukocytes in healthy HIV carriers and from 1 in 900 to 1 in 30,000 in AIDS patients [47]. Bagasra *et al.* report that there are from 1 in 30 to 1 in 1,000 infected leukocytes in healthy carriers and from 1 in 10 to 1 in 1,000 in patients with fatal AIDS. [48] Thus there are healthy persons with 43 times (30,000:700) and 33 times (1,000:30) more HIV-infected cells than in AIDS patients.

It follows that there is neither a correlation between HIV titers, nor between the number of HIV-infected cells and AIDS—the hallmark of a passenger virus.

(4) Even as an active passenger, HIV does not aggravate the course of AIDS by any HIV-specific symptom, as some other passenger viruses or microbes do. For example, cytomegalovirus, herpes virus, *Pneumocystis carinii* and *Candida* each cause corresponding opportunistic infections if they are activated by acquired immunodeficiency (table 1). By contrast, the AIDS cases with active or passive HIV appear to be identical, according to several groups of investigators [42, 44, 45, 48]. Indeed no HIV-specific AIDS symptom has ever been described, as all AIDS-defining diseases have been known previously [10, 49] and occur in HIV-free AIDS patients [11]. Thus HIV is not even a cofactor for AIDS.

It follows that HIV is a harmless passenger virus that does neither cause AIDS nor even contribute an HIV-specific symptom to AIDS. Since AIDS is not caused by HIV nor consistently associated with another active infectious agent [5], it may not be infectious.

AIDS Fails All Criteria of Infectious Disease

Proponents of the HIV-AIDS hypothesis acknowledge that "AIDS does not have the characteristics of an ordinary infectious disease. This view is incontrovertible" [50]. More specifically, the epidemiologists Eggers and Weyer [51] state that "the spread of AIDS does not behave like the spread of a disease that is caused by a single sexually transmitted agent." To reconcile AIDS with infectious disease they "simulated a cofactor [that] cannot be identified with any known infectious agent" [52]. The epidemiologists Anderson and May [53] had to invent "assortative sce-

narios" for different AIDS risk groups to match AIDS with infectious disease. Indeed, AIDS does not meet even one of the common criteria of all known infectious diseases:

Known infectious diseases	**AIDS**
(1) All infectious diseases are equally distributed between the sexes [54, 55].	For 10 years American and European AIDS has been 90% and 86% male [4, 5].
(2) The causative microbe or virus is abundant and very active in target tissues during the course of the disease [8, 38, 39, 54, 56].	There is no common, active microbe in all AIDS cases [5]. HIV is typically extremely rare and inactive and frequently not even present in AIDS (see above) [5, 11], the reason that leading AIDS researchers had notorious difficulties in isolating HIV [12, 57]. Typically only 1/1000 T-cells is infected in AIDS patients (see above and ref. [5]). Indeed, AIDS occurs only after HIV is neutralized by antiviral immunity, a positive "AIDS test."
3) Infectious diseases typically follow within days or weeks after infection by a causative microbe or virus and occur prior to immunity [38, 39]. This is because all microbes and viruses replicate within 0.5–48 hours and multiply exponentially until stopped by immunity and other host resistance. "Slow viruses" or lentiviruses, which are said to take months or years to replicate, have never been isolated [56, 58].	The latent period between infection and AIDS currently averages 10 years, although HIV replicates within 24 to 48 hours, just like all other retroviruses [5].

Thus AIDS does not fit even one of the classical criteria of an infectious disease.

The Drug-AIDS Hypothesis

The paradoxa of the virus-AIDS hypothesis are all readily resolved by postulating noninfectious AIDS. In view of this I have proposed that AIDS in America and Europe is caused by the long-term consumption of recreational drugs and AZT [5, 59]. African AIDS has been proposed to be an unrelated epidemic caused by malnutrition, parasitic infections and poor sanitation [5].

Indeed, AIDS in America and Europe fits all classical criteria of a drug-induced disease syndrome. AIDS correlates epidemiologically and chronologically with the drug epidemics that started in America and Europe after the Vietnam war:

(1) About 30% of all American and European AIDS patients are intravenous drug users [4, 5]. This group includes nearly all heterosexuals with AIDS [4, 5]. It also includes 80% of all American and European babies with AIDS who were intrauterine drug users, because their mothers injected drugs during pregnancy [5].

It is known since 1982 that virtually 100% of homosexual males with AIDS or at risk for AIDS have been longterm users of oral, aphrodisiac drugs, particularly nitrite inhalants, that confer euphoria and facilitate anal intercourse [60–69]. Epidemiological studies from San Francisco and Vancouver have just confirmed, in 1993, that 100% of several hundred male homosexuals with AIDS had used multiple recreational drugs [70, 71, 81]. In addition some had also used the cytotoxic DNA chain terminator AZT as antiviral drug [72–75, 81]. The immunotoxicity of these recreational drugs has been documented in the literature since 1909 [5, 76].

About 200,000 HIV-positive healthy people and AIDS patients are currently treated four times daily with AZT and other DNA chain terminators as anti-HIV drugs. These drugs kill all growing cells, particularly those of the highly proliferative immune system [5]. Thus AZT is AIDS by prescription.

(2) In the US recreational drug use increased over the last years at

about the same rate as AIDS [5]. For example, cocaine consumption increased 200-fold from 1980 to 1990 based on cocaine seizures that increased from 500 kg in 1980 to 100,000 kg in 1990 [5]. During the same time cocaine-related hospital emergencies increased 24-fold from 3,296 cases in 1981 to 80,355 cases in 1990 [5] (fig. 1b). Note the parallelisms between the spreads of AIDS (fig. 1a) and the spreads of cocaine and cocaine-related hospital emergencies since 1981, and the contrast with the non-spread of HIV since 1984 (fig. 1a).

(3) 90% of the American AIDS patients are male, because according to the US Bureau of Justice Statistics males consume about 75% of all illicit injected drugs, and because homosexual males are virtually the only consistent users of aphrodisiac drugs like alkyl nitrites [5, 59].

(4) AIDS occurs on average 10 years after initiation of risk behavior, because it takes years of recreational drug consumption to cause disease [5, 63, 77], e.g., 20 years of smoking to get lung cancer [78] or emphysema, or years of alcoholism to develop liver cirrhosis. The great variations in "latent periods" from HIV to AIDS that currently average 10 years [10] are euphemisms for the time required by individuals to accumulate sufficient drug toxicity to generate AIDS diseases [5].

(5) Different risk groups have risk-group-specific AIDS diseases, e.g., Kaposi sarcoma is observed almost exclusively in homosexuals [79], because homosexuals are the almost-exclusive users of aphrodisiac nitrite inhalants [5, 65]; tuberculosis and weight loss is observed in intravenous drug users, because intravenous drugs cause those symptoms [5]; anemia and lymphocytopenia is observed in recipients of AZT which kills proliferating bone marrow cells [5, 80]; and hemophiliacs get pneumonias and candidiases almost exclusively, because long-term transfusion of foreign proteins is immunosuppressive [5].

The drug-AIDS hypothesis is experimentally and epidemiologically testable and provides a rational basis for AIDS prevention and control.

Acknowledgements

I thank Jody Schwartz for a critical review and Bryan Ellison for discussions. Supported in part by the Council for Tobacco Research, USA, and private donations from Glenn Braswell (Los Angeles, Calif., USA),

Dr. Richard Fischer (Annandale, Va., USA), Dr. Fabio Franchi (Trieste, Italy) and Dr. Friedrich Luft (Berlin, FRG).

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Chapter Ten

"The Duesberg Phenomenon": Duesberg and Other Voices

Science 267: 313–314; 20 January 1995.

In the Special News report of 9 December (p. 1642) by Jon Cohen, *Science* struggles with what is called "The Duesberg phenomenon"—"a Berkeley virologist and his supporters continue to argue that HIV [human immunodeficiency virus] is not the cause of AIDS [acquired immunodeficiency syndrome]." Cohen tries to explain why "mainstream AIDS researchers" believe that HIV causes AIDS and why "HIV now fulfills the classic postulates ... by Robert Koch." One week later (16 Dec., p. 1803), Cohen himself appears to become part of the phenomenon, when he writes: "Is a new virus the cause of KS [Kaposi's sarcoma]?" One should realize the heresy of this question. *KS has been and still is the signal disease of the AIDS Syndrome.* The Centers for Disease Control include it in its list of 29 diseases defining AIDS in the presence of HIV (1). No other AIDS-defining disease has increased more than KS over its long-established background. It was so rare before AIDS that many doctors told me that they had never seen it before in young men. This is the reason why KS has become a hallmark for AIDS. And now, according to Cohen, "solid headway will have been made ..." if HIV is found *not* to be the cause of KS.

Since "mainstream AIDS researchers" now consider one non-HIV cause for AIDS, why not consider others. Accordingly, I submit two experimental tests to find such causes.

1) Cohen wonders (16 Dec., p. 1803) about the "mystery" that "KS is almost exclusively confined to male homosexuals," but he reports (9 Dec., p. 1648) that "use of nitrite inhalants, known as 'poppers' ... has

been high among some subgroups in the homosexual population" and that "nitrite inhalants [are] popular among gay men" (16 Dec., p. 1803). Cohen also interviewed the authors of a study that had shown in 1993 that every one of 215 homosexual AIDS patients from San Francisco had used poppers in addition to other recreational drugs and AZT (*2*).

Since nitrites are some of the best known mutagens and carcinogens (*3*) and AIDS KS typically occurs on the skin and in the lungs, the primary site of nitrite inhalant exposure, I propose to solve the "mystery": Expose 100 mice, or cats, or monkeys to nitrite inhalants at doses comparable with human recreational use and for time periods approximating the so-called 10-year latent period between infection by HIV to the onset of AIDS—possibly a euphemism for the time of drug use necessary for AIDS to develop. (It takes 10 to 20 years of smoking for emphysema or lung cancer to develop.) I would predict this result: immunodeficiency, pneumonia, and pulmonary KS in animals.

2) According to Cohen, mainstream AIDS researchers argue that it is "impossible" to eliminate confounding factors from HIV in typical AIDS risk groups, as for example in hemophiliacs "because [they] do not keep track of each factor VIII treatment" (9 Dec., p. 1645). Therefore, we are asked to accept confounded epidemiological studies of HIV-positives—who are either male homosexuals using immunotoxic nitrites (*2*), or are intravenous drug users, or are hemophiliacs subject to immunosuppressive transfusions, or are being treated with AZT, or are subject to exotic lifestyles—as evidence that HIV causes AIDS.

In view of this, I propose a very possible epidemiological test of whether HIV or non-HIV factors cause AIDS: Compare the incidence of AIDS-defining diseases in 3650 homo- or heterosexual American men, who are not on transfusions and recreational drugs or AZT, but are HIV-positive, to the incidence in 3650 HIV-negative counterparts. These healthy subjects could be found by the U.S. Army, which tests more than 2.5 million per year, or among those contributing to the blood banks, which test more than 12 million a year. If the 3650-day latent period is correct, every 2 days one of the people that are HIV-positive would develop AIDS. I would predict this result: The percentage incidence in the HIV-positive group will be the same as in the HIV-negative group.

If the mainstream AIDS researchers are not already doing these experiments, I would be delighted to do them provided I can get funded.

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Chapter Eleven

Foreign-protein-mediated Immunodeficiency in Hemophiliacs With and Without HIV

Genetica, Vol. 95, pp. 51–70. 1995.

Abstract

Hemophilia-AIDS has been interpreted in terms of two hypotheses: the foreign-protein-AIDS hypothesis and the Human Immunodeficiency Virus (HIV)-AIDS hypothesis. The foreign-protein-AIDS hypothesis holds that proteins contaminating commercial clotting factor VIII cause immunosuppression. The foreign-protein hypothesis, but not the HIV hypothesis, correctly predicts seven characteristics of hemophilia-AIDS: 1) The increased life span of American hemophiliacs in the two decades before 1987, although 75% became infected by HIV—because factor VIII treatment, begun in the 1960s, extended their lives and simultaneously disseminated harmless HIV. After 1987 the life span of hemophiliacs appears to have decreased again, probably because of widespread treatment with the cytotoxic anti-HIV drug AZT. 2) The distinctly low, 1.3–2%, annual AIDS risk of hemophiliacs, compared to the higher 5–6% annual risk of intravenous drug users and male homosexual aphrodisiac drug users—because transfusion of foreign proteins is less immunosuppressive than recreational drug use. 3) The age bias of hemophilia-AIDS, i.e. that the annual AIDS risk increases 2-fold for each 10-year increase in age—because immunosuppression is a function of the lifetime dose of foreign proteins received from transfusions. 4) The restriction of hemophilia-AIDS to immunodeficiency diseases—because

foreign proteins cannot cause non-immunodeficiency AIDS diseases, like Kaposi's sarcoma. 5) The absence of AIDS diseases above their normal background in sexual partners of hemophiliacs—because transfusion-mediated immunotoxicity is not contagious. 6) The occurrence of immunodeficiency in HIV-free hemophiliacs—because foreign proteins, not HIV, suppress their immune system. 7) Stabilization, even regeneration, of immunity of HIV-positive hemophiliacs by long-term treatment with pure factor VIII. This shows that neither HIV nor factor VIII plus HIV are immunosuppressive by themselves. Therefore, AIDS cannot be prevented by elimination of HIV from the blood supply and cannot be rationally treated with genotoxic antiviral drugs, like AZT. Instead, hemophilia-AIDS can be prevented and has even been reverted by treatment with pure factor VIII.

1. The Drug- and Hemophilia-AIDS Epidemics in America and Europe

About 30 previously known diseases are now called AIDS if they occur in the presence of antibody against human immunodeficiency virus (HIV) (Institute of Medicine, 1988; Centers for Disease Control and Prevention, 1992). These diseases are thought to be consequences of an *a*cquired *i*mmuno *d*eficiency *s*yndrome and hence are grouped together as AIDS (Institute of Medicine, 1988). From its beginning in 1981, AIDS has been restricted in America and Europe to specific risk groups (Centers for Disease Control, 1986; World Health Organization, 1992b). Currently, over 96% of all American AIDS cases come from AIDS risk groups, rather than from the general population (Centers for Disease Control, 1993). These include over 60% male homosexuals who have been long-term oral users of psychoactive and aphrodisiac drugs, 33% mostly heterosexual, intravenous drug users and their children, 2% transfusion recipients, and about 1% hemophiliacs (Duesberg, 1992a; Centers for Disease Control, 1993). Altogether, about 90% of all American and European AIDS patients are males (World Health Organization, 1992a; Centers for Disease Control, 1993).

Each risk group has specific AIDS diseases. For example, Kaposi's sarcoma is almost exclusively seen in male homosexuals, tuberculosis

is common in intravenous drug users, and pneumonia and candidiasis are virtually the only AIDS diseases seen in hemophiliacs (Duesberg, 1992a).

In view of these epidemiological and clinical criteria, American and European AIDS has been interpreted alternatively as an infectious and a non-infectious epidemic by the following hypotheses:

1) *The virus-AIDS hypothesis.* This hypothesis postulates that all AIDS is caused by the retrovirus HIV, and thus an infectious epidemic. The inherent danger of a transmissable disease quickly promoted the HIV hypothesis to the favorite of "responsible" health care workers, scientists and journalists (Booth, 1988). For example, a columnist of *The New York Times* wrote in July 1994 that all non-HIV AIDS science is "cruelly irresponsible anti-science" (Lewis, 1994). And the retrovirologist David Baltimore warned in *Nature* "There is no question at all that HIV is the cause of AIDS. Anyone who gets up publicly and says the opposite is encouraging people to risk their lives." (Macilwain, 1994).

Moreover, the U.S.' Centers for Disease Control (CDC) have favored the HIV-AIDS hypothesis from the beginning (Centers for Disease Control, 1982; Centers for Disease Control, 1986; Shilts, 1987; Booth, 1988; Oppenheimer, 1992), because—according to Red Cross official Paul Cumming in 1983—"the CDC increasingly needs a major epidemic to justify its existence" (Associated Press, 1994). Indeed, there has been no viral or microbial epidemic in the U.S. and Europe since polio in the 1950s. All infectious diseases combined now account for less than 1% of morbidity and mortality in the Western World (Cairns, 1978). The control of infectious diseases is the primary mission of the CDC.

2) *The drug-AIDS hypothesis.* This hypothesis holds that AIDS in the major risk groups is caused by group-specific, recreational drugs and by anti-HIV therapy with cytocidal DNA chain terminators, like AZT, and is thus not infectious (Lauritsen & Wilson, 1986; Haverkos & Dougherty, 1988; Duesberg, 1991, 1992a; Oppenheimer, 1992). The drug-AIDS hypothesis was favored by many scientists, including some from the CDC, before the introduction of the HIV-AIDS hypothesis in 1984 (Marmor *et al.,* 1982; Mathur-Wagh *et al.,* 1984; Haverkos *et al.,*

1985; Mathur-Wagh, Mildvan & Senie, 1985; Newell *et al.,* 1985; Haverkos & Dougherty, 1988; Duesberg, 1992a; Oppenheimer, 1992).

3) *The foreign-protein-hemophilia AIDS hypothesis.* This hypothesis holds that hemophilia-AIDS is caused by the long-term transfusion of foreign proteins contaminating factor VIII and other clotting factors and thus not infectious. This hypothesis also preceded the virus hypothesis and has coexisted with it, despite the rising popularity of the HIV hypothesis (see Section 3).

The infectious and non-infectious AIDS hypotheses indicate entirely different strategies of AIDS prevention and therapy. Here we analyze the cause of hemophilia-AIDS in the lights of the HIV-AIDS hypothesis and the foreign-protein-AIDS hypothesis. The hemophiliacs provide the most accessible group to test AIDS hypotheses of infectious versus non-infectious causation. This is because the time of infection via transfusion can be estimated more accurately than HIV infection from sexual contacts, and because the role of treatment-related AIDS risks can be controlled and quantitated much more readily than AIDS risks due to the consumption of illicit, recreational drugs.

2. The HIV-AIDS Hypothesis

The HIV hypothesis claims that AIDS began to appear in hemophiliacs in 1981 (Centers for Disease Control, 1982) because (i) hemophiliacs were accidentally infected via transfusions of factor VIII contaminated with HIV since the 1960s, when widespread prophylactic factor VIII treatment began (but no longer after 1984 when HIV was eliminated from the blood supply) and because (ii) AIDS is currently assumed to follow HIV infection on average only after 10 years (Centers for Disease Control, 1986; Institute of Medicine, 1988; Chorba *et al.,* 1994). Indeed, about 15,000 of the 20,000 American hemophiliacs, or 75 %, are HIV antibody-positive from transfusions of HIV-contaminated clotting factors received before HIV was detectable (Tsoukas *et al.,* 1984; Institute of Medicine and National Academy of Sciences, 1986; Sullivan *et al.,* 1986; McGrady, Jason & Evatt, 1987; Institute of

Medicine, 1988; Koerper, 1989). Contamination of factor VIII with HIV reflects the practice, developed in the 1960s and 1970s, of preparing factor VIII and other clotting factors from blood pools collected from large numbers of donors (Aronson, 1983; Koerper, 1989; Chorba *et al.,* 1994).

The HIV hypothesis claims that 2,214 American hemophiliacs developed AIDS-defining diseases between 1982 and the end of 1992 because of HIV (Centers for Disease Control, 1993). However, this corresponds only to a 1.3% annual AIDS risk, i.e. 201 cases per 15,000 HIV-positive hemophiliacs per year. (Note that the non-age adjusted annual mortality of an American with a life expectancy of 80 years is 1.2%). Further, the HIV-AIDS hypothesis claims that the mortality of hemophiliacs has increased over 2-fold in the 3-year period from 1987 to 1989 compared to periods from 1968 to 1986, although infection with HIV via transfusions had already been halted with the HIV-antibody test in 1984 (Chorba *et al.,* 1994).

HIV is thought to cause immunodeficiency by killing T-cells, but paradoxically only after the virus has been neutralized by antiviral immunity, and only on average 10 years after infection (Institute of Medicine, 1988; Duesberg, 1992a; Weiss, 1993). However, HIV, like all other retroviruses, does not kill T-cells or any other cells *in vitro*; in fact, it is mass-produced for the HIV antibody test in immortal T-cell lines (Duesberg, 1992a). Moreover, the basis for the 10-year latent period of the virus, which has a generation time of only 24—48 h, is entirely unknown (Duesberg, 1992a; Weiss, 1993; Fields, 1994). It is particularly paradoxical that the loss of T-cells in hemophiliacs over time does not correspond to viral activity and abundance. No T-cells are lost prior to antiviral immunity, when the virus is most active (Duesberg, 1993a; Piatak *et al.,* 1993). Instead, most T-cells are lost when the virus is least active or latent in hemophiliacs (Phillips *et al.,* 1994a) and other risk groups (Duesberg, 1992a; 1993a, 1994; Piatak *et al.,* 1993; Sheppard, Ascher & Krowka, 1993), namely after it is neutralized by antiviral immunity (a positive HIV-antibody test). Indeed, there are healthy, HIV-antibody positive persons in which 33 to 43 times more cells are infected by latent HIV than in AIDS patients (Simmonds *et al.,* 1990; Bagasra *et al.,* 1992; Duesberg, 1994). Even Gallo, who claims credit for the HIV-

AIDS hypothesis (Gallo *et al.,* 1984), has recently acknowledged: "I think that if HIV is not being expressed and not reforming virus and replicating, the virus is a dud, and won't be causing the disease ... nobody is saying that indirect control of the virus is not important ...." (Jones, 1994).

There is also no explanation for the profound paradoxes that AIDS occurs only after HIV is neutralized and that antiviral immunity does not protect against AIDS, although this immunity is so effective that free virus is very rarely detectable in AIDS patients (Duesberg, 1990, 1992a, 1993a; Piatak *et al.,* 1993). The high efficiency of this antiviral immunity is the reason that leading AIDS researchers had notorious difficulties in isolating HIV from AIDS patients (Weiss, 1991; Cohen, 1993).

All of the above associations between HIV and AIDS support the hypothesis that HIV is a passenger virus, instead of the cause of AIDS (Duesberg, 1994). A passenger virus differs from one that causes a disease in three criteria:

1. The time of infection by the passenger virus is unrelated to the initiation of the disease. For example, the passenger may infect 10 years prior to, or just immediately before, initiation of the disease—just as HIV does in AIDS.

2. The passenger virus may be active or passive during the disease, i.e. the disease is not influenced by the activity of the passenger virus or the number of virus-infected cells, as is the case for HIV in AIDS.

3. The disease may occur in the absence of the passenger virus. In the case of AIDS, over 4621 HIV-free AIDS cases have been clinically diagnosed (Duesberg, 1993b; see also Section 4.6).

Therefore, HIV meets each of the classical criteria of a passenger virus—exactly (Duesberg, 1994).

Moreover, since HIV is not active in most AIDS patients, and often more active in healthy carriers than in AIDS patients (Duesberg, 1993a, 1994; Piatak *et al.,* 1993), and since AIDS patients with and without

HIV are clinically identical (Duesberg, 1993b), HIV is in fact only a harmless passenger virus. It is harmless, because it does not contribute secondary diseases to AIDS pathogenicity, as for example pneumocystis pneumonia, candida or herpes virus do. These microbes each cause typical AIDS-defining opportunistic infections. But HIV does not appreciably affect the pathogenicity of AIDS as HIV-free and HIV-positive AIDS cases are clinically indistinguishable (Duesberg, 1993b, 1994). Likewise, there is no clinical distinction between AIDS cases in which HIV is active and those in which it is totally latent and restricted to very few cells (Duesberg, 1993a; Piatak *et al.*, 1993).

Thus, despite enormous efforts in the last 10 years, there is no rational explanation for viral pathogenesis, and the virus-AIDS hypothesis stands unproved (Weiss & Jaffe, 1990; Duesberg, 1992a; Weiss, 1993; Fields, 1994). Above all, the hypothesis has failed to make any verifiable predictions, the acid test of a scientific hypothesis. For example, the predicted explosion of AIDS into the general population, or among female prostitutes via sexual transmission of HIV, or among health care workers treating AIDS patients via parenteral transmission did not occur (Duesberg, 1992a, 1994).

As yet, the hypothesis is supported only by circumstantial evidence, i.e. correlations between the occurrence of AIDS and antibodies against HIV in AIDS patients (Blattner, Gallo & Temin, 1988; Institute of Medicine, 1988; Weiss & Jaffe, Weiss, 1993). However, because AIDS is defined by correlation between diseases and antibodies against HIV (Institute of Medicine, 1988), the relevance of the correlation argument for AIDS etiology has been challenged (Duesberg, 1992a, 1993b, 1994; Thomas Jr., Mullis & Johnson, 1994). States Mullis, at a *London Sunday Times* Nobel Laureate lecture in 1994, "Any postgraduate student who had written a convincing paper demonstrating that HIV 'causes' AIDS would ... have published 'the paper of the century' " (Dickson, 1994).

In view of the circularity of the correlation argument, the apparent transmission of AIDS to hemophiliacs via transfusion of HIV-infected blood or factor VIII has been cited as the most direct support for the virus-AIDS hypothesis (Blattner, Gallo & Temin, 1988; Institute of Medicine, 1988; Weiss & Jaffe, 1990; Weiss, 1993). However, the HIV-

hemophilia-AIDS hypothesis is weakened by the extremely long intervals between infection and AIDS, averaging between 10 years (Institute of Medicine, 1988) and 35 years (Duesberg, 1992a; Phillips *et al.*, 1994b), compared to the short generation time of HIV which is only 24 to 48 h (see Section 4.2). During such long intervals other risk factors could have caused AIDS diseases, particularly in hemophiliacs who depend on regular transfusions of clotting factors for survival. The fact that HIV is typically not more active, and often even less active, in those who develop AIDS than in those who are healthy, further weakens the HIV-hemophilia-AIDS hypothesis (see above).

3. The Foreign-protein-hemophilia-AIDS Hypothesis

Before the introduction of the HIV-AIDS hypothesis, but after the introduction of prophylactic long-term treatment of hemophilia with blood-derived clotting factors had begun, numerous hematologists had noticed immunodeficiency and corresponding opportunistic infections in hemophiliacs. Several of these had advanced the foreign-protein-hemophilia-AIDS hypothesis, which holds that the long-term transfusion of foreign proteins contaminating commercial factor VIII, and possibly factor VIII itself, is the cause of immunosuppression in hemophiliacs. Indeed, until recently most commercial preparations of factor VIII contained from 99% to 99.9% foreign, non-factor VIII proteins (Brettler & Levine, 1989; Mannucci *et al.*, 1992; Seremetis *et al.*, 1993; Gjerset *et al.*, 1994). According to the foreign-protein hypothesis immunodeficiency in hemophilia patients is proportional to the lifetime dose of foreign proteins received (Menitove *et all.*, 1983; Madhok *et al.*, 1986; Schulman, 1991).

Long before HIV had been discovered, it was known empirically that "transfusion of patients undergoing renal transplantation is associated with improved graft survival and it has been suggested that transfusion is immunosuppressive in an as yet unidentified way." (Jones *et al.*, 1983). The authors had cited this empirical knowledge to explain immunosuppression in eight, and *Pneumocystis* pneumonia in six British hemophiliacs (Jones *et al.*, 1983). A multicenter study investigating the immune systems of 1,551 hemophiliacs, treated with factor VIII from 1975 to 1979, documented lymphocytopenia in 9.3% and thrombocy-

topenia in 5% (Eyster *et al.,* 1985). Further, the CDC reported AIDS-defining opportunistic infections in hemophiliacs between 1968 and 1979, including 60% pneumonias and 20% tuberculosis (Johnson *et al.,* 1985). An American hematologist commented on such opportunistic infections in hemophiliacs, including two candidiasis and 66 pneumonia deaths that had occurred between 1968 and 1979, "... it seems possible that many of the unspecified pneumonias in hemophiliacs in the past would be classified today as AIDS" (Aronson, 1983).

In 1983, Gordon from the National Institutes of Health noted that all hemophiliacs with immunodeficiency identified by the CDC had received factor VIII concentrate. While acknowledging the possibility of a "transmissible agent," Gordon argued that "repeated administration of factor VIII concentrate from many varied donors induces a mild disorder of immune disregulation by purely immunological means, without the intervention of infection." (Gordon, 1983). Froebel *et al.* also argued against the hypothesis that immunodeficiency in American hemophiliacs was due to a virus, and suggested that it was due to treatments with factor VIII because "Scottish patients with hemophilia, most of whom had received no American factor VIII concentrate for over two years, were found to have immunological abnormalities similar to those in their American counterparts ..." (Froebel *et al.,* 1983). Already in 1983 Menitove *et al.* described a correlation between immunosuppression of hemophiliacs and the amount of factor VIII received over a lifetime; the more factor a hemophiliac had received the lower was his T4/T8-cell ratio. Their data were found to be "consistent with the possibility that commercially prepared lyophilized factor VIII concentrates can induce an AIDS-like picture ..." (Menitove *et al.,* 1983). Also in 1983, Kessler *et al.* proposed that "Repeated exposure to many blood products can be associated with development of T4/T8 abnormalities" and "significantly reduced mean T4/T8 ratios compared with age and sex-matched controls" (Kessler *et al.,* 1983).

After the introduction of the HIV-AIDS hypothesis in 1984, Carr *et al.* studied immunodeficiency in HIV-positive and HIV-negative hemophiliacs and proposed "that the abnormalities [low T4 to T8 cell ratios] result from transfusion of foreign proteins" (Carr *et al.,* 1984). Likewise, Tsoukas *et al.* concluded "These data suggest that another factor, or fac-

tors, instead of, or in addition to, exposure to HTLV-III [old term for HIV] is required for the development of immunedysfunction in hemophiliacs" (Tsoukas *et al.,* 1984).

In 1985 even the retrovirologist Weiss reported "the abnormal T-lymphocyte subsets are a result of the intravenous infusion of factor VIII concentrates per se, not HTLV-III infection" (Ludlam *et al.,* 1985). Likewise, the hematologists Pollack *et al.* deduced that, "Derangement of immune function in hemophiliacs results from transfusion of foreign proteins or a ubiquitious virus rather than contracting AIDS infectious agent" (Pollack *et al.,* 1985). The "AIDS infectious agent" was a reference to HIV, because in 1985 HIV was extremely rare in blood concentrates outside the U.S., but immunodeficiency was observed in Israeli, Scottish, and American hemophiliacs (Pollack *et al.,* 1985). A French AIDS-hemophilia group also observed "... allogenic or altered proteins present in factor VIII ... seem to play a role of immunocompromising agents." They stated that "A correlation between treatment intensity and immunologic disturbances was found in patients infused with factor VIII preparations, irrespective of their positive or negative LAV [HIV] antibody status" (AIDS-Hemohilia French Study Group, 1985). Likewise, Hollan *et al.* reported in 1985 "an immunodeficiency independent of HTLV-III infection" in Hungarian hemophiliacs (Hollan *et al.,* 1985).

In 1986, Madhok *et al.* arrived at the conclusion that "clotting factor concentrate impairs the cell mediated immune response to a new antigen in the absence of infection with HIV" (Madhok *et al.,* 1986). Moreover, Jason *et al.* from the CDC observed that, "Hemophiliacs with immune abnormalities may not necessarily be infected with HTLV-III/LAV, since factor concentrate itself may be immune suppressive even when produced from a population of donors not at risk for AIDS" (Jason *et al.,* 1986). Sullivan *et al.* deduced from a comprehensive study of hemophiliacs that "hemophiliacs receiving commercial factor VIII concentrate experience several stepwise incremental insults to the immune system: alloantigens in factor VIII concentrate [etc.] ..." (Sullivan *et al.,* 1986).

In 1987, Sharp *et al.* commented that "Five out of 12 such patients had a mild T4 lymphocytopenia, and this may have been related to par-

enteral administration of large quantities of protein." (Sharp *et al.,* 1987). And Aledort observed that "chronic recipients ... of factor VIII, factor IX and pooled products ... demonstrated significant T-cell abnormalities regardless of the presence of HIV antibody" (Aledort, 1988). Brettler and Levine proposed in 1989 that "Factor concentrate itself, perhaps secondary to the large amount of foreign-protein present, may cause alterations in the immune systems of hemophiliac patients" (Brettler & Levine, 1989). And even Stehr-Green *et al.* from the CDC conceded that foreign proteins were at least a cofactor of HIV in immunosuppression: "Repeated exposure to factor concentrate ... could also account for more rapid progression of HIV infection with age." (Stehr-Green *et al.,* 1989).

Although Becherer *et al.* claimed in 1990 that clotting factor does not cause immunodeficiency, they showed that immunodeficiency in hemophiliacs increases with both the age and the cumulative dose of clotting factor received during a lifetime (Becherer *et al.,* 1990). Likewise, Simmonds *et al.* observed in 1991 that even among HIV-positive hemophiliacs "The rate of disease progression, as assessed by the appearance or not of AIDS symptoms or signs within five years of seroconversion, was related ... to the concentration of total plasma IgM before exposure to infection ..." (Simmonds *et al.,* 1991). The hematologist Prince noted in a review from 1992 that "When serum samples from these [immunodeficient hemophilia] patients were tested for antibodies to HIV-1, it was found that a sizable group of hemophilia patients, usually 25% to 40%, were seronegative for HIV-1," and "... all found marked anergy, lack of response, in HIV-seronegative concentrate recipients. Taken together, these findings were interpreted as evidence that clotting factor concentrates suppressed the immunocompetence of recipients ..." (Prince, 1992).

In 1991, Schulman concluded that "immunosuppressive components in F VIII concentrates" cause immunodeficiency not only in HIV-positive but also in HIV-negative hemophiliacs (Schulman, 1991). Schulman had observed reversal of immunodeficiency and thrombocytopenia in HIV-positive hemophiliacs treated with purified factor VIII, and that immunity "was inversely correlated with the annual amount of factor VIII infused" (Schulman, 1991).

At the same time several groups have reported that T-cell counts are stabilized, or even increased in HIV-positive hemophiliacs treated with factor VIII free of foreign proteins (de Biasi *et al.,* 1991; Hilgartner *et al.,* 1993; Seremetis *et al.,* 1993; Goedert *et al.,* 1994) (see also Section 4.7). And in 1994, the editor of *aids News,* published by the Hemophilia Council of California, granted foreign proteins the role of a cofactor of HIV in hemophilia AIDS with an editorial "Factor concentrate is a Co-factor" (Maynard, 1994).

According to the foreign-protein hypothesis, antibodies against HIV and against other microbes would merely be markers of the multiplicity of transfusions received (Evatt *et al.,* 1984; Pollack *et al.,* 1985; Brettler *et al.,* 1986; Sullivan *et al.,* 1986; Koerper, 1989). Since HIV has been a rare contaminant of blood products, even before 1984, only those who have received many transfusions would become infected. The more immunosuppressive transfusions a person has received, the more likely that person is to become infected by HIV and other microbes contaminating factor VIII (see Section 4.6). For example, only 30% of hemophiliacs who had received less than 400 units factor VIII per kg per year were HIV-positive, but 80% of those who had received about 1000 units, and 93% of those who had received over 2100 units per kg per year were HIV-positive (Sullivan *et al.,* 1986).

4. Predictions of the Foreign-protein- and HIV-AIDS Hypotheses

Here we compare the HIV- and the foreign-protein-AIDS hypotheses in terms of how well their predictions can be reconciled with hemophilia-AIDS:

4.1 *Mortality of hemophiliacs with and without HIV.* The virus-AIDS hypothesis predicts that the mortality of HIV-positive hemophiliacs will be higher than that of matched HIV-free counterparts. Considering the high, 75%-rate of infection of American hemophiliacs by HIV since 1984, one would expect that the median age of all American hemophiliacs would have significantly decreased and that their mortality increased. The HIV-AIDS hypothesis predicts that in 1994, at least one

10-year-latent-period after most American hemophiliacs were infected, over 50% of the 15,000 HIV-positive American hemophiliacs would have developed AIDS or died from AIDS (Institute of Medicine, 1988; Duesberg, 1992a). But despite the many claims that HIV causes AIDS in hemophiliacs (Centers for Disease Control, 1986; Institute of Medicine, 1988; Weiss & Jaffe, 1990; Chorba *et al.,* 1994), there is not a single controlled study showing that the morbidity or mortality of HIV-positive hemophiliacs is higher than that of HIV-negative controls matched for the lifetime consumption of factor VIII.

Instead, the mortality of American hemophiliacs has decreased and their median age has increased since 75% were infected by HIV. The median age of American hemophiliacs has increased from 11 years in 1972, to 20 years in 1982, to 25 years in 1986, and to 27 years in 1987, although 75% had become HIV antibody-positive prior to 1984 (Institue of Medicine and National Academy of Sciences, 1986; Koerper, 1989; Stehr-Green *et al.,* 1989). Likewise, their median age at death has increased from about 40 to 55 years in the period from 1968 to 1986 (Chorba *et al.,* 1994).

Contrary to the HIV-AIDS hypothesis, one could make a logical argument that HIV, instead of decreasing the life span of hemophiliacs, has in fact increased it. A more plausible argument suggests that the life span of American hemophiliacs has increased as a consequence of the widespread use of factor VIII that started in the late 1960s (see above). As predicted by the foreign-protein hypothesis, the price for the extended life span of hemophiliacs by treatment with commercial factor VIII was immunosuppression due to the long-term parenteral administration of large quantities of foreign protein (see Section 4.2). Prior to factor VIII therapy, most hemophiliacs died as adolescents from internal bleeding (Koerper, 1989).

However, a recent CDC study reports that the mortality of American hemophiliacs suddenly increased 2.5-fold in the period from 1987 to 1989, after it had remained almost constant in the period from 1968 to 1986 (Chorba *et al.,* 1994). Since American hemophiliacs became gradually infected via the introduction in the 1960s of pooled factor VIII treatments until 1984, when HIV was eliminated from the blood supply (see above), one would have expected first a gradual increase in

hemophilia mortality and then a rather steep decrease. The increase in mortality would have followed the increase of infections with a lag defined by the time that HIV is thought to require to cause AIDS. The presumed lag between HIV and AIDS has been estimated at 10 months by the CDC in 1984 (Auerbach *et al.,* 1984) and at 10 years by a committee of HIV researchers, including some from the CDC, in 1988 (Institute of Medicine, 1988). Therefore the sudden increase in hemophilia deaths in 1987 is not compatible with HIV-mediated mortality. Hemophilia mortality should have gradually decreased after 1984, when HIV was eliminated from the blood supply, depending on the lag period assumed between infection and AIDS. Even if the lag period from HIV to AIDS were 10 years, the mortality of hemophiliacs should have significantly decreased by 1989, 5 years after new infections had been stopped.

An obvious explanation for the chronological inconsistency between infection of hemophiliacs with HIV since the 1960s and the sudden increase in their mortality 20 years later is the introduction of the cytotoxic DNA chain terminator AZT as an anti-HIV drug in 1987. AZT has been recommended and prescribed to symptomatic HIV carriers since 1987 (Fischl *et al.,* 1987; Richman *et al.,* 1987) and to healthy HIV carriers with lower than 500 T-cells since 1988 (Volberding *et al.,* 1990; Goldsmith *et al.,* 1991; Phillips *et al.,* 1994b). Approximately 200,000 HIV antibody-positives with and without AIDS diseases are currently prescribed AZT worldwide (Duesberg, 1992a). According to a preliminary survey of hemophiliacs from a national group, Concerned Hemophiliacs Acting for Peer Strength (CHAPS), 35 out of 35 HIV-positive hemophiliacs asked had taken AZT, and 20 out of 35 who had taken AZT at some time were currently on AZT (personal communication, Brent Runyon, executive director of CHAPS, Wilmington, N.C.).

The DNA chain terminator AZT was developed 30 years ago to kill growing human cells for cancer chemotherapy. Because of its intended toxicity, chemotherapy is typically applied for very limited periods of time, i.e. weeks or months, but AZT is now prescribed to healthy HIV-positives indefinitely, despite its known toxicity (Nussbaum, 1990; Volberding *et al.*, 1990). Indeed, AZT has been shown to be toxic in HIV-positives and proposed as a possible cause of AIDS diseases since

1991 (Duesberg, 1991, 1992c, 1992a, 1992b). Recently, the European "Concorde trial" (Seligmann *et al.,* 1994) and several other studies have shown that, contrary to earlier claims, AZT does not prevent AIDS (Oddone *et al.,* 1993; Tokars *et al.,* 1993; Lenderking *et al.,* 1994; Lundgren *et al.,* 1994). The Concorde trial even showed that the mortality of healthy, AZT-treated HIV-carriers was 25% higher than that of placebo-treated controls (Seligmann *et al.,* 1994). Likewise, an American multicenter study showed that the death risk of hemophiliacs treated with AZT was 2.4 times higher, and that their AIDS risk was even 4.5 times higher than that of untreated HIV-positive hemophiliacs (Goedert *et al.,* 1994). Thus, the widespread use of AZT in HIV-positives could be the reason for the sudden increase in hemophilia mortality since 1987.

The AZT-hemophilia-AIDS hypothesis and the foreign-protein-AIDS hypothesis both predict that hemophilia-AIDS would stay constant or increase as long as unpurified factor VIII is used and AZT is prescribed to HIV-positive hemophiliacs. By contrast, the HIV-AIDS hypothesis predicts that hemophilia-AIDS should have decreased with time since 1984 when HIV was eliminated from the blood supply. The HIV hypothesis further predicts that AIDS should have decreased precipitously since 1989 when AZT was prescribed as AIDS prevention to inhibit HIV.

But the decrease in hemophilia-AIDS predicted by the HIV-AIDS hypothesis was not observed. Instead, the data confirm the AZT-/foreign-protein-AIDS hypotheses: The CDC reports 300 hemophilia AIDS cases in 1988, 295 in 1989, 320 in 1990, 316 in 1991,316 in 1992 and, after broadening the AIDS definition as of January 1993 (Centers for Disease Control and Prevention, 1992), 1096 in 1993 (Centers for Disease Control, 1993; Centers for Disease Control and Prevention, 1994; and prior *HIV/AIDS Surveillance* reports).

4.2 *Annual AIDS risk of HIV-positive hemophiliacs compared to other HIV-positive AIDS risk groups.* The HIV-AIDS hypothesis predicts that the annual risk of HIV-positive hemophiliacs would be the same as that of other HIV-infected risk groups. One could in fact argue that it should be higher, because the health of hemophiliacs is compromised compared to AIDS risk groups without congenital health deficiencies.

By contrast, the foreign-protein-AIDS hypothesis makes no clear prediction about the annual AIDS risk of hemophiliacs compared to drug-AIDS risk groups, because the relative risks have not been studied and are hard to quantitate.

By the end of 1992, 2,214 American hemophiliacs with AIDS were reported to the CDC (Centers for Disease Control, 1993; Chorba *et al.*, 1994). Since there are about 15,000 HIV-positive American hemophiliacs, an average of only 1.3% (201 out of 15,000) have developed AIDS annually between 1981 and 1992 (Tsoukas *et al.*, 1984; Hardy *et al.*, 1985; Institute of Medicine and National Academy of Sciences, 1986; Sullivan *et al.*, 1986; Stehr-Green *et al.*, 1988; Goedert *et al.*, 1989; Koerper, 1989; Morgan, Curran & Berkelman, 1990; Gomperts, De Biasi & De Vreker, 1992). But after the inclusion of further diseases into the AIDS syndrome (Institute of Medicine, 1988), and the introduction of AZT as an anti-HIV drug, both in 1987, the annual AIDS risk of American hemophiliacs appears to have stabilized at 2%, e.g. about 300 out of 15,000 per year until 1993 when the AIDS definition was changed again (Centers for Disease Control, 1993) (see Section 4.1).

Hemophilia-AIDS statistics from Germany are compatible with American counterparts: about 50% of the 6,000 German hemophiliacs are HIV-positive (Koerper, 1989). Only 37 or ~ 1% of these developed AIDS-defining diseases during 1991 (Leonhard, 1992), and 186 or 1.5% annually during the four years from 1988 to 1991 (Schwartlaender *et al.*, 1992).

The 1.3% to 2% annual AIDS risk indicates that the average HIV-positive hemophiliac would have to wait for 25 to 35 years to develop AIDS diseases from HIV. Indeed latent periods of over 20 years have just been calculated for HIV-positive hemophiliacs based on the loss of T-cells over time (Phillips *et al.*, 1994b).

By contrast, the annual AIDS risk of the average, HIV-positive American is currently 6%, because there are now about 60,000 annual AIDS cases (Centers for Disease Control, 1993) per 1 million HIV-positive Americans (Curran *et al.*, 1985; Centers for Disease Control, 1992b; Duesberg, 1992a). This reflects the annual AIDS-risks of the major risk groups, the male homosexuals and intravenous drug users who make up about 93% of all American AIDS patients (Centers for Disease Con-

trol, 1993). The annual AIDS risks of intravenous drug users (Lemp *et al.,* 1990) and male homosexuals appear to be the same, as both were estimated at about 5–6% (Anderson & May, 1988; Lui *et al.,* 1988; Lemp *et al.,* 1990) (Table 1).

In view of the compromised health of hemophiliacs, it is surprising that the annual AIDS risk of HIV-infected hemophiliacs is only 1.3% to 2% and thus 3–5 times lower than that of the average HIV-infected, non-hemophiliac American or European (Table 1). Commenting on the relatively low annual AIDS risk of hemophiliacs compared to that of homosexuals, the hematologists Sullivan *et al.* noted that "The reasons for this difference remain unclear" (Sullivan *et al.,* 1986). Hardy *et al.* from the CDC also noted the discrepancy in the latent periods of different risk groups. "The magnitude of some of the differences in rates is so great that even gross errors in denomination estimates can be overcome" (Hardy *et al.* 1985). And Christine Lee, senior author of the study that had estimated latent periods of over 20 years from infection to hemophilia AIDS (Phillips *et al.,* 1994b), commented on the paradox "It may be that hemophiliacs have got that cofactor [of foreign blood contaminants], homosexuals have got another cofactor, drug users have got another cofactor, and they all have the same effect, so that at the end of the day you get [approximately] the same progression rate." (Jones, 1994).

Thus, the 3–5-fold difference between the annual AIDS risks of HIV-positive hemophiliacs and the other major risk groups is not compatible with the HIV hypothesis. However, it can be reconciled with the foreign-protein and drug-AIDS hypothesis (Duesberg, 1992a, 1994), because different causes, i.e. drugs and foreign proteins, generate AIDS diseases at different rates.

4.3 *The age bias of hemophilia-AIDS.* The HIV-AIDS hypothesis predicts that the annual AIDS risks of HIV-positive hemophiliacs is independent of their age, because virus replication is independent of the age of the host. Predictions would have to be adjusted, however, by the hypothetical lag period between infection and AIDS. If the average latent period from HIV to AIDS is 10 months, as was postulated in 1984 (Auerbach *et al.,* 1984), less than 10-month-old HIV-positive hemo-

philiacs would have a lower probability of having AIDS. If the average latent period from HIV to AIDS is 10 years (Institute of Medicine, 1988; Lui *et al.,* 1988; Lemp *et al.,* 1990; Weiss, 1993), HIV-positive hemophiliacs under 10 years of age would have a lower probability of having AIDS. In other words, if the time of infection is unknown, the annual AIDS risks of HIV-positive hemophiliacs over 10 months or 10 years, respectively, would be independent of the age of the HIV-positive hemophiliac.

By contrast, the foreign-protein hypothesis predicts that the annual AIDS risk of HIV-positive and negative hemophiliacs increases with age because immunosuppression is the result of the lifetime dose of proteins transfused (Pollack *et al.,* 1985; Brettler *et al.,* 1986; Sullivan *et al.,* 1986; Koerper, 1989) (see above). The more years a hemophiliac has been treated with unpurified blood products, the more likely he is to develop immunodeficiency. Thus, the foreign-protein hypothesis predicts that the annual AIDS risk of a hemophiliac would increase with age.

Table 1
Annual AIDS risks of HIV-infected groups.

American/European Risk Group	**Annual AIDS in %**	**References**
Hemophiliacs	1.3–2	see text
Male homosexuals	5–6	Lui *et al.,* 1988, Anderson & May, 1988, Lemp *et al.,* 1990
Intravenous drug users	5–6	Lui *et al.* 1988, Anderson & May, 1988, Lemp *et al.,* 1990

Statistics show that the median age of hemophiliacs with AIDS in the U.S. (Evatt *et al.,* 1984; Koerper, 1989; Stehr-Green *et al.,* 1989) and other countries (Darby *et al.,* 1989; Biggar and the International Registry of Seroconverters, 1990; Blattner, 1991) is about 5–15 years higher

than the average age of hemophiliacs. In the U.S., the average age of hemophiliacs was 20–27 years from 1980 to 1986, while that of hemophiliacs with AIDS was 32–35 years (Evatt *et al.,* 1984; Koerper, 1989; Stehr-Green *et al.,* 1989).

Likewise, the annual AIDS risk of HIV-positive hemophiliacs shows a strong age bias. An international study estimated the annual AIDS risk of children at 1% and that of adult hemophiliacs at 3% over a 5-year period of HIV-infection (Biggar and the International Registry of Seroconverters, 1990). In the U.S., Goedert *et al.* reported that the annual AIDS risk of 1- to 17-year-old hemophiliacs was 1.5%, that of 18- and 34-year-old hemophiliacs was 3%, and that of 64- year-old hemophiliacs was 5% (Goedert *et al.*, 1989). Goldsmith *et al.* reported that the annual T-cell loss of hemophiliacs under 25 years was 9.5% and for hemophiliacs over 25 years 17.5% (Goldsmith *et al.,* 1991).

Lee *et al.* reported that the annual AIDS risk of hemophiliacs 11 years after HIV seroconversion was 31% under 25 years and 56% over 25 years (Lee *et al.,* 1991). They estimated that the relative risk of AIDS increased 5-fold over 25 years. The same group confirmed in 1994 that the annual AIDS risk of HIV-positive hemophiliacs over 30 years is 2-times higher than in those under 15 years of age (Phillips *et al.,* 1994b). Stehr-Green *et al.* estimated that "... the risk of AIDS increased two fold for each 10 year increase in age after controlling for year of seroconversion." (Stehr-Green *et al.,* 1989). Likewise, Fletcher *et al.* reported a 4-fold higher incidence of AIDS in hemophiliacs over 25 years of age than in those aged 5 to 13 years (Fletcher *et al.,* 1992). Thus, the annual AIDS risk of hemophiliacs increases about 2-fold for each 10-year increase in age.

This confirms the foreign-protein hypothesis, which holds that the cumulative dose of transfusions received is the cause of AIDS-defining diseases among hemophiliacs. According to the hematologist Koerper, "this may reflect lifetime exposure to a greater number of units of concentrate, ..." and to Evatt *et al.*, "This age bias may be due to differences in duration of exposure to blood products ..." (Evatt *et al.,* 1984; Koerper, 1989). A recent study of HIV-free hemophiliacs is directly compatible with the foreign-protein hypothesis. The study showed that despite the absence of HIV "with increasing age, numbers of

$CD4^+CD45RA^+$ cells decreased and continued to do so throughout life" (Fletcher *et al.*, 1992).

By contrast, AIDS caused by an autonomous infectious pathogen would be independent of the age of the recipient because the replication cycle of viruses, including HIV, is independent of the age of the host. Thus the foreign-protein-AIDS hypothesis, rather than the HIV-AIDS hypothesis, correctly predicts the age bias of hemophilia-AIDS.

4.4 *Hemophilia-specific AIDS diseases.* The 30 AIDS diseases fall into two categories, the microbial immunodeficiency diseases and the non-immunodeficiency diseases, i.e. diseases that are neither caused by, nor consistently associated with, immunodeficiency (Duesberg, 1992a, 1994). Based on their annual incidence in America in 1992, 61% of the AIDS diseases were microbial immunodeficiency diseases, including pneumocystis pneumonia, candidiasis, tuberculosis, etc., and 39% were non-immunodeficiency diseases, including Kaposi's sarcoma, lymphoma, dementia, and wasting disease (Table 2) (Centers for Disease Control, 1993).

Table 2
AIDS defining diseases in the U.S. in 1992[a]

Immunodeficiencies	**Non-immunodeficiencies**
42% pneumonia	20% wasting disease
7% candidiasis	9% Kaposi's sarcoma
12% mycobacterial, including 3% tuberculosis	6% dementia
8% cytomegalovirus	4% lymphoma
5% toxoplasmosis	
5% herpesvirus	
Total = 61% (> 61% due to overlap)	**Total = 39%**

a. Centers for Disease Control, 1993.

The virus-AIDS hypothesis predicts that the probability of all HIV-infected persons to develop a given immunodeficiency or non-immunodeficiency AIDS disease is the same and independent of the AIDS risk group. By contrast, the hypothesis that AIDS is caused by drugs or by foreign proteins predicts specific diseases for specific causes (Duesberg, 1992a).

In America, 99% of the hemophiliacs with AIDS have immunodeficiency diseases, of which 70% are fungal and viral pneumonias (Evatt *et al.,* 1984; Koerper, 1989; Papadopulos-Eleopulos *et al.,* 1994). Only one study reports that 1% of hemophiliacs with AIDS had Kaposi's sarcoma (Selik, Starcher & Curran, 1987). The small percentage of Kaposi's sarcoma may be due to aphrodisiac nitrite inhalants used by male homosexual hemophiliacs as sexual stimulants (Haverkos & Dougherty, 1988; Duesberg, 1992a). There are no reports of wasting disease or dementia in American hemophiliacs. An English study also reported predominantly pneumonias and other immunodeficiency diseases among hemophiliacs, and also three cases of wasting syndrome (Lee *et al.,* 1991). It appears that the AIDS diseases of hemophiliacs are virtually all immunodeficiency diseases, whereas 39% of the AIDS diseases of intravenous drug users and male homosexuals are non-immunodeficiency diseases (Table 2). Since AIDS diseases in hemophiliacs and non-hemophiliacs are not the same, their causes can also not be the same.

The almost exclusive occurrence of immunodeficiency AIDS diseases among hemophiliacs is correctly predicted by the foreign-protein-AIDS hypothesis, but not by the HIV-AIDS hypothesis. The prediction of the HIV hypothesis, that the distribution of immunodeficiency and non-immunodeficiency diseases among hemophiliacs is the same as in the rest of the American AIDS population, is not confirmed.

4.5 *Is hemophilia-AIDS contagious?* The virus-AIDS hypothesis predicts that AIDS is contagious, because HIV is a parenterally and sexually transmitted virus. It predicts that hemophilia-AIDS is sexually transmissible. Indeed, AIDS researchers claim that the wives of hemophiliacs develop AIDS from sexual transmission of HIV (Booth, 1988; Lawrence *et al.,* 1990; Weiss & Jaffe, 1990; Centers for Disease Con-

trol, 1992a, 1993). Further, the HIV-AIDS hypothesis predicts that wives of hemophiliacs will develop the same AIDS diseases as other risk groups.

The foreign-protein hypothesis predicts that AIDS is not contagious and that the wives and sexual partners of hemophiliacs do not contract AIDS from their mates.

To test the hypothesis that immunodeficiency of hemophiliacs is sexually transmissible, the T4 to T8-cell ratios of 41 spouses and female sexual partners of immunodeficient hemophiliacs were analyzed (Kreiss *et al.,* 1984). Twenty-two of the females had relationships with hemophiliacs with T-cell ratios below 1, and 19 with hemophiliacs with ratios of 1 and greater. The mean duration of relationships was 10 years, the mean number of sexual contacts was 111 during the previous year, and only 12% had used condoms (Kreiss *et al.,* 1984). Since the T-cell ratios of all spouses were normal, averaging 1.68—exactly like those of 57 normal controls—the authors concluded that "there is no evidence to date for heterosexual or household-contact transmission of T-cell subset abnormalities from hemophiliacs to their spouses . . ." (Kreiss *et al.,* 1984).

The CDC reports that between 1985 and 1992, 131 wives of American hemophiliacs were diagnosed with unnamed AIDS diseases (Centers for Disease Control, 1993). If one considers that there have been 15,000 HIV-positive hemophiliacs in the U.S. since 1984 and that one-third are married, then there are 5,000 wives of HIV-positive hemophiliacs. About 16 of these women have developed AIDS annually during the 8 years (131: 8) from 1985 to 1992. But these 16 annual AIDS cases would have to be distinguished from the at least 80 wives of hemophiliacs that are expected to die per year based on natural mortality. Considering the human life span of about 80 years and that on average at least 1.6% of all those over 20 years of age die annually, about 80 out of 5,000 wives over 20 would die naturally per year. Thus, until controls show that among 5,000 HIV-positive wives of hemophiliacs 16 more than 80, i.e. 96, die annually, the claim that wives of hemophiliacs die from sexual or other transmision of HIV is unfounded speculation.

Moreover, it has been pointed out that all AIDS-defining diseases of the wives of hemophiliacs are typically age-related opportunistic

infections, including 81% pneumonia (Lawrence *et al.,* 1990). Kaposi's sarcoma, dementia, lymphoma, and wasting syndrome are not observed in wives of hemophiliacs (Lawrence *et al.,* 1990).

Again, the foreign-protein, but not the HIV hypothesis, correctly predicts the non-contagiousness of hemophilia-AIDS. It also predicts the specific spectrum of AIDS diseases in wives of hemophiliacs. By contrast, the virus-AIDS hypothesis predicts the same spectrum of AIDS diseases among wives of hemophiliacs as among the major risk groups (see Table 2). It appears that the virus-AIDS hypothesis is claiming normal morbidity and mortality of the wives of hemophiliacs for HIV.

4.6 *Immunodeficiency in HIV-positive and -negative hemophiliacs.* The HIV hypothesis predicts that immunodeficiency is observed only in HIV-positive hemophiliacs. By contrast, the foreign-protein hypothesis predicts that immunodeficiency is a function of the lifetime dose of transfusions received, and not dependent on HIV or antibodies against HIV. The foreign-protein hypothesis also predicts that HIV-positive hemophiliacs are more likely to be immunosuppressed than HIV-negatives because HIV is a rare contaminant of blood transfusion and thus is a marker for the number of transfusions received (see Section 3, and below) (Tsoukas *et al.,* 1984; Ludlam *et al.,* 1985; Kreiss *et al.,* 1986; Sullivan *et al.,* 1986; Koerper, 1989; Fletcher *et al.,* 1992).

Twenty-one studies, summarized in Table 3, have observed 1,186 immunodeficient hemophiliacs, 416 of whom were HIV-free. Immunodeficiency in these studies was either defined by a T4 to T8-cell ratio of about 1 or less than 1, compared to a normal ratio of 2, or by other tests such as immunological anergy. Since immunodeficiency was observed in the absence of HIV, most of the studies listed in Table 3 have concluded that immunodeficiency in hemophiliacs was caused by transfusion of factor VIII and contaminating proteins. According to the first of Koch's postulates (Merriam-Webster, 1965), the absence of a microbe, i.e. HIV, from a disease excludes it as a possible cause of that disease. Thus, transfusion of foreign protein, not the presence of HIV, emerges as the common denominator of all hemophiliacs with immunodeficiency.

Table 3
Immunosuppression in HIV-negative and -positive hemophiliacs

Study	HIV-negative	HIV-positive
1. Tsoukas *et al.*, 1984	6/14	9/15
2. Carr *et al.*, 1984	18/53	
3. Ludlam et al., 1985	15	
4. Moffat and Bloom, 1985	23	23
5. AIDS-Hemophilia French Study Group, 1985	33	55
6. Hollan *et al.*, 1985	30/104	
7. Sullivan *et al.*, 1986	28	83
8. Madhok *et al.*, 1986	9	10
9. Kreiss *et al.*, 1986	6/17	22/24
10. Gill *et al.*, 1986	8/24	30/32
11. Brettler *et al.*, 1986	4	38
12. Sharp *et al.*, 1987	5/12	
13. Matheson *et al.*, 1987	5	3
14. Mahir *et al.*, 1988	6	5
15. Antonaci *et al.*, 1988	15	10
16. Aledort, 1988	57	167
17. Jin *et al.*, 1989	12	7
18. Lang *et al.*, 1989	24	172
19. Jason *et al.*, 1990	31	
20. Becherer *et al.*, 1990	74	136
21 Smith *et al.*, 1993	7	
Totals	**416**	**770**

If two numbers are listed per category, the first reports immunodeficient and the second healthy plus immunodeficient hemophiliacs per study group. In most studies immunodeficiency was expressed by the T4/T8 cell ratio, in others by anergy. In a normal immune system the T4/T8 cell ratio is about 2. In immunodeficient persons it is about 1 or below 1. Studies which list both HIV-positive and negative groups indicate that HIV-positives are more likely to be immunodeficient than negatives. This is because HIV is a marker for the number of transfusions received, and transfusion of foreign proteins causes immunodeficiency (see Sections 3 and 4.6).

Nevertheless, several of the controlled studies listed in Table 3, which compare HIV-negative to HIV-positive hemophiliacs, have shown that immunodeficiency is more often associated with HIV-positives than with negatives. Although some studies did not report immunodeficiency in HIV-positives, Table 3 lists 770 HIV-positives and 416 HIV-negatives per 1,186 immunodeficient hemophiliacs. In view of this, one could argue that HIV is one of several possible causes of immunodeficiency.

However, some of the investigators listed in Table 3 (Tsoukas *et al.,* 1984; Ludlam *et al.,* 1985; Kreiss *et al.*, 1986; Madhok *et al.,* 1986; Sullivan *et al.,* 1986) and others who have not performed controlled studies (Koerper, 1989) have proposed that HIV is just a marker for the number of transfusions received (Section 3). As a rare contaminant of factor VIII, HIV has in fact been a marker for the number of transfusions received before it was eliminated from the blood supply in 1984, just like hepatitis virus infection was a marker of the number of transfusions received until it was eliminated from the blood supply earlier (Anonymous, 1984; Koerper, 1989). According to Kreiss *et al.*, "seropositive hemophiliac subjects, on average, had been exposed to twice as much concentrate ... as seronegative[s]" (Kreiss *et al.,* 1986). Sullivan *et al.* also reported that "Seropositivity to LAV/HTLV-III (HIV) was 70% for the hemophiliac population and ... varied directly with the amount of factor VIII received" (see Section 3) (Sullivan *et al.,* 1986). More recently, Schulman reported that "a high annual consumption" of factor VIII concentrate "predisposed" to HIV-seroconversion (Schulman, 1991), and Fletcher *et al.* described a positive "relationship between the amount of concentrate administered and anti-HIV prevalence rate ..." (Fletcher *et al.,* 1992).

The chronology of studies investigating immunodeficiency in HIV-free hemophiliacs faithfully reflects the popularity of the HIV hypothesis: the more popular the HIV hypothesis became over time the fewer studies investigated immunodeficiency in HIV-free hemophiliacs. Indeed, most of the controlled studies investigating the role of HIV in immunodeficiency of HIV-positive and matched HIV-negative hemophiliacs were conducted before the virus hypothesis became totally dominant in 1988 (Institute of Medicine, 1988), namely between 1984 and 1988 (Table 3). The studies by Jin, Cleveland and Kaufman, and Lang *et al.,*

both dated 1989, and the studies by Becherer *et al.* and by Jason *et al.*, both dated 1990, all described data collected before 1988 (Table 3). After 1988 the question whether HIV-free hemophiliacs developed immunodeficiency became increasingly unpopular. As a result, only a few studies have described immunodeficiency in HIV-free hemophiliacs.

For example, Schulman reported "worrisome evidence of similar immunological disturbances has been observed, albeit to a lesser degree, in anti-HIV-negative hemophiliacs" and that immunodeficiency in hemophiliacs "correlates more strongly with annual consumption of factor concentrates than with HIV status" (Schulman, 1991). Fletcher *et al.* published a median T4/T8-cell ratio of 1.4, with a low 10-percentile of 0.8, in a group of 154 HIV-free hemophiliacs, and also showed a steady decline of T-cell counts with treatment years (Fletcher *et al.*, 1992). Likewise, Hassett *et al.* reported that "patients with hemophilia A without human immunodeficiency virus type 1 (HIV-1) infection have lower $CD4^+$ counts and $CD4^+/CD8^+$ ratios than controls" (Hassett *et al.*, 1993). The study observed an average T4/T8-cell ratio of 1.47 in a group of 307 HIV-free hemophiliacs, differing over 50 years in age, compared to an average of 1.85 in normal controls. Unlike others Hassett *et al.* attributed the lowered $CD4^+$ counts to a hemophilia-related disorder rather than to foreign proteins, but like others they attributed increased $CD8^+$ counts to treatment with commercial factor VIII. However, Fletcher *et al.*'s and Hassett *et al.*'s practice of averaging immunodeficiency markers of large numbers of people, differing over 50 years in age, obscures how far the immunity of the longest, and thus most treated cases had declined compared to cases which have received minimal treatments.

Since the authors of these studies did not report the life time dosage of factor VIII treatments of HIV-free hemophiliacs, a correlation between foreign-protein dosage and immunosuppression cannot be determined. On the contrary, averaging immunodeficiency parameters of newcomers and long-term treatment recipients obscures the relationship between the lifetime dosage of factor VIII and immunosuppression.

Moreover, the CDC reported 7 HIV-free hemophiliacs with AIDS (Smith *et al.*, 1993). This study was one of a package that proposed to set apart HIV-free AIDS from HIV-positive AIDS with the new term *idiopathic CD4 lymphocytopenia.* The goal of these studies was to save the

virus-AIDS hypothesis, despite the presence of HIV-free AIDS (Duesberg, 1993b, 1994; Fauci, 1993). Nevertheless all of the 7 HIV-free hemophiliacs met one or more criteria of the CDC's clinical AIDS definition from 1993 (Centers for Disease Control and Prevention, 1992), e.g. they all had less than 300 T-cells per microliter (range from 88 to 296), and three also had AIDS defining diseases such as herpes and thrombocytopenia (Smith *et al.,* 1993).

The occurence of immunodeficiency in HIV-free hemophiliacs demonstrates most directly that long-term transfusion of foreign proteins contaminating factor VIII is sufficient to cause immunodeficiency in hemophiliacs. To prove the foreign-protein hypothesis it would be necessary to show that treatment of HIV-positive hemophiliacs with pure factor VIII does not cause immunodeficiency. It is shown below that this is actually the case.

4.7 *Stabilization, even regeneration of immunity of HIV-positive hemophiliacs by treatment with pure factor VIII.* Commercial preparations of factor VIII contain between 99% and 99.9% non-factor VIII proteins (Eyster & Nau, 1978; Brettler & Levine, 1989; Gjerset *et al.,* 1994; Mannucci *et al.,* 1992; Seremetis *et al.,* 1993). The foreign-protein-hemophilia-AIDS hypothesis predicts that long-term transfusion with commercial factor VIII would be immunosuppressive, because of the presence of contaminating proteins. Further, it predicts that pure factor VIII, containing 100- to 1,000-times less foreign protein per functional unit, may not be immunosuppressive.

Several studies have recently tested whether the impurities of factor VIII or factor VIII by itself are immunosuppressive in HIV-positive hemophiliacs. De Biasi *et al.* showed that over a period of two years the average T-cell counts of ten HIV-positive hemophiliacs treated with non-purified, commercial factor VIII declined two-fold, while those of matched HIV-positive controls treated with pure factor VIII remained unchanged. Moreover, four out of six anergic HIV-positive patients treated with purified factor VIII recovered immunological activity (de Biasi *et al.,* 1991). Goldsmith *et al.* also found that the T-cell counts of 13 hemophiliacs treated with purified factor VIII remained stable for 1.5 years (Goldsmith *et al.,* 1991). Seremetis *et al.* have confirmed and

extended de Biasi *et al.*'s conclusion by establishing that the T-cells of HIV-positive hemophiliacs were not depleted after treatment with pure factor VIII for three years (Seremetis *et al.*, 1993). Indeed, the T-cell counts of 14 out of 31 HIV-positive hemophiliacs increased up to 25% over the three-year period of treatment with purified factor VIII—despite infection by HIV. By contrast, in the group treated with unpurified factor VIII, the percentage of those with less than 200 T-cells per ml increased from 7% at the beginning of the study to 47% at the end.

Likewise Hilgartner *et al.* reported individual increases of T-cell counts of up to 50% in a group of 36 HIV-positive hemophiliacs treated with purified factor VIII whose average T-cell count had declined 1% during 6 months (Hilgartner *et al.*, 1993). Goedert *et al.* have also reported that "T-cell counts fell less rapidly with high purity products" (Goedert *et al.*, 1994). Moreover, Schulman observed that four HIV-positive hemophiliacs recovered from thrombocytopenia upon treatment with pure factor VIII for 2–3 years, and others from CD8-related immunodeficiency upon treatment for 6 months (Schulman, 1991).

However, despite the evidence that purified factor VIII is beneficial in maintaining or even increasing T-cell counts, several studies testing purified factor VIII are ambiguous about its effectiveness in preventing or treating AIDS (Goldsmith *et al.*, 1991; Hilgartner *et al.*, 1993; Gjerset *et al.*, 1994; Goedert *et al.*, 1994; Phillips *et al.*, 1994a). Some of these studies have only tested partially purified, i.e. 2–10 units/mg, instead of highly purified, i.e. 2000–3000 units/mg, factor VIII (Gjerset *et al.*, 1994). But each of the studies that are ambiguous about the benefits have also treated their patients with toxic antiviral DNA chain terminators like AZT. Indeed the study by de Biasi *et al.* was the only one that has tested purified factor VIII in the absence of AZT. The study by Seremetis *et al.* initially called for no AZT, but later allowed it anyway. Thus in all but one study, the potential benefits of highly purified factor VIII have been obscured by the toxicity of AZT (see Section 5.4).

It is concluded that treatment of HIV-positive hemophiliacs with pure factor VIII provides lasting stabilization of immunity, and even allows regeneration of lost immunity. It follows that foreign proteins, rather than factor VIII or HIV, cause immunosuppression in HIV-positive hemophiliacs.

5. Conclusions and Discussion

Four criteria of proof have been applied to distinguish between the virus and the foreign-protein hypothesis of hemophilia-AIDS: (i) correlation, (ii) function (Koch's third postulate), (iii) predictions, (iv) therapy and prevention. Each of these criteria proved the foreign-protein hypothesis valid and the HIV hypothesis invalid.

5.1 *Correlations between hemophilia-AIDS and the long-term administration of foreign proteins or HIV.* Although correlation is not sufficient, it is necessary to prove causation in terms of Koch's postulates (Merriam-Webster, 1965). The first of Koch's postulates calls for the presence of the suspected cause in all cases of the disease, i.e. a perfect correlation; the second calls for the isolation of the cause; and the third for causation of the disease with the isolated causative agent.

All hemophiliacs with immunodeficiency described here have been subject to long-term treatment with foreign proteins contaminating factor VIII. This establishes a perfect correlation between foreign-protein transfusion and hemophilia-AIDS, and fulfills Koch's first postulate.

By contrast, a summary of 21 separate studies showed that 416 of 1,186 immunodeficient hemophiliacs were HIV-free (Table 3). Since HIV does not correlate well with hemophilia-AIDS, it fails Koch's first postulate and is thus not even a plausible cause of AIDS.

5.2 *Foreign-protein hypothesis, but not HIV hypothesis, meets Koch's third postulate as cause of immunodeficiency.* The fact that all hemophiliacs with immunodeficiency had been subject to long-term treatment with foreign proteins, and that factor VIII treatment in the absence of foreign proteins does not cause immune suppression, and may even revert it, provides functional proof for the foreign-protein hypothesis. Thus, the foreign-protein hypothesis meets Koch's third postulate of causation.

Regeneration of immunity of HIV-positives by treatment with pure factor VIII further indicates that HIV by itself or in combination with factor VIII is not sufficient for hemophilia-AIDS. Therefore, HIV fails Koch's third postulate as a cause of AIDS.

5.3 *Foreign-protein hypothesis correctly predicts hemophilia-AIDS and resolves paradoxa of HIV hypothesis.* The ability to make verifiable predictions is the hallmark of a correct scientific hypothesis. Application of the two competing hypotheses to hemophilia-AIDS proved that the foreign-protein hypothesis, but not the HIV hypothesis, correctly predicts seven characteristics of hemophilia-AIDS (see Sections 4.1—4.7):

1. The increased life span of American hemophiliacs, despite infection of 75% by HIV, due to factor VIII treatment, that extended their lives and disseminated harmless HIV;
2. the 3–5 times lower annual AIDS risk of hemophiliacs, compared to other AIDS risk groups;
3. the age bias of the annual AIDS risk of hemophiliacs, increasing 2-fold for each 10-year increase in age;
4. the restriction of hemophilia-AIDS to immunodeficiency-related AIDS diseases, setting it apart from the spectrum of AIDS diseases in other risk groups;
5. the non-contagiousness of hemophilia-AIDS, i.e. the absence of AIDS diseases above their normal background in sexual partners of hemophiliacs;
6. the occurrence of immunodeficiency in HIV-free, factor VIII-treated hemophiliacs;
7. the stabilization, even regeneration, of immunity of HIV-positive hemophiliacs upon long-term treatment with pure factor VIII.

It follows that the foreign-protein hypothesis, but not the HIV hypothesis, correctly predicts hemophilia-AIDS. In addition, the foreign-protein hypothesis resolves all remaining paradoxa of the HIV hypothesis (see Section 2):

1. The failure of HIV neutralizing antibody to protect against AIDS—because HIV is not the cause of AIDS.
2. The non-correlation between the loss of T-cells and HIV activity—because foreign proteins rather than HIV are immunotoxic.

3. The failure of HIV to kill T-cells—because T-cell synthesis is suppressed by immunotoxic foreign proteins.

4. The latent periods of 10 to 35 years between HIV and hemophilia-AIDS—because the lifetime dosage of foreign proteins, not HIV, causes AIDS.

5.4 *Treatment and prevention of AIDS.* The prevention or cure of a disease, by eliminating or blocking the suspected cause, provides empirical proof of causation.

(i) Drug-treatment based on HIV hypothesis: On the basis of the HIV hypothesis, AIDS has been treated since 1987 with anti-HIV drugs, such as the DNA chain terminators AZT, ddI, etc. (Duesberg, 1992a). The rationale of the AZT treatment is to prevent HIV DNA synthesis at the high cost of inhibiting cellular DNA synthesis, the original target of AZT cancer chemotherapy (see above). However, not a single AIDS patient has ever been cured with AZT. Since 1989, healthy HIV-positive hemophiliacs have also been treated with DNA chain terminators in efforts to prevent AIDS. But the alleged ability of AZT to prevent AIDS has recently been discredited by several large clinical trials (Oddone *et al.,* 1993; Tokars *et al.,* 1993; Goedert *et al.,* 1994; Lenderking *et al.,* 1994; Lundgren *et al.,* 1994; Seligmann *et al.,* 1994). Moreover, all studies of AZT treatments have confirmed the unavoidable cytotoxicity of DNA chain terminators (Duesberg, 1992; Oddone *et al.,* 1993; Tokars *et al.,* 1993; Lenderking *et al.,* 1994; Lundgren *et al.,* 1994; Seligmann *et al.,* 1994). One study observed a 25% increased mortality (Seligmann *et al.,* 1994), and another a 4.5-fold higher annual AIDS risk and a 2.4-fold higher annual death risk in AZT-treated HIV-positive hemophiliacs compared to untreated controls (Goedert *et al.,* 1994).

The failure of AZT therapy to cure or prevent AIDS indicates either that the drug is not sufficient to inhibit HIV or that HIV is not the cause of AIDS. The lower mortality and much lower incidence of AIDS defining diseases among hemophiliacs not treated with AZT compared to those treated indicates that AZT causes AIDS defining diseases and mortality. Thus, there is currently no rational or empirical justification for AZT treatment of HIV-positives with or without AIDS.

The apparent ability of AZT to cause AIDS defining and other dis-

eases in hemophiliacs is just one aspect of the many roles that drugs play in the origin of AIDS (see footnote).[1]

(ii) Treatment based on foreign-protein hypothesis: In the light of the foreign-protein hypothesis, hemophiliacs have been treated with factor VIII freed of foreign proteins. This treatment has provided lasting stabilization of immunity in HIV-positive hemophiliacs. Moreover, the long-term treatment of immunodeficient, HIV-positive hemophiliacs with purified factor VIII has even regenerated lost immunity. Immunological anergy has disappeared and the T-cells in HIV-positive hemophiliacs have increased up to 25% in the presence of pure factor VIII (see Section 4.7) (de Biasi *et al.*, 1991; Seremetis *et al.*, 1993). Thus, therapeutic benefits including AIDS prevention and even recovery of lost

1. The drug-AIDS hypothesis, which applies to most American and European AIDS cases other than hemophiliacs (see Section 1) (Duesberg. 1992a), also derives support either from the absence of AIDS, or from the stabilization of, or spontaneous recovery from AIDS conditions in HIV-positives who don't use drugs. For example, in August 1993 there was no mortality during 1.25 years in a group of 918 British HIV-positive homosexuals who had "avoided the experimental medications on offer," and chose to "abstain from or significantly reduce their use of recreational drugs, including alcohol" (Wells, 1993). Assuming a 10-year latent period from HIV to AIDS, the virus AIDS-hypothesis would have predicted at least 58 (918/10 x 1.25 x 50%) AIDS cases among 918 HIV-positives over 1.25 years. Indeed, the absence of mortality in this group over 1.25 years corresponds to a minimal latent period from HIV to AIDS of over 1,148 (918 x 1.25) years. On July 1st 1994 there was still not a single AIDS case in this group of 918 HIV-positive homosexuals (J. Wells, London. pers. Comm.). Further, the T-cell counts of 197 (58% of 326) HIV-positive homosexuals remained constant over 3 years, despite the presence of HIV (Detels *et al.*, 1988). These were probably those in the cohort.who did not use recreational drugs or AZT. Moreover, it has been observed that the T-cells of 29% of 1,020 HIV-positive male homosexuals and intravenous drug users even increased up to 29% per year over 2 years (Hughes *et al.*, 1994). These HIV-positives belonged to the placebo arm of an AZT trial for AIDS prevention and thus were not intoxicated by AZT. It is probable that the 29% whose T-cells increased despite HIV may have given up or reduced immunosuppressive recreational drug use in the hope that AZT would work.

immunity by omission of foreign proteins from factor VIII lend credence to the foreign-protein-AIDS hypothesis.

(iii) Two treatment hypotheses—and one treatment dilemma: The failure to distinguish between two alternative hypothetical AIDS causes, HIV and foreign proteins, has created a dilemma for contemporary hemophilia treatment. For example, Goedert *et al.* acknowledge that "CD4 count fell less rapidly with high purity products" (Goedert *et al.*, 1994). But since they are also treating their patients with toxic AZT (see Section 4.1), they observe that "F VIII related changes in CD4 concentration may have little relevance to clinical disease" (Goedert *et al.*, 1994). Indeed the group had published a rare comparison between the annual AIDS- and death risks of hemophiliacs treated and not treated with AZT which indicated that the AIDS risk of AZT-treated hemophiliacs is 4.5-times and the death risk 2.4-times higher than in untreated controls.

In order to reconcile the apparent benefits of purified factor VIII on T-cell counts with the apparent toxicity of simultaneous AZT treatment, they try to separate T-cell loss from AIDS diseases. However, despite non-immunodeficiency AIDS diseases (see Table 2, Section 4.4), AIDS is defined as a T-cell deficiency (Institute of Medicine and National Academy of Sciences, 1986; Institute of Medicine, 1988) and dozens of AIDS researchers have observed that "AIDS tends to develop only after patients' CD4 lymphocyte counts have reached low levels ..." (Phillips *et al.*, 1994b). Indeed, as of January 1993 the CDC defined less than 200 T-cells per ml as an AIDS disease (Centers for Disease Control and Prevention, 1992), and sequential T-cell counts of hemophiliacs are used as a basis to calculate their long-term survival (Phillips *et al.*, 1994b).

Because of their exclusive faith in the HIV-AIDS hypothesis, readers of the study by Seremetis *et al.* (Seremetis *et al.*, 1993), which had demonstrated that foreign proteins associated with factor VIII suppress T-cell counts, have even proposed to "consider the use of high-purity factor VIII concentrates in non-hemophiliac-HIV-positive patients" as a treatment for other AIDS patients, i.e. intravenous drug users and homosexuals. Since hemophiliacs treated with pure factor VIII did either not develop immunodeficiency or even recovered lost immunity, they

assumed, in view of the HIV-hypothesis, that pure factor VIII must inhibit HIV and thus would help all AIDS patients (Schwarz *et al.,* 1994).

The solution to the treatment dilemma can only come from treatments that are each based only on one hemophilia-AIDS hypothesis: To test the foreign-protein hypothesis, two groups of hemophiliacs must be compared that are matched for their life time dosage of factor VIII, for their percentage of HIV-positives (for their percentage and dosage of prior AZT treatment, if applicable), and for their age. All AIDS-defining diseases must be diagnosed in each group clinically for the duration of the test. No anti-HIV treatments must be performed. One group would be treated with purified factor VIII, the other with commercial factor VIII contaminated with foreign proteins.

To test the HIV-AIDS hypothesis, two groups of hemophiliacs must be compared that are matched for their life time dosage of factor VIII treatment and their age. The two groups must differ only in the presence of antibody against HIV. Both groups would be treated with the same factor VIII preparation. Only the HIV-positive group would receive AZT. All compensatory treatments of AZT recipients, e.g. blood transfusions to treat for AZT-induced anemia, neutropenia or pancytopenia (Richman *et al.,* 1987; Volberding *et al.,* 1990; Duesberg, 1992), would have to be recorded. During the duration of the test, all AIDS-defining diseases would each be recorded clinically in both groups.

The outcome of each treatment strategy, purified factor VIII or AZT, would be determined based on morbidity and mortality, including AZT morbidity and mortality, and corrected for treatments compensating for AZT toxicity. As yet, no controlled treatment studies based on a single AIDS hypothesis have been performed.

Nevertheless, the study by de Biasi *et al.* (de Biasi *et al.,* 1992) and with reservations that by Seremetis *et al.* (Seremetis *et al.,* 1993) come close to the stated criteria for a test of the foreign-protein hypothesis (Section 4.7). Seremetis *et al.* initially excluded, but later allowed AZT treatment. Both studies showed that purified factor VIII improved immunodeficiency (see ii). However, since all subjects in these studies were HIV-positive, one could indeed argue that the improvement of those treated with purified factor VIII was due to a cooperation between HIV and purified factor VIII.

The definitive treatment of immunodeficiency in hemophiliacs, or of hemophilia-AIDS, could be only as far away as the duration of one carefully controlled treatment test.

Acknowledgements

I thank Siggi Sachs, Russell Schoch, and Jody Schwartz (Berkeley) for critical reviews, and Robert Maver (Overland Park, MO), Scott Tenenbaum, Robert Garry (Tulane University, New Orleans), Jon Cohen *(Science,* Washington, DC) and Michael Verney-Elliot (MEDITEL, London) for critical information. This investigation was supported in part by the Council for Tobacco Research, USA, and private donations from Tom Boulger (Redondo Beach, CA, USA), Glenn Braswell (Los Angeles, CA, USA), Dr. Richard Fischer (Annandale, VA, USA), Dr. Fabio Franchi (Trieste, Italy), Dr. Friedrich Luft (Berlin, Germany) and Dr. Peter Paschen (Hamburg, Germany).

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Chapter Twelve

Duesberg and the Right of Reply According to Maddox—*Nature*

Peter H. Duesberg and Harvey Bialy*

Genetica Monograph "AIDS: Virus- or Drug-Induced?" 1995.
Kluwer Academic Publishers, Dordrecht, The Netherlands.

In 1993 John Maddox, the editor of *Nature,* commissioned a commentary refuting the hypothesis that drugs cause AIDS (Ascher *et al.,* 1993). The piece described 215 patients each of which had used drugs (Duesberg, 1993a; Duesberg, 1993b; Duesberg, 1993c). In view of this Duesberg sent a letter to *Nature* arguing that the perfect correlation between drug use and AIDS confirmed, rather than refuted, the drug hypothesis. Maddox censored the letter and wrote an editorial "Has Duesberg a Right of Reply?" (Maddox, 1993). The editorial pointed out that the world's oldest science journal could not afford an open scientific debate on the cause of AIDS because of the perceived dangers of infectious AIDS.

In an editorial on January 19, 1995, Maddox promised to lift the censorship to give "Duesberg and his associates an opportunity to comment" on two *Nature* studies that in his opinion prove the HIV-AIDS hypothesis.

In the following we document how Maddox—*Nature* honors its commitments. Our documentation includes:

(i) A photocopy of Maddox' *News and Views* article of January 19, 1995,

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* Harvey Bialy is a molecular biologist who is currently the science editor of *Biotechnology*, New York, NY.

(ii) A summary of a phone conversation between Maddox and Bialy,
(iii) Our letter to Maddox answering his invitation,
(iv) Our commentary on the two new *Nature* studies,
(v) Maddox' response to our commentary,
(vi) Our response to Maddox,
(vii) What *Nature* published from and about Duesberg and Bialy on May 18, 1995,
(viii) *Nature*'s final letter.

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Duesberg and the New View of HIV

John Maddox, "News and Views," *Nature* 373: 189, 19 January 1995

This journal has offered Dr. Peter Duesberg and his associates an opportunity to comment on last week's publications suggesting that the immune system reacts hyperactively to HIV infection.

The publication last week of two important articles on the dynamics of the infection of people by HIV is agreed to have been a important landmark in the process of understanding the disease called AIDS, but not everybody will be aware of that. Reporting of the event has been curiously selective. In particular, the British newspaper *The Sunday Times,* which as recently as a year ago was replete with accounts of how HIV can have little or nothing to do with the causation of AIDS, chose not even to mention the new developments in last Sunday's edition.

Is it planning a major account of how it came to be so misled, thus to mislead its readers? Or is it waiting for a sign from Professor Peter

Duesberg, of Berkeley, California, who started the hare the newspaper followed eagerly for two years?

The reasons why the new developments are (or should be) an embarrassment for Duesberg are simply put. Almost from the outset of AIDS as a recognized disease in the early 1980s, the objective index of an infected person's state of health has been the concentration in the blood of T lymphocytes carrying the CD4 antigen. The more advanced the infection, the smaller the concentration of $CD4^+$ cells.

But Duesberg was quick to point to a paradox in the observations: although the concentration of $CD4^+$ cells might decline with the persistence of infection, there was no dramatic increase of the frequency of infected T cells as infection gave way to overt disease. Cell death by inter-cellular infection could hardly be consistent with that state of affairs.

In essence, the new developments resolve the paradox by showing that the T cells in an infected person's blood are likely to have been created only in the few days previously. There will not have been time enough for more than a small proportion of them to have become infected, while those that harbour virus will be killed off very soon. So the scarcity of T cells from which virus can be recovered in test-tube experiments is consistent with the assertion that the immune system is in overdrive from the onset of infection by HIV.

On this (new) view, the progressive decline of the $CD4^+$ concentration with the duration of infection is rather a symptom of the underlying infection than the crux of its mechanism. What seems to matter is that there should be cells (including T cells) somewhere in the body (the lymph nodes are likely candidates) from which virus particles continue to leak into the blood plasma. In other words, Duesberg is right to have argued all along that the usually slow decline of $CD4^+$ cells is not consistent with what one would expect from a specific cytotoxic viral mechanism. The explanation is that the $CD4^+$ population in the blood at any time has been freshly created.

Despite this journal's severe line, some months ago, on Duesberg's right of reply to critics of his position, it is now in the general interest that his and his associates' views on the new developments should be made public. Duesberg was not available to take a single telephone call

one day last week, nor able to return it, but one of his associates appeared to welcome the idea of a comment on the articles by Wei *et al.* and Ho *et al.* (*Nature* 373, 117–122 & 123–126; 1995). That will be eagerly awaited and will be published with the usual provisos—that it is not libelous or needlessly rude, that it pertains to the new results and that it should not be longer than it needs to be.

Meanwhile, one important question stands out like a sore thumb: why, after more than a decade of research, has it only now emerged that the response of the immune system to infection by HIV is hyperactivity rather than the opposite? Simon Wain-Hobson, writing in News and Views last week (*Nature* 373, 102; 1995), remarked that the investigators were able to reach their startling conclusions "by teaming up with mathematicians."

Intuitively, the sharp recovery of $CD4^+$ cells in the first few days after the administration of antiviral drugs pointed to their rapid production by the immune system. But in retrospect the good fortune of the investigators is clear. Only with the advent of highly specific drugs directed against HIV was it possible to cut off viral production so abruptly that the decline in plasma viremia could form the basis for a model of viral production. New techniques for assaying the low levels of virus involved were also necessary; had the drugs been available only a few years earlier, these studies would have been impossible on that account.

In retrospect, the dynamics of the immune system would seem to be central to any consideration of the body's response to infection, by measles virus as well as HIV. And modelling of such processes as the production of lymphocytes (B as well as T cells) in the immune response should be a relatively easy task (compared with, say, the appearance of endless molecular species in the evolution of a molecular cloud).

To be sure, immunologists are no strangers to quantitation in this spirit. And the involvement of mathematicians is simply explained by the authors' desire to be sure that even experts in this area approved of their data analysis. But the rarity of such studies says something depressing about the state of biology, for all its modernity. Despite the explosion in molecular knowledge (including molecular knowledge of viruses), the information to perform this kind of quantitative modelling is almost never available. In this case, the relevant data have emerged only after

a decade of intensive research, fuelled by intense public interest in a most unpleasant pathogen. But virology is not the only field in which biology would benefit from more quantitative methods.

What more is to come? Now that the basis for the low $CD4^+$ T-cell count in AIDS patients is clear, further studies of the viral dynamics will be eagerly awaited. How much virus is produced by each productively infected cell? How fast is the virus produced by the lymph nodes? And what is responsible for killing the $CD4^+$ T cells? If these last are indeed being destroyed by the $CD8^+$ cells of the immune system, as Wain-Hobson suggests (and this remains to be seen), it will undoubtedly lend further support to the idea that individuals who are repeatedly exposed to HIV while remaining unaffected are protected by their cytotoxic T lymphocytes (Rowland-Jones *et al., Nature Medicine* 1, 59–64; 1995).

The search for effective antiviral therapy will also benefit. Already Wei *et al.* have followed the emergence of mutants resistant to one drug, and studies of others, alone and in combination, will surely follow. Here too, improved quantitation of the size of viral pools in different tissues, and their respective replication rates, will be vital.

What does this mean for basic research on AIDS, the cause eloquently advocated a year ago by Dr. Bernie Fields *(Nature* 369, 95; 1994)? Wei *et al.* and Ho *et al.* have provided the basis for a much more pointed programme of investigation from which, no doubt, a complete picture of the dynamics of this hitherto perplexing disease will emerge. A return to basics seems already to have happened. The prospects of therapy are much more difficult to tell, but has a fuller understanding ever failed to deliver improvements of technique? The danger for the Duesbergs of this world is that they will be left high and dry, championing a cause that will have ever fewer adherents as time passes. Now may be the time for them to recant.

Summary of Phone Conversation between John Maddox and Harvey Bialy

On the afternoon of January 12, [1995] the day the *Nature* issue containing the Ho and Wei *et al.* papers appeared, and one day after the

press conference announcing these landmark publications, I received a rare telephone call from my colleague, the newly knighted, Sir John Maddox, editor of *Nature*. The essence of the ensuing conversation is summarized below.

After congratulating John on his recently acquired honorific, I asked to what did I owe the pleasure of his call. He then asked me what I thought of the "HIV-1 dynamics" papers. I replied by thanking him for publishing them, as they were so transparently bad, they would convince any reasonable scientist who had the endurance to read them that the HIV-AIDS hypothesis was absolutely intellectually bankrupt. I also chided him by saying that even Wain-Hobson didn't know what to make of them, judging by his incoherent *News & Views* piece that accompanied their publication.

To my surprise, his response to these remarks was remarkably devoid of any outrage. We discussed in a cursory manner some of the more obvious criticisms of the papers, such as their lack of controls, and the methodological and biological problems with their estimates of free infectious virus. I also mentioned that I thought it ironic that after years of denying that T cells turned over at the rate of 5% in two days, the HIV-AIDS protagonists were now at last admitting this well known fact. He responded by asking how did I explain the "dramatic increase in T cells after treatment with the protease inhibitor." I replied that this transient, hardly dramatic, increase was also a well known phenomena called lymphocyte trafficking, which occurs in response to many chemical insults.

The conversation then changed direction and John said that he had, without success, been trying to reach Peter (Duesberg) to inform him that he was, in this instance, willing to rescind his previous "refusal of the right of reply" and would welcome a correspondence from Peter (and myself) addressing what we perceived as the shortcomings of Ho and Wei *et al.* He promised me that if the piece was relevant, succinct and not personally rude, he would publish it "unslagged." When I asked him what this meant, he said that it would be published as received, without prior review and without a response appearing in the same issue. I said "do you mean it will be allowed to generate its own replies?," and he said

"yes." I congratulated him on his willingness to open a proper scientific debate, and said I would communicate our conversation to Peter.

I was a bit surprised to see his editorial in the following week's *Nature* in which he went much further than our conversation in offering the pages of *Nature* to uncensored debate. I was, however, not surprised to discover, some weeks later, that the response which appears unedited in this issue of *Genetica,* was deemed "too long by half and too unfocussed" to warrant publication in his own highly esteemed journal.

Letter to John Maddox from Peter Duesberg and Harvey Bialy

February 7, 1995

Sir John Maddox
Nature, Macmillan Publishing
4 Little Essex St.
London, WC2R 3LF England

Dear John,

As per your invitation, published in *News and Views* "Duesberg and the new view of HIV," and your invitation to Harvey Bialy over the phone, "to comment on last week's publications" by Wei *et al.* and Ho *et al.* we submit "Responding to 'Duesberg and the new view of HIV'" by Duesberg & Bialy. We are delighted that after years of editorials, News & Views, and letters and censored letters we have been invited at last to make our case in our own words.

As you can see, our report meets your criteria of "not libellous or needlessly rude, that it pertains to the new results and that it should not be longer than it needs to be." The length of our commentary is compatible with the results presented in the two papers covering 10 pages, and the challenges delivered by the two accompanying News & Views from you and Wain-Hobson.

We both respect your courage and integrity to undertake an uncensored debate on the HIV-AIDS hypothesis.

Best regards

Peter Duesberg
Harvey Bialy

P.S. A hard copy is in the mail. We can send a disc if that helps.

Responding to "Duesberg and the New View of HIV"
Peter H. Duesberg and Harvey Bialy*

The editor of *Nature,* John Maddox, has issued a published invitation to "Peter Duesberg and his associates ... to comment" on two new studies by Wei *et al.*[1] and Ho *et al.*[2] that he feels lend strong support to the hypothesis that HIV causes AIDS.[3] Maddox credits us for having identified two paradoxes of this hypothesis, (i) "Duesberg was quick to point to a paradox ... [that] there was no dramatic increase of the frequency of infected T-cells as infection gave way to overt disease," and that (ii) "Duesberg is right to have argued all along that the usually slow decline of $CD4^+$ cells [T-cells] is not consistent with ... a specific cytotoxic viral mechanism."[3]

According to Maddox, "the new developments are (or should be) an embarrassment for Duesberg," because they "resolve the paradox." But we do not see any reason why a scientist should be embarrassed for having pointed out paradoxes in the past, which ever way these paradoxes are subsequently solved. We also object to rhetoric personalizing a scientific debate. However, it is embarrassing that in the name of science clinical, public health, journalistic, and political decisions have been made in the past, based on a hypothesis that—we all agree now—was unproven at that time.

Since the HIV-AIDS hypothesis makes many assumptions that are paradoxical, if not bewildering, for pre-HIV virologists, and since the new studies do not clearly define the HIV hypothesis, we shall first state the hypothesis and then explain why, in light of these "new" studies, it remains paradoxical.

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* This draft is revised as per our letter of March 7 (see below).

In 1984 it was proposed that the retrovirus HIV can cause such diametrically different diseases as Kaposi's sarcoma, pneumonia, dementia, diarrhea, and weight loss.[4,5] All of these diseases and over two dozen more are now collectively called acquired immunodeficiency syndrome (AIDS)[6] if antibody to HIV is present. But many of these diseases, including Kaposi's sarcoma, lymphoma, dementia and weight loss, are neither consequences of, nor consistently associated with immunodeficiency.[7,8] For example Kaposi's sarcoma and dementia have been diagnosed in male homosexuals whose immune systems were normal.[9–13] As a cause of these diseases HIV was proposed to follow an entirely unprecedented course of action:

1) HIV was proposed to cause immunodeficiency by killing T-cells. But retroviruses do not kill cells.[14,15]

2) Within weeks after infection, HIV would reach moderate to high titers of $10–10^4$ infectious units per ml blood,[16] sufficient to induce antiviral immunity and antibodies (a positive "AIDS-test"). According to Shaw, Ho and their collaborators, HIV activity is "rapidly and effectively limited" by this antiviral activity.[17,18] Prior to antiviral immunity, HIV would neither kill T-cells nor cause AIDS.[16,19] But all other viruses are primarily pathogenic prior to immunity; the reason vaccination protects against disease. Not one virus exists that causes diseases only after it is neutralized by antiviral immunity.[20,21]

3) On average 10 years after HIV is neutralized, the virus is postulated to cause AIDS diseases.[5,22] But all other viruses typically cause disease within days or weeks after infection, because they replicate exponentially with generation times of 8 to 48 hours.[20,23,24]

4) As a consequence of antiviral immunity, the virus titer is typically undetectably low prior to and even during AIDS.[25–29] Only in rare cases HIV titers are as high as in the asymptomatic, primary infection.[16,30] But in all other viral diseases the virus titer is maximally high when viruses cause disease.[20,21]

5) Antiviral immunity would typically restrict HIV-infected lymphocytes to less than 1 in 500—prior to and even during AIDS.[14,26,27,30–32] But all other viruses infect more cells than the host can spare or regenerate when they cause disease.[20,21]

6) The hypothesis fails to shed any light on the causation of non-

immunodeficiency AIDS diseases, like Kaposi's sarcoma, dementia, lymphoma and weight loss which make up 39% of all American AIDS cases.[8,33]

Today this HIV-AIDS hypothesis stands unproven and has failed to produce any public health benefits.[34–36]

The new studies are claimed by two News and Views articles from Maddox[3] and Wain-Hobson[43] to resolve the paradoxa, (1) how HIV kills T-cells, (2) how HIV causes AIDS, and (3) why HIV needs 10 years to cause AIDS. But we argue that the new studies have failed to resolve any of these paradoxa, in fact they have added new ones:

(1) *How HIV kills T-cells.* Until HIV appeared on the scene, retroviruses did not kill their host cells. This is the reason they were considered possible tumor viruses. Since retroviruses integrate their genes into the chromosome of the host, they can only replicate as long as the host survives integration and remains able to express integrated viral genes. Therefore a cytocidal retrovirus would be suicidal. Indeed, HIV proved to be non-cytocidal. It is mass-produced for the "AIDS-test" in immortal T-cells in culture at titers of 10^6 infectious units per ml.[37,38] Luc Montagnier and others have confirmed that HIV does not kill T-cells.[39–42] Hence the claim that HIV causes AIDS by killing T-cells is paradoxical.

The new papers have indeed resolved this paradox by shifting the paradigm: According to Maddox, T-cells "that harbour virus will be killed off very soon"—but not by HIV—by the immune system. Also consistent with a non-cytocidal virus, Wei *et al.* report that "the average half-life of infected PBMCs [peripheral blood mononuclear cells] is very long and of the same order of magnitude as the half-life of uninfected PBMCs." But, paradoxically, the same investigators also report that "the life span of virus-producing cells is remarkably short ($t_{1/2} = 2 \pm 0.9$ days)," although these cells are in the same system as their long-lived HIV-infected peers.[1] Ho *et al.* state that "there is virus- and immune-mediated killing of CD4 lymphocytes."[2] According to the News and Views article by Simon Wain-Hobson "an intrinsic cytopathic effect of the virus is no longer credible."[43]

It is consistent with this "new view of HIV" that there is no correlation between virus titers and T-cell counts in the patients that Wei *et*

al. and Ho *et al.* have studied. In some of Ho *et al.*'s patients, i.e. #303 and #403, a 100-fold variation in virus titers corresponds to no changes in T-cell counts. In Wei *et al.*'s patients 100-fold variations in virus titers correspond to only 0.25 and 3-fold variations in T-cell counts—hardly a correlation to prove that HIV kills T-cells.

Since HIV is no longer viewed as a T-cell killer, the above paradox is solved. However, if T-cell killing via antiviral immunity were the cause of AIDS, we would have a bigger HIV-AIDS paradox than before. Since only 1 in 500 T-cells are ever infected, and most of these cells contain latent HIV not making viral proteins,[25,26,30,44] only less than 1 in 500 T-cells could ever be killed by antiviral immunity.

(2) *How HIV causes AIDS.* Until HIV appeared on the scene, the pathogenicity of a virus was a direct function of the number of virus-infected cells: the more infectious virus there was, the more cells were infected, and the more pathogenic an infection was.

But in typical AIDS patients HIV is so rare, that even leading AIDS retrovirologists from the US, like Robert Gallo, and the UK, like Robin Weiss, failed for years to isolate HIV from AIDS patients.[45,46] Likewise, virus-infected cells are so rare that they could not be found by George Shaw, the senior investigator of the new study by Wei *et al.*, Gallo and their collaborators in most AIDS patients[27]—until the rare proviral DNA could be amplified with the polymerase chain reaction (PCR).[31,44,47]

Although the new studies never mention the percentage of infected T-cells, Maddox confirms the status quo: "the scarcity of T-cells from which virus can be recovered in test-tube experiments is consistent with the assertion that the immune system is in overdrive from the onset of infection by HIV." But the new studies claim on average 10^5 units of "free virus"[1] or "plasma virion" per ml blood[2] in AIDS patients. That should be enough virus to eliminate all remaining T-cells of these patients, 10^5 per ml, within the two days HIV needs to replicate[48]—unless, as Maddox suggests, the "new techniques for assaying the low levels of virus involved were also necessary"[3] (amplifying viral RNA with the polymerase chain reaction) possibly because no infectious HIV could be detected by conventional infectivity tests.

Indeed, Wei *et al.* acknowledge "substantial proportions of defec-

tive or otherwise non-infectious virus." "To determine whether the viral genomes represented in total viral nucleic acid correspond to infectious virus . . ." they had to resort to the same techniques that the "old HIV hands," as Wain-Hobson calls them,[43] had used to isolate HIV from rare infected lymphocytes of AIDS patients: "We cocultivated PBMCs . . . with normal donor lymphoblasts in order to establish primary virus isolates." Shaw together with some of the investigators of Wei *et al.* had shown in 1993 how to convert "plasma viral RNA" to infectious virus. They concluded that the "quantitative competitive PCR" is "as much as 60,000 times more sensitive"[49] than infectious virus.[16, 19] Divide 10^5 "plasma viral RNA" units by 60,000 and you have 1.6 infectious units per ml, a number that is consistent with numerous previous reports (see above). Ho and a different group of collaborators just published a paper in which they show that over 10,000 "plasma virions," detected by the "branched DNA signal-amplification assay" used in their *Nature* paper correspond to less than one (!) infectious virus.[50] Thus Wei *et al.* and Ho *et al.* both reported titers of 10^5 biochemical virus-units that really correspond to one or even less than one infectious virus. However, infectivity is the only clinically relevant criterion of a virus.

In other words, there is no evidence for infectious virus in Wei and Ho *et al.*'s patients. Wei and Ho *et al.* had apparently detected non-infectious virus that had been neutralized by "the immune system [that] reacts hyperactively to HIV infection"—just as Maddox suggests. Infectious virus was only obtained by activating latent HIV from a few infected cells out of millions of mostly uninfected cells from a given AIDS patient. Such virus activation is only achieved by growing cells in culture away from the hyperactive immune system of the host, just as the "old HIV hands" used to do it, when they tried to isolate HIV from AIDS patients.[45,46] Thus the paradox of too few viruses to cause immunodeficiency remains unresolved.

In view of the evidence that there are no more than 1.6 infectious HIVs per ml blood in Wei's and Ho's patients, one wonders whether the 10^5 viral RNAs per ml are real or are an artifact reflecting inherent difficulties in quantifying the input number of "plasma viral RNA" molecules after many rounds of amplification by the PCR. The problem with the quantification of input RNAs—after 30 to 50 rounds of ampli-

fication by the PCR[51]—is like calculating the number of the original settlers in America, from the current number of Americans and their current growth rates. But even if the 10^5 "plasma viral RNAs" per ml were real, it is hard to guess where they came from in view of "the scarcity of T-cells from which virus can be recovered . . ." acknowledged by Maddox.[3]

However, the apparent lack of infectivity of the "free virus" or "virions"[2] resolves the paradox of the coexistence of 10^5 T-cells with 10^5 plasma viral RNAs per ml blood in Ho *et al.*'s and Wei *et al.*'s AIDS patients.[1] Even HIV cannot kill T-cells that it can not infect. The fact that over 99% of T-cells in persons with AIDS are not infected by HIV,[14, 26, 27, 31, 32, 44] is definitive evidence that there is no infectious HIV in typical AIDS patients. Clearly, in AIDS patients with 1.6 infectious HIV units per ml something other than HIV must cause AIDS.

In earlier efforts to resolve the paradox, that there is too little HIV in AIDS patients to cause AIDS, both groups have observed huge discrepancies between virus titers and AIDS symptoms. In 1993, George Shaw and colleagues have described otherwise identical AIDS patients of which 5 contained 0 infectious HIV per ml, and 22 contained between 5 and 10^5.[16,19] In 1989, David Ho *et al.* have also described 40 AIDS patients with virus titers ranging from less than 1 to 10^5 infectious units per ml.[30] In 1993, Ho *et al.* even reported 12 AIDS patients, including 8 who had AIDS "risk factors," who were totally HIV-free: "Specific antibody assays, viral cultures, and polymerase chain reaction (PCR) techniques" for HIV were all negative. Their T-cell counts ranged from 3 to 308 per μl.[52]

There is only one consistent hypothesis to reconcile the bewildering ranges of HIV titers in Ho's and Shaw's patients with the role of the virus in AIDS—HIV is a passenger virus, rather than the cause of AIDS. Indeed, non-correlation between the titers of a virus and disease, and between the very presence of a virus and disease—is one of the hallmarks of a passenger virus. Both Ho *et al.* and Shaw *et al.* have failed to understand that rare correlations between a virus-at-high-titer and a disease are the hallmark of a passenger virus, and that consistent correlations between a virus-at-high-titer and a disease are the hallmark of causative virus.[8, 53, 54] Therefore they have, contrary to their claims,

established HIV as a passenger virus of AIDS patients.

(3) *Why HIV needs 10 years to cause AIDS.* Until HIV appeared on the scene, the latent period from infection to disease was a function of the generation time of a virus. A virus that replicates in 2 days and produces 100 viruses per generation would cause disease in about two weeks—provided there is no antiviral immunity. This is because 100 viruses infect 100 cells producing 100 x 100 or 10,000 viruses 2 days later. Within 14 days of such exponential growth 10^{14} cells—the equivalent of a human body—would be infected. Therefore the latent periods of pathogenic retroviruses, like Rous sarcoma virus, and non-retroviruses like flu, measles, mumps, herpes, hepatitis, mononucleosis, chicken pox are all 7 to 14 days.[23]. Since HIV replicates in 2 days, like all other retroviruses,[48] and since according to Ho an infected cell produces over 1000 viruses per 2 days,[32] HIV should cause AIDS,—if it could cause AIDS—just as fast as other viruses.

Yet, as Maddox points out, the failure of HIV to cause AIDS within weeks after infection presents another paradox for the HIV-AIDS hypothesis, "... the usually slow decline of CD4+ cells is not consistent with what one would expect from a specific cytotoxic viral mechanism." Indeed, both studies confirm the paradox. Since the AIDS patients contain 10^5 "free viruses/virions" and 10^5 T-cells per ml plasma, the plasma of these patients should be T-cell free within 2 days, the generation time of HIV. But Ho *et al.* report that the T-cells of AIDS patients are either steady or even increasing over 1 month, and Wei *et al.* report that the T-cells of their patients remain either steady or decline slowly over 5 to 8 months.[1,2]

Even if there are 50-times more T-cells in hidden reservoirs—as Ho *et al.* report—, they, too, should be infected within two weeks, because according to Wei *et al.*, the "plasma viral RNA" titer can rise two orders of magnitude within two weeks. In fact, the ability of HIV to increase from 10^3 "plasma viral RNA" units to 10^5 units per ml described by Wei *et al.* should only be a fraction of the real "dynamics of the infection of people by HIV,"[3] since it occurred despite the presence of two DNA chain terminators, AZT and ddI, used as anti-HIV drugs in addition to a new coded antiviral drug.

Therefore it remains paradoxical that—dated from the time of HIV

infection—AIDS occurs at entirely unpredictable times, currently estimated to average 10 years.[5] To determine whether the currently unpredictable time from HIV infection to AIDS can be reconciled with a viral mechanism at all, one needs to know whether HIV kills T-cells, how much *infectious* virus there is, and the *percentage of infected cells* at a given time. Since the new studies by Wei *et al.* and Ho *et al.* provide none of these data, all new calculations "on the dynamics of the infection of people by HIV ... in the process of understanding the disease called AIDS" are worthless.

However, the hypothesis that HIV is a passenger virus provides a consistent explanation for the unpredictable time intervals between HIV infection and AIDS. It is one hallmark of a passenger virus, that the time of infection is unrelated to, and independent of the time when a disease occurs—just as with HIV and AIDS. Another hallmark of a passenger virus is that its titer and even its presence are not correlated with disease—just as was shown above for HIV and AIDS.

The simplest interpretation of the slow decline of T-cells in Ho's and Wei's AIDS patients is a non-viral cause, e.g. long-term intoxication.[7] Take for example the slow decline of liver cells in long-term alcoholics or of lung cells in long-term smokers.

Maddox seems concerned that "reporting of the new event has been curiously selective." Perhaps even science reporters begin to wonder how much further the virus-AIDS hypothesis can be stretched to explain its most obvious failures and inconsistencies: Why is there no vaccine? Why does American/European AIDS stay in the classical risk groups, male homosexuals, intravenous drug users and transfusion recipients? Why do AZT-treated HIV-positives get AIDS?[55,56] Why do 918 HIV-positive male homosexuals who had "avoided experimental medications on offer" and chose to abstain or significantly reduce their use of recreational drugs ..." remain AIDS-free, long-term survivors?[57] Why did the T-cells of 29% of 1020 HIV-positive male homosexuals and former intravenous drug users from the placebo arm of a clinical AZT trial increase up to 22% over two years—despite the presence of HIV?[58] Why did the T-cells of 14 out of 31 HIV-positive hemophiliacs treated with highly purified factor VIII increase up to 25% over three years—despite the presence of HIV?[59] Why is there not a single study show-

ing that HIV-positive 20 to 50-year-old men or women who are not drug users or recipients of transfusions ever get AIDS?[60]

Why did neither Ho *et al.* nor Wei *et al.* identify the risk groups their patients came from or indicate whether they had Kaposi's sarcoma, dementia, or diarrhea or lymphoma? Can they exclude that recreational drugs used by AIDS risk groups, like nitrite inhalants, amphetamines, and cocaine are immunotoxic or carcinogenic?[61] Why is it that among 10 long-term (10 to 15 years) survivors of HIV recently described by Ho *et al.*[50] "none had received antiretroviral therapy . . ."? Can Wei *et al.* and Ho *et al.* exclude that the DNA chain terminators, AZT and ddI, that their patients received in addition to the new experimental drugs, do not play any role in the "slow decline of CD4+ cells"? Are they aware that the manufacturer of AZT says in the *Physician's Desk Reference* that "it was often difficult to distinguish adverse events possibly associated with zidovudine [AZT] administration from underlying signs of HIV diseases . . ."?[62] Are they aware that the DNA chain terminators were developed 30 years ago to kill growing human cells for chemotherapy, not as anti-HIV drugs?

It seems to us that the "new developments" of Wei *et al.* and Ho *et al.* are a Mayday of AIDS virologists—rather than a "virological mayhem."[43]

Acknowledgments

We thank Serge Lang (Yale University), Siggi Sachs (UC Berkeley) and Russel Schoch (UC Berkeley) for critical comments. Supported by the Council for Tobacco Research, USA, and private donations.

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Letter from John Maddox to Peter Duesberg

Nature
4 Little Essex St.
London, WC2R 3LF

2 March 1995

Peter H Duesberg
Department of Molecular and Cell Biology
University of California
Berkelety, CA 94720

Dear Peter,

First, the good news: we shall publish the essence of what you have to say. But there are obvious snags. Let me retail my original conversation with Harvey Bialy. What format? he asked. A letter, I said. That's too little, he said; what about 1,000 words. I said I was not prepared to negotiate the length of a letter not yet written. But what you have sent would take at least 3 pages of *Nature*.

Second, I resent the way in which you appear to have alerted the world's press to the existence of your piece. Why do that?

Third, and this may not be such good news, I plan to go through your piece with a fine-tooth comb with the intention of ridding it of repetitions and various misrepresentations.

Let me illustrate the last point by reference to your page 3 and the continuation of the main paragraph on page 4. You start with the phrase "HIV was proposed to follow an entirely unprecedented course of action," you document various misconceptions about the functioning of HIV and then you conclude with the phrase "this HIV-hypothesis." Frankly, that smacks of the old Goebbels technique, that of creating a straw man from a farrago of indefensible propositions and then knocking it down. I know of nobody who, in the past decade, has put forward your points (1) to (5) as a unified statement of the conventional position. (Even you have to assemble the position with 20 references.) On the contrary, the "HIV-hypothesis" is much simpler: "HIV causes AIDS,

in some manner not understood; most of those infected will develop the disease."

Nor is it a fair representation of Wei *et al.* and Ho*et al.* to say that they "claim" to resolve the three specific "paradoxes" you list. In truth, they do nothing of the kind. The only conceivable reference to the 10-year latency period, for example, is in Ho *et al.*, and consists of the simile of the tap and drain. To quote from Wei *et al.*, "The kinetics of virus and $CD4^+$ lymphocyte replication" imply "First, ... continuous rounds of *de novo* virus infection, replication and rapid cell turnover ... probably represent a primary driving force in HIV pathogenesis ... Second ... a striking capacity of the virus for biologically relevant change. Third ... that virus production *per se* is directly involved in $CD4^+$ cell destruction." Ho *et al.* go further, but only to this extent: " ... our findings strongly support the view that AIDS is primarily a consequence of continuous high-level replication of HIV-1, leading to virus and immune-mediated killing of CD4 lymphocytes."

My position as an editor is that straight misrepresentations such as these have no place in a journal like this. You complain at an earlier stage that I have improperly "personalized" this argument. How do you suppose that Wei *et al.* and Ho *et al.* would feel if we were to publish your travesty of what they have said?

My suggestion, therefore, is that you throw away the first four pages of your introduction, and devise a less inflammatory introduction in which you state that the two papers have not changed your view, and go on to give the reasons. Please let me know whether that is acceptable. I have some other less radical comments on the remainder of the text, but there's no point in sending them at this stage if you cannot agree to something along the lines I have suggested.

Yours sincerely,

John Maddox
Editor

cc: Harvey Bialy

Letter from Peter Duesberg to *Nature*

7 March 1995

Sir John Maddox
Nature, Macmillan Publishing
4 Little Essex St., London WC2R 3LF
England

Dear John,

After you have invited us with an editorial "to comment" on "the new view of HIV" (*Nature,* 19 January 1995), we are surprised to learn that you only want to "publish the essence of what [we] have to say."

We have followed your advice that "it should be no longer than it needs to be." Since neither of the two new *Nature* studies nor the two accompanying News and Views by you and Wain-Hobson have explained the old view of HIV, we had to explain the old view first for the reader of *Nature* to understand our comments on "the new view of HIV." We are not interested in a discussion between experts restricted just to titers of HIV. Therefore we cannot accept your suggestion to "throw away the first four pages" of our commentary.

Moreover, if our commentary comes out to be 3 pages in *Nature,* as you say, that would only be a fourth of the space you have already dedicated to the "new view of HIV"—10 pages for the two papers and 2 pages for the two editorials. A 3-page commentary on 12 pages in *Nature,* supplemented by an international press release, is hardly a convincing argument that "it is longer than it needs to be."

You write that you "resent the way in which [we] appear to have alerted the world press to the existence of [our] piece." However, we are afraid, if alerting the world's press is a reason for resentment, we should resent you. After all, you have alerted the world's press using the power of your office about the "embarrassment for Duesberg" and that you "eagerly awaited" our "comment." But you did not respond to our commentary from February 7 until March 2. As a result of your activities the world's press has called us, and some callers were given our commentary, weeks after you had received it, with the proviso that

it may not be published in its present form by *Nature*. Indeed, the exchange of opinions is protected by the free-speech amendment in this country.

Are you aware that both Wei *et al.* and Ho *et al.* gave their papers to John Coffin and David Baltimore prior to publication in *Nature* to write editorials for *Science* (267, 483, 1995) and *NEJM* (332, 259–260, 1995) respectively?

If you plan to meet your published commitment that "his [Duesberg] and his associates' views on the new developments should be made public" by first cutting, and then editing our commentary with a "fine-tooth comb with the intention of ridding it of ... various misrepresentations," we do not see a basis for an open debate with you.

In response to your letter we resubmit our manuscript with some revisions:

1) page 2, third paragraph: Replace "despite these 'new studies' " by "in light of these new studies."

2) page 2, fourth paragraph: Insert after "immunodeficiency syndrome (AIDS)," "if antibody to HIV is present."

3) page 3, item (2): According to Shaw, Ho and their collaborators, HIV activity is "rapidly and effectively limited" by this antiviral activity.[17,18]

4) page 4, second paragraph: Replace the sentence "The new studies claim to resolve ..." by "The new studies are claimed by two News and Views articles from Maddox (3) and Wain-Hobson (43) to resolve the paradoxa, (I) How HIV kills T-cells, (II) how HIV causes AIDS, and (III) why HIV needs 10 years to cause AIDS."

5) page 6, end; Insert the following paragraph after "... numerous previous reports (see above)": "Ho and a different group of collaborators just published a paper in which they show that over 10,000 "plasma virions," detected by the "branched DNA signal-amplification assay" used in the *Nature* paper correspond to less than one (!) infectious virus.[50] Thus Wei *et al.* and Ho *et al.* both reported titers of 10^5 biochemical virus-units that really correspond to one or even less than one infectious virus. However, infectivity is the only clinically relevant criterion of a virus."

6) page 11: Insert after "are immunotoxic or carcinogenic?" "Why

is it that among 10 long-term (10 to 15 years) survivors of HIV recently described by Ho *et al.*[50] 'none had received antiretroviral therapy ...'?"

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Sincerely, Peter Duesberg, Harvey Bialy (faxed)

On May 18, 1995, *Nature* published a Duesberg-Bialy letter flanked by two editorial comments:

1.

"AIDS pathology unknown"

Nature, 375: 167, 18 May 1995

HIV infection provokes hyperactivity of the immune system, but the causes of that are far from understood.

The clutch of contributions to *Scientific Correspondence* (page 193) this week deserves a reading, both for its inherent interest and for what it says about the present state of AIDS research. It will be recalled this journal published in January an account of research that showed that the infection of a person by the virus HIV ordinarily evokes not the previously suspected quiescence of the immune system, but a rapid turnover both of the vulnerable lymphocytes and of the virus itself. The then-general opinion that the first reaction of the human body to infection by HIV is a kind of indifference was dramatically and directly challenged. Nothing that has since come to light denies the challenge. But it has also become plain that too little is yet known of the dynamics of the immune system. That is a gap to fill.

The second arresting feature of this correspondence is the letter from Dr. Peter Duesberg and his colleague, Dr. Harvey Bialy, which has been published without change. Sadly, there seems no way in which the authors concerned can be persuaded that "free and fair scientific debate" is ordinarily understood to mean a progressive process, one in which each of two sides learns from what the other says. A restatement of earlier and well-known positions is not that at all. On this occasion, Duesberg and Bialy's citation of Loveday in their cause is especially inappropriate, given Loveday's name among the authors of a letter supporting Wei *et al.* and Ho *et al.* But no further solicitation of Duesberg's opinion is called for.

2.

"HIV an illusion"

Letter from Peter Duesberg and Harvey Bialy, Nature 375: 197, 18 May 1995

SIR—In an editorial in the 19 January issue of *Nature,* John Maddox invited "Duesberg and his associates" to comment on the "HIV-1 dynamics" papers published the previous week, indicating that these new results should prove an embarrassment to us. Although we do not think that a scientist should be embarrassed for pointing out inconsistencies and paradoxes in a hypothesis that have only been reportedly resolved 10 years later, we nonetheless prepared a fully referenced, approximately 2,000-word critique of the Ho *et al.*[2] and Wei *et al.*[3] papers that we believed met the criteria of "not being longer than it needs to be, and pertaining to the papers at hand" that Maddox set out in his widely read challenge.

Unfortunately, he did not share our view and agreed to publish only a radically shortened version, and only after he had personally "gone over it with a fine-tooth comb" to remove our perceived misrepresentations of the issues. We found these new conditions so totally at variance with the spirit of free and fair scientific debate that we could not agree to them.

Readers of *Nature* who are interested in these questions, and feel

that they do not need to be protected by Maddox from our ill-conceived logic, can find the complete text of our commentary in the monograph supplement to the most recent issue of *Genetica*[4]. Here we would point out only that the central claim of the Ho *et al.*[2] and Wei *et al.*[3] papers—that 10^5 HIV virions per ml plasma can be detected in AIDS patients with various nucleic-acid amplification assays is misleading. The senior author of the Wei *et al.* paper has previously claimed that the PCR method they used overestimates by at least 60,000 times the real titer of infectious HIV[5]: 100,000/60,000 is 1.7 infectious HIVs per ml, hardly the "virological mayhem" alluded to by Wain-Hobson.[6] Further, Ho and a different group of collaborators have just shown[7] that more than 10,000 "plasma virions," detected by the branched-DNA amplification assay used in their *Nature* paper, correspond to less than one (!) infectious virus per ml. And infectious units, after all, are the only clinically relevant criteria for a viral pathogen.

Finally, in view of Wain-Hobson's statement[6] that "the concordance of their [Wei and Ho's] data is remarkable," note that Loveday *et al.*[8] report the use of a PCR-based assay and find only 200 HIV "virion RNAs" per ml of serum of AIDS patients—1,000 times less than Ho and Wei. So much for the "remarkable concordance."

Peter Duesberg
Department of Molecular and Cellular Biology,
University of California, Berkeley, California 94720, USA

Harvey Bialy
Bio/Technology, New York, New York 10010, *USA*

Notes and References

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3·
Editorial Statement

This letter was followed by the editorial statement: "Peter Duesberg was offered space in *Scientific Correspondence* for 500 words of his own choice, but declined.—Editor, *Scientific Correspondence.*"

Letter from Peter Duesberg to John Maddox

Sir John Maddox
Editor, *Nature*
Porters South, Crinnan St.
London, England

10 July 1995

Dear John,

Following publication of the Duesberg-Bialy letter on May 18, *Nature* added: "Peter Duesberg was offered space in Scientific Correspondence for 500 words of his own choice but declined."

Since our letter used up that "space," *Nature*'s comment is erroneous and should be retracted.

Could you please confirm or un-confirm our conclusion. I have faxed to you twice before requesting an answer to this question (June 20 and June 22, 1995) but have not received a reply.

Sincerely,

Peter Duesberg

cc: Harvey Bialy

Letter from *Nature* to Peter Duesberg

Nature
Porters South, 4–6 Crinan Street
London, England

19 July 1995

Dr. P. Duesberg
Department of Molecular and Cell Biology
University of California
Berkeley, CA 94720

Dear Dr. Duesberg,

Thank you for your various faxes. We offered to publish a 500-word version of your response to Ho/Shaw in our issue in which we published other comments on those papers. You declined, and instead sent us a complaint that we would not publish your long manuscript. We published that complaint. As far as we are concerned, the matter rests.

Yours sincerely,

Dr. Maxine Clarke
Executive Editor, *Nature*

Chapter Thirteen

How Much Longer Can We Afford the AIDS Virus Monopoly?

To be published in the *Genetica* monograph, "AIDS: Virus- or Drug-Induced?" (1995)

Abstract

Until 1984 AIDS science was open. Initially, the new epidemic of pneumonias and Kaposi's sarcomas, since called AIDS, was considered a collection of non-infectious "lifestyle" diseases. But the Centers for Disease Control in Atlanta published that the pneumonias and Kaposi's sarcomas of male homosexuals, who were addicted to recreational drugs, were caused by a common infectious agent because patients had been "linked" by sexual contacts. On the basis of the CDC's sexual linkage study, the Secretary of Health and Human Services announced in 1984 the hypothesis that the retrovirus HIV is the cause of AIDS. The HIV-AIDS hypothesis currently holds a monopoly on all AIDS research and treatment. However, the HIV hypothesis is scientifically unproven. It has failed each of 15 testable predictions, as for example that AIDS would explode via sexual transmission of HIV into the general population. Moreover, HIV meets all classical criteria of a harmless passenger virus: unpredictable intervals between infection and any subsequent disease, and unpredictable presence and activity of the virus during a disease. Since HIV is rare in the US, it is a marker of real AIDS risks, frequent injection of intravenous drugs, thousands of drug-mediated sexual contacts, and transfusions. Indeed, AIDS does not meet even one of the classical criteria of an infectious disease, as for example equal distribution between the sexes, disease within days or weeks after infection, and exponential spread of the disease in an un-immunized population (Farr's law).

Far from being beneficial, the HIV-AIDS hypothesis has become a threat to public health in the last 10 years: It is the sole basis for (1) the daily treatment of at least 200,000 HIV-positives with cytotoxic DNA chain terminators originally designed to kill growing human cells for chemotherapy, like AZT, that are now prescribed as anti-HIV drugs; (2) the clean-needle programs that encourage intravenous drug use, and the misinformation that HIV-infection is the only health risk of recreational drug use. However, recreational drugs, such as heroin, cocaine, amphetamines and nitrite inhalants, have long been known to have immunotoxic, cytotoxic and/or carcinogenic effects; and (3) the anxiety and the many restrictions of human rights associated with a positive HIV-test.

Here it is proposed that American and European AIDS is caused by the long-term consumption of recreational and of anti-HIV drugs like AZT. The drug-AIDS hypothesis correctly predicts American/European AIDS: (1) AIDS is restricted to intravenous and oral users of recreational drugs and AZT; (2) AIDS is 87% male, because males consume this share of recreational drugs; (3) AIDS occurs in newborns, because mothers use recreational drugs during pregnancy; (4) AIDS is new in America, because AIDS is a consequence of the recreational drug use epidemic that started in the 1960s, and of AZT prescriptions that started in 1987; (5) AIDS occurs only in a small fraction of recreational drug users, because only the highest life-time dose of drugs causes irreversible AIDS-defining diseases – likewise only the heaviest smokers get emphysema or lung cancer; (6) AIDS manifests as specific diseases in specific risk groups, because each group has specific drug habits. For example, pulmonary Kaposi's sarcoma is exclusively diagnosed in male homosexuals who inhale carcinogenic alkyl nitrites; (7) AIDS does not occur in millions of HIV-positive non-drug users, and there are thousands of HIV-free AIDS cases, because AIDS is not caused by HIV; (8) AIDS is stabilized, even cured, if patients stop using recreational drugs or AZT – regardless of the presence of HIV. The drug hypothesis predicts that AIDS is an entirely preventable and in part curable disease. The solution to AIDS could be as close as a very testable and affordable alternative to the HIV hypothesis – the drug-AIDS hypothesis.

Table of Contents

Introduction

> The emperor marched in the procession under the beautiful canopy, and all who saw him in the street and out of the windows exclaimed: "Indeed, the emperor's new suit is incomparable! What a long train he has!" ... "But he has nothing on at all," said a little child at last.... "But he has nothing on at all," cried at last the whole people. That made a deep impression upon the emperor, for it seemed to him that they were right; but he thought to himself, "Now I must bear up to the end." And the chamberlains walked with still greater dignity, as if they carried the train which did not exist.
>
> Hans Christian Andersen, *The Emperor's New Suit*

I. Fabricating the case for infectious AIDS

Hardly anybody remembers that in its first three years, from 1981 to 1984, AIDS science was open. The new epidemic of pneumonias and Kaposi's sarcomas, that was called AIDS, was considered infectious by some, but many independent investigators and even scientists from the Centers for Disease Control (CDC) in Atlanta considered AIDS behavioral diseases. Recreational drugs such as nitrite and ethylchloride inhalants, cocaine, heroin, amphetamines, phenylcyclidine, LSD, and some others were proposed by epidemiologists and toxicologists as the

causes of AIDS because in the early 1980s nearly all AIDS patients were either male homosexuals who had used these drugs as aphrodisiacs and psychoactive agents, or were heterosexual intravenous drug users (Goedert *et al.,* 1982; Marmor *et al.,* 1982; Jaffe *et al.,* 1983; Mathur-Wagh *et al.,* 1984; Haverkos *et al.,* 1985; Newell *et al.,* 1985a; Newell *et al.,* 1985b; Lauritsen and Wilson, 1986; Haverkos and Dougherty, 1988). Drugs seemed to be the most plausible explanation for the restriction of AIDS to these risk groups, because drug consumption was their only specific common denominator—not shared with the general population. This original drug-AIDS hypothesis was called the "lifestyle hypothesis" (Oppenheimer, 1992).

But in April 1984 the secretary of Health and Human Services and AIDS researcher Robert Gallo from the National Institutes of Health (NIH) announced at an international press conference in Washington that a virus is the "probable cause of AIDS" (Altman, 1984). This "AIDS virus" (Altman, 1984) had been discovered a year earlier in France, in a male homosexual *without* AIDS (Barré-Sinoussi *et al.,* 1983). Within two years after that announcement an international committee of retrovirologists had named this virus, the Human Immunodeficiency Virus (HIV), to indicate that it was the accepted cause of AIDS (Coffin *et al.,* 1986).

The road for the ready acceptance of the "AIDS virus" by the scientific community had been paved by epidemiologists from the CDC. By tracing sexual contacts of male homosexual AIDS patients the CDC claimed that it could "link patients," "who had sexual exposure with other AIDS patients within five years of the onset of symptoms." (Auerbach *et al.,* 1984). On that basis the CDC proposed that AIDS "may be caused by an infectious agent that is transmissible from person to person in a manner analogous to hepatitis B virus infection: through sexual contacts; through parenteral exposure by intravenous drug abusers...; through blood products; and, perhaps, through mothers who are ... intravenous drug users to their infants." (Auerbach *et al.,* 1984).

However, compared to hepatitis B or any other authentic infectious disease, the CDC's case for infectious AIDS was bizarre with regard to the diversity of the diseases linked. The CDC had "linked by sexual contact" the Kaposi's sarcomas of some patients to the pneumonias of others and vice versa. The uncritical acceptance by the scientific com-

munity of a common infectious cause for such diametrically different diseases as cancer and pneumonia allowed the CDC to fabricate infectious AIDS. Since cancer, pneumonia, and by now about 30 different diseases were all said to have the same cause, they would soon all be called by the same new name, AIDS (Institute of Medicine, 1988; Centers for Disease Control and Prevention, 1992; National Institute of Allergy and Infectious Diseases, 1994).

A second bizarre element in the CDCs case for infectious AIDS was the assumption of an average "latency period" from infection to AIDS of 10 months (Auerbach *et al.,* 1984), now 10 years (see below). The assumption of a microbe that *only* causes disease after an average latency period of 10 months was without proven precedent. It was necessary, because prospective patients "were asymptomatic at the time of sexual exposure," and only developed AIDS up to 5 years after a critical contact (Auerbach *et al.,* 1984). Indeed, the carriers of the assumed infectious agent had to be exceedingly healthy during the latency period, because they had "large numbers" of "approximately 250 different male sexual partners each year." In view of such large numbers of sexual contacts and the long latency periods between infection and AIDS, tracing the one contact that would cause a disease had to be a masterpiece of epidemiological detective work. Therefore the CDC's case for sexual transmission of AIDS was about as compelling as the claim that one car had a flat tire at an intersection, because another car had blown a head gasket at the same intersection in the previous 5 years. Nevertheless, the sexual contact study was accepted by the scientific community as proof for infectious AIDS without further scrutiny.

The fact that "linked patients" "have been frequent users of inhaled amyl and butyl nitrite" and "of recreational drugs other than nitrite" was not considered an AIDS risk by the CDC in 1984 (Auerbach *et al.,* 1984), although CDC scientists had originally proposed recreational drugs as the cause of AIDS (Oppenheimer, 1992).

In 1984, the CDC also presented typical hemophilia diseases, like pneumonia and candidiasis, as AIDS from parenteral infection via blood transfusions—in support of its claim that AIDS was infectious (Curran *et al.,* 1984; Evatt *et al.,* 1984; Duesberg, 1995b). The paradox that none of the CDC's hemophiliacs with AIDS would have devel-

oped Kaposi's sarcoma from an infectious agent that presumably caused Kaposi's sarcoma in homosexuals was effectively hidden because all these entirely unrelated diseases had been named AIDS (Duesberg, 1992; Duesberg, 1994a; Duesberg, 1995b).

Indeed the CDC, originally established to fight infectious diseases, had grown desperate for a new infectious disease, because ever since polio had been eliminated by vaccines over 30 years ago, no new infectious diseases had plagued the Western World. In the words of a Red Cross official, "... the CDC increasingly needs a major epidemic to justify its existence" (Associated Press, 1994). Infectious AIDS, but not the drug-AIDS hypothesis, offered such an opportunity. A new infectious epidemic readily generates fear and funding. But research on the toxicity of recreational drugs is trivial, not likely to make headlines in the scientific literature. As a possible investment in its future existence, the CDC has recently launched a new journal, *Emerging Infectious Diseases,* to raise "public awareness of exotic bugs." (Kaiser, 1994). For example, in 1994 the CDC promoted the Hanta virus –after it presumably killed some Indians (Denetclaw and Denetclaw, 1994a; Denetclaw and Denetclaw, 1994b)– into a threat to the nation, and in 1995 the Ebola virus, that had apparently killed some Zairens, was promoted into a global "killer virus" (Associated Press, 1995a). The CDC claimed that 108 people may have been killed by the Ebola outbreak in Zaire in 1995 (Centers for Disease Control, 1995). But it failed to mention that 20% of the 55 million Zairens are Ebola virus antibody-positive, having survived the virus without apparent disease (Dietrich J., 1995).

As AIDS claimed ever more victims and gained ever more media attention, the CDC's message that AIDS was a new infectious disease was enthusiastically picked up by the stars of medical research, particularly the virologists. A new infectious disease is a magnet for virologists, microbiologists and immunologists because it holds the promise for a new microbial pathogen and new vaccines. Since the discovery of pathogenic microbes by Robert Koch and Louis Pasteur in the 1880s, the identification of a new microbial pathogen has been the key for many brilliant careers—like those of Walter Reed, John Enders, and Albert Sabin. Stated the *New York Times* on the search for an AIDS virus "... the greatest thrills for a scientist are in discovering a new

microbe, a new disease, cure and prevention ..." (Altman, 1992).

After decades of basic research in the War on Cancer, an army of highly sophisticated virologists had failed to prove that viruses can cause cancer in humans (Greenberg, 1986; Booth, 1988). Among these were the current leaders of AIDS research, Luc Montagnier from France, Robin Weiss from the U.K., David Baltimore, Jay Levy, Robert Gallo and even Peter Duesberg from the U.S. among others. Searching for other diseases for their viruses, most cancer virologists welcomed AIDS as a new frontier to apply their considerable skills (Duesberg, 1987; Booth, 1988; Duesberg and Schwartz, 1992). With an *AIDS virus,* the medical virologists could continue their familiar research, and their companies could extend their markets from the narrow confines of conventional virus tests and vaccines to the new multi-billion dollar markets of HIV-antibody tests, HIV vaccines, and anti-HIV drugs (Weiss and Jaffe, 1990; Duesberg, 1992).

The AIDS virus also proved to be the politically correct cause of AIDS. No AIDS risk group could be blamed for being infected by a God-given egalitarian virus. A virus could reach all of us. Nobody would be ostracized since "We are all in this together." Not so with drugs: The consumption of illicit psychoactive drugs implies individual and social responsibilities that nobody wanted to face.

Once accepted as the politically correct explanation of AIDS, the HIV hypothesis has become the central investment for a whole generation of AIDS scientists, AIDS companies, AIDS journalists, AIDS politicians and gay activists.

The perceived danger of an AIDS virus decimating the general public also provided the scientific and moral arguments for quick and unreflective action and for the complete dismissal of the competing drug-AIDS hypothesis. The fear of nature's presumably uncontrollable microbes created an unscientific war-mentality that has since dominated the field (Christie, 1994). Scientists, health care workers, and journalists would rather be safe and fast in protecting against HIV, than sorry and slow in reflecting about the clinical and political consequences of drug use (Lang, 1994). The confrontation with man-made drugs, after all, would have to take second place in urgency, as they would not reach the innocent public.

Claiming this priority, the virus-AIDS orthodoxy justifies intolerance, even censorship, of all those who question infectious AIDS (San Francisco Project Inform, 1992; Maddox, 1993b; Maddox, 1993a; Cohen, 1994a; Lang, 1994; see Chapter 12). Epidemiologists from the CDC warn that to "ignore this [HIV-AIDS] concept would result in an unconscionable tragedy." (Garza, Drotman and Jaffe, 1994). Virologists are quick to call those who question the virus-AIDS hypothesis "irresponsible and pernicious" (Booth, 1988; Baltimore and Feinberg, 1989). And the *New York Times* still calls all non-HIV science "cruelly irresponsible anti-science" (Lewis, 1994).

Therefore, the "AIDS virus" won unprecedented popularity within a short time after its announcement.

But eleven years later, in 1995, the virus-AIDS hypothesis has still failed to produce any public health benefits in the war on AIDS. No vaccine, no antiviral drug, no cure, not even an effective AIDS prevention have been developed. It cannot even be predicted whether and when an infected person will get ill. And it cannot predict which of the about 30 AIDS diseases it will be (Duesberg, 1992; Benditt and Jasny, 1993; Cohen, 1994a; Cohen, 1994b; Wade, 1995). Moreover, the very basis of the virus-AIDS hypothesis, the assumption that AIDS is infectious, has since become questionable on several grounds. For example:

(1) Would you have believed AIDS is infectious 11 years ago, if you had known that until now not even one of the doctors and health-care workers who have treated the over 400,000 American AIDS patients since 1984 (Centers for Disease Control and Prevention, 1994c) is confirmed to have contracted AIDS from a patient? Even if that would not have changed your mind, would you still believe in infectious AIDS if you had considered that the health care workers were neither protected by an anti-HIV vaccine nor by an antiviral drug (Duesberg, 1992)?

(2) Would you have believed that a sexually transmitted virus was causing AIDS if you had known that none of the wives of the 15,000 HIV-positive American hemophiliacs has contracted AIDS from their husbands in the last 10 years? Their risk of developing an AIDS-defining disease is the normal background of these diseases in the U.S. (Duesberg, 1992; Duesberg, 1995b).

(3) Would you have believed that AIDS was contagious if you had known that after a marriage of 10 years, neither the wife nor the 6-year old daughter of the late tennis star and AIDS patient Arthur Ashe have developed AIDS or even become HIV-positive (Ashe and Rampersad, 1993); or that the long-term lover of the movie star Rock Hudson has no AIDS symptoms, 10 years after Hudson died from AIDS in 1985? Would you believe that AIDS was sexually transmitted if you had known that, after a 13-year marriage and 2 children, the husband of the late AIDS patient Elizabeth Glaser is healthy and HIV-free (Champkin, 1994)?

(4) Would you have believed in an AIDS virus if you had known that nobody ever contracted Kaposi's sarcoma in the US from a blood donor with Kaposi's sarcoma (Haverkos, Drotman and Hanson, 1994)?

(5) Would you have believed AIDS is a sexually transmitted disease in 1984 if you had known that 11 years later there is still no AIDS in American heterosexuals, not even in prostitutes, unless they are drug addicts (Duesberg, 1992)?

(6) Would you have believed in a sexually transmitted AIDS virus if you had considered that such a virus would be incompatible with life? Because sex is the only known source of human life, a sexually transmitted, fatal virus would have exterminated itself together with its host (Duesberg, 1992).

Have we lost the war on AIDS because we have mistaken a harmless virus for its real cause?

II. The HIV-AIDS hypothesis proves to be unprovable

The HIV-AIDS hypothesis (Institute of Medicine, 1988; National Institute of Allergy and Infectious Diseases, 1994) postulates that:

1. HIV causes immunodeficiency by killing T-cells (lymphocytes);
2. immunodeficiency occurs on average only 10 years after this virus has been neutralized by antiviral immunity—a condition termed a "positive HIV test";
3. immunodeficiency is the basis for about 30 previously known dis-

eases, including pneumocystis pneumonia, tuberculosis, candidiasis, Kaposi's sarcoma, dementia, diarrhea, >10% weight loss, and many others (Table 1);

4. AIDS is a sexually transmitted disease, because HIV is a sexually transmitted virus.

Owing to the immense popularity of this hypothesis, over 100,000 scientific papers have been published on HIV since 1984. But not even one of these has been able to explain *how* HIV causes AIDS. Worse yet, not one paper exists that proves that HIV causes AIDS (Duesberg, 1992; Dickson, 1994; Fields, 1994; Schoch, 1994; Thomas Jr., Mullis and Johnson, 1994).

Circular Definition of AIDS

In view of this proof-deficit, the HIV-AIDS establishment cites the "perfect" correlation between HIV and AIDS as support for the hypothesis that HIV causes AIDS (Blattner, Gallo and Temin, 1988; Weiss and Jaffe, 1990; San Francisco Project Inform, 1992; Maddox, 1993b; Garza, Drotman and Jaffe, 1994; National Institute of Allergy and Infectious Diseases, 1994). However, this argument is inadequate as an element of proof for three reasons:

(1) According to the HIV-AIDS hypothesis, the 30 AIDS-defining diseases are diagnosed as AIDS only when antibody against HIV is present. In its absence these diseases are called by their old name and caused by their old causes. In other words, AIDS is defined entirely by its hypothetical cause, HIV. Therefore, the perfect correlation is not a natural coincidence but a perfect artifact of the definition of AIDS by its hypothetical cause, HIV. It is one of the purest examples of circular logic.

(2) The HIV antibody-test for the detection of HIV is indirect, because it does not assay for the virus. Moreover it is not reliable; up to 90% false-positives are obtained, depending on the subjects tested and on the tests used (Duesberg, 1993f; Papadopulos-Eleopulos, Turner and Papadimitriou, 1993).

(3) Even a perfect correlation is not sufficient to prove causation.

For example, perfect correlations between yellow teeth and lung cancer, or between hospitalization and death do not prove that one causes the other (Duesberg, 1989; Smith and Phillips, 1992; Duesberg, 1993d).

Predictions of the HIV Hypothesis

In the absence of direct proof, the merit of a scientific hypothesis is determined by the accuracy of its predictions. For example, there is no direct proof for the hypothesis that smoking causes lung cancer and emphysema, but the prediction that long-term smoking causes these diseases has validated this hypothesis. In the following we will analyze the predictions of the HIV-AIDS hypothesis (Duesberg, 1994a):

(1) *HIV-infected persons will get AIDS, and otherwise matched HIV-negatives will not.* In the face of the relentless propaganda for the HIV hypothesis, it comes as a big surprise to almost everybody that there is not even one study to show that American, heterosexual or homosexual men, who are HIV-positive but not drug users or hemophiliacs ever get AIDS. More precisely, there is no study to show that such men would get AIDS-defining diseases that exceed the long-established, low background of these diseases in otherwise matched, HIV-free counterparts (Duesberg, 1995a, see Chapter 10). There is not a single epidemiological study to support the most frightening slogan of the HIV orthodoxy; that HIV-positives develop AIDS-defining diseases because of HIV.

All studies that claim HIV causes AIDS have instead analyzed the AIDS risks of HIV-positive people who were recreational drug users, were treated with AZT or other anti-viral drugs, had received transfusions, suffered from congenital diseases, or were subject to exotic life styles as in Africa. The AIDS risks of such groups were then determined by comparisons, either with normal HIV-free people or with HIV-negative people from risk groups who were not matched for drug use or other AIDS risks (Duesberg, 1992; Duesberg, 1993a; Duesberg, 1993c; Duesberg, 1993d, see Chapter 8). In other words, there is no epidemiological evidence properly controlled for confounding factors that HIV is a "deadly virus" or "the virus that causes AIDS."

In view of the enormous experimental difficulties and costs in sorting out the possible role HIV plays in AIDS from the roles that recre-

ational drugs, AZT, transfusions, congenital diseases and exotic life styles play, it is surprising that the assumption that HIV causes AIDS has never been studied in people who are free of confounding AIDS risks. There can only be one plausible explanation for the absence of an epidemiological study that shows that HIV causes AIDS in people who are not in risk groups: HIV does not cause AIDS.

Indeed, there are 1 million HIV-positive Americans (National Institute of Allergy and Infectious Diseases, 1994) and 17 million HIV-positive humans (Merson, 1993; World Health Organization, 1995) who are healthy, probably because they are not subject to real AIDS risks other than the hypothetical AIDS risk HIV. Moreover, HIV-positives who stop practicing risk behavior or stop being subjected to AIDS risks even recover lost immunity—despite the presence of HIV (see below Section VIII). For example, HIV-positive hemophiliacs treated for 3 years with highly purified blood clotting factor regained lost immunity, while controls treated with unpurified blood products continued to lose immunity (Seremetis *et al.,* 1993; Duesberg, 1995b and Chapter 11).

Thus HIV is only ever deadly for people who are at risk for AIDS from toxic drugs or who depend on long-term blood transfusions to treat underlying deadly diseases (Duesberg, 1992, see Chapter 6).

(2) *American AIDS is new, because HIV is new in America.* However, in America HIV is a long-established retrovirus (Duesberg, 1992, see Chapter 6). Ever since the virus could be detected in 1984, an unchanging 1 million Americans are HIV-positive (Fig 1A) (Curran *et al.,* 1985; National Institute of Allergy and Infectious Diseases, 1994, Farber, 1995b). By contrast, a new microbe/virus spreads exponentially in a susceptible population (see V). Thus the non-spread of HIV establishes it as an old virus in America (Duesberg, 1992).

(3) *HIV is active and abundant in persons with AIDS, and inactive and rare in healthy virus carriers.* All microbes cause diseases by killing or alterating a larger number of target cells than the host can spare or regenerate during the course of an infection. Thus HIV would have to infect and kill at least 50% of all human T-cells to cause AIDS.

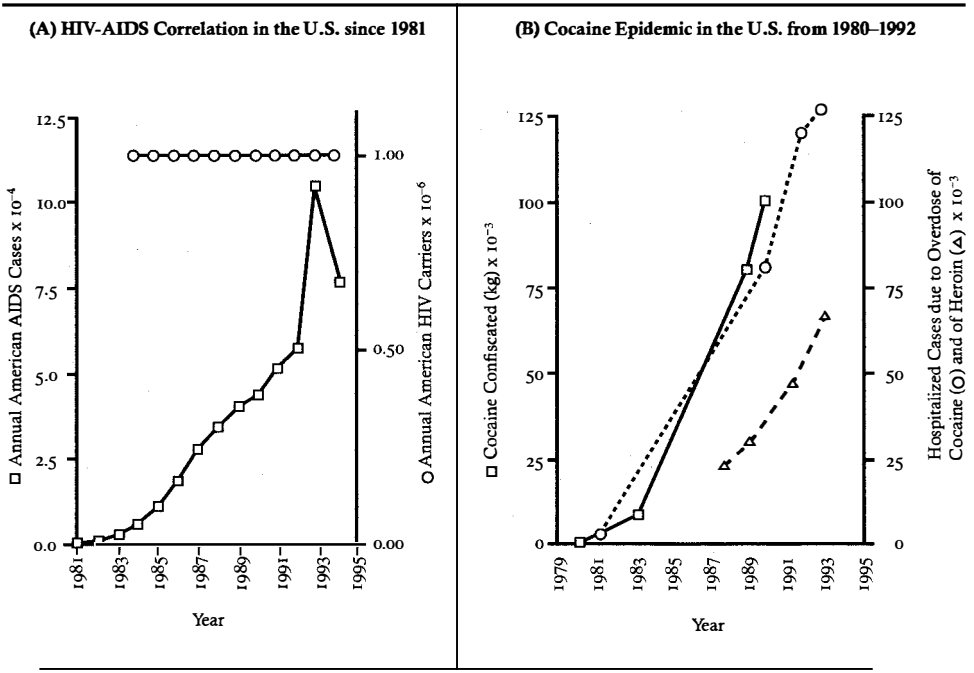

Figure 1

However, in AIDS patients HIV is found hibernating in only 0.1% of T-cells, and biochemically active in less than 0.01% of T-cells (Duesberg, 1992; Duesberg, 1993e; Piatak *et al.,* 1993). Indeed, there are healthy HIV-positive people with 30- to 40-times more infected T-cells than in AIDS patients (Simmonds *et al.,* 1990; Bagasra *et al.,* 1992; Duesberg, 1992). The fact that the vast majority of susceptible T-cells remain uninfected, even in people dying from AIDS, is the definitive evidence that there is no active HIV in HIV-antibody-positive persons. HIV is neutralized by antiviral immunity, even in AIDS patients. If there were un-neutralized HIV, all T-cells would be infected.

The fundamental problem for the HIV-hypothesis is not just how HIV works, but how it causes fatal diseases when it does not work at all. Since there is no rational explanation for how HIV could cause AIDS, HIV researchers now postulate a multiplicity of indirect mechanisms of pathogenesis (Blattner, Gallo and Temin, 1988; Booth, 1988;

Gallo, 1991; Maddox, 1991; Weiss *et al.,* 1992; Maddox, 1993b; Maddox, 1995; Wade, 1995; Wain-Hobson, 1995).

(4) *HIV causes AIDS by killing T-cells.* However, viruses that integrate their genomes with that of the host, like HIV, cannot kill the host cell. Since the genes of such viruses are part of the host's genes, integrated viruses can only replicate as long as the host survives integration and remains able to express integrated viral genes. All integrated viruses survive from passive, and some retroviruses also from active replication with the host. This strategy only works if the host survives integration. If the virus were to kill the cell as it is integrated, integration would be a useless exercise and it would be undetectable. Indeed, HIV is mass-produced for the "HIV test" in *immortal* T-cell lines in cell culture at titers of 10^6 infectious units per ml (Rubinstein, 1990; Karpas *et al.,* 1992). Luc Montagnier, the discoverer of HIV, and many other researchers have confirmed that HIV does not kill T-cells (Lemaitre *et al.,* 1990; Duesberg, 1992).

(5) *Since the generation time of HIV is two days, HIV will cause AIDS two weeks after infection.* The HIV-hypothesis predicts AIDS within 2 weeks after infection, because HIV, like all other retroviruses, replicates within two days. During that time one infected cell produces at least 100 new viruses (Weiss *et al.,* 1985). In the absence of antiviral immunity, these 100 viruses would in turn infect 100 cells producing 100 x 100 viruses, or 10^4 infected cells within 4 days after infection. Within 14 days of such exponential growth, 10^{14} cells –the equivalent of a human body– would be infected. This is the typical latent period of proven pathogenic retroviruses, like Rous sarcoma virus, and of pathogenic human viruses like flu, measels, mumps, chicken pox, and herpes, which all have generation times like HIV (Fenner *et al.,* 1974; Mims and White, 1984).

However, if dated from the time of HIV infection, AIDS occurs at totally unpredictable times. The latent period between infection and AIDS was estimated to average 10 months in 1984 (Auerbach *et al.,* 1984), 10 years in 1988 (Institute of Medicine, 1988) and over 20 years in HIV-positive hemophiliacs in 1994 (Phillips *et al.,* 1994). A Berkeley mathematician recently has determined the most accurate formula for

the latent period of HIV, by subtracting 1984, the year when HIV was proposed to cause AIDS, from the current calendar year. But blaming AIDS on a HIV infection that occured 10 years earlier is the logical equivalent of blaming today's broken leg on stumbling over a crack in the sidewalk 10 years ago.

(6) *Viral AIDS will spread exponentially ("explode").* The AIDS orthodoxy has predicted that according to Farr's law (Bregman and Langmuir, 1990), AIDS would spread exponentially ("explode") into the general, unimmunized population (Duesberg, 1992)—just like all other new infectious diseases.

However, AIDS in America and Europe remained confined to the original risk groups, i.e. male homosexuals practicing risk behaviour and intravenous drug users (National Commission on AIDS, 1991; Centers for Disease Control and Prevention, 1994b). Instead of growing exponentially, AIDS in America (and Europe) has increased slowly, over 15 years, far from reaching saturation of the susceptible population of over 100 million sexually active adults (Fig. 1A). AIDS behaved just like an occupational disease.

(7) *The spread of AIDS will follow the dissemination of HIV.* However, there is no correlation between the spreads of AIDS and HIV in America. In the last 10 years, AIDS increased in America from a few hundred to about 100,000 cases annually (Fig. 1A) (Centers for Disease Control and Prevention, 1994c). (The burst of AIDS cases in 1993 is largely an artifact of the most recent redefinition of AIDS, which nearly doubled the AIDS cases in one year (Centers for Disease Control and Prevention, 1994c).)

However, during those same 10 years HIV did not spread at all (Fig. 1A). Ever since HIV became detectable in 1985, an unchanging one million Americans have been HIV-positive up to 1994 (Fig. 1A) (Duesberg, 1992; Duesberg, 1994a; National Institute of Allergy and Infectious Diseases, 1994). To hide this discrepancy, a latency period of 10 years has been postulated between HIV and AIDS.

(8) *Like all other sexually transmitted diseases, AIDS in America will equilibrate between the sexes.* However, since 1981, AIDS has remained in the

original risk groups in America, i.e. male homosexuals, intravenous drug users of which over 75% are males (Duesberg, 1992), and hemophiliacs which are nearly all males. Since 1981, 347,767 out of 401,749, or 87% of all American AIDS cases, have been males (Centers for Disease Control and Prevention, 1994c).

(9) *HIV is a sexually transmitted virus.* However, HIV could never survive in evolution from sexual transmission. Based on studies of discordant couples, e.g. hemophiliacs with HIV and spouses without, conducted by the CDC and others, it takes on average 1000 unprotected sexual contacts to transmit HIV (Hearst and Hulley, 1988; Peterman *et al.,* 1988; Rosenberg and Weiner, 1988; Lawrence *et al.,* 1990; Blattner, 1991). According to Rosenberg and Weiner, "HIV infection in non-drug using prostitutes tends to be low or absent, implying that sexual activity alone does not place them at high risk." The efficiency of transmission in homosexual contacts is also estimated at 1 in 1000 contacts (Jacquez *et al.,* 1994).

Since about 10 to 30 sexual contacts are required to generate a child, but 30 contacts are required to transmit HIV, HIV could never survive natural selection on the basis of sexual transmission, because the host would outgrow the parasite. Conventional venereal microbes, like syphilis and gonorrhea, survive because they are transmitted by about two sexual contacts (Freeman, 1979). HIV also could not survive from transmission to newborns if it were fatally pathogenic to babies, as is claimed by the proponents of the HIV hypothesis (Blattner, Gallo and Temin, 1988; Institute of Medicine, 1988).

The extremely low efficiency of sexual transmission of HIV also predicts that the safe-sex-campaigns conducted by the HIV orthodoxy will be of very limited value. Only those would benefit who either have on average 1,000 sexual contacts with HIV positives or those who have on average 250,000 contacts with average Americans, of which only 1 million in 250 million is HIV positive (Fig. 1A) (Duesberg, 1992; National Institute of Allergy and Infectious Diseases, 1994).

(10) *AIDS will be restricted by controlling sexual transmission of HIV via "safe sex," and parenteral transmission of HIV via "clean needles."* But AIDS con-

tinues to increase steadily despite the "safe sex" and "clean needle" programs (Centers for Disease Control and Prevention, 1994c) (see Fig. 1A).

(11) *Health-care workers will contract AIDS from their patients, scientists from propagating virus, and prostitutes from their clients.* Not a single confirmed case exists in the scientific literature of a health-care worker who contracted AIDS (Duesberg, 1992; Duesberg, 1994a) from one of the over 400,000 American AIDS patients (Centers for Disease Control and Prevention, 1994c). None of the tens of thousands of HIV researchers have developed AIDS from propagating HIV. And no prostitutes picked up AIDS from their clients—despite the absence of antiviral vaccines or effective anti-HIV drugs (Duesberg, 1992; Duesberg, 1994a).

A few unpublished cases have been claimed, but each of these seemed to have been treated with the cytotoxic drug AZT that is sufficient to cause immunodeficiency (see below) (Cohen, 1994a).

(12) *Chimpanzees inoculated with HIV will develop AIDS, and the 15,000 American hemophiliacs who were infected by transfusions before 1984 will die from AIDS.* Not one of the 150 chimpanzees inoculated with HIV since 1983 has developed AIDS (Duesberg, 1992). Contrary to prediction, the median life of American hemophiliacs has increased 2.5-fold from 11 to 27 years between 1972 and 1987 (Institute of Medicine, 1988; Stehr-Green *et al.,* 1989), although 75% (15,000) were infected with HIV by transfusions received before 1984 (Duesberg, 1992). However, in 1987 the median life of HIV-positive hemophiliacs started to decrease again (Chorba *et al.,* 1994) because since then they have been treated with the cytotoxic AZT (Duesberg, 1995b, See Chapter 11) (see below).

(13) *Natural or vaccine-induced anti-HIV immunity will cure AIDS or protect against future AIDS.* Natural antiviral immunity, a positive HIV-test, is observed in many AIDS patients, but does not protect against AIDS. Paradoxically, anti-HIV immunity is by HIV-AIDS definition the only criterion to predict who gets AIDS. With all other viruses and microbes –there is no exception– immunity is the only criterion to predict who does not get a disease. It is for this reason that antiviral/micro-

bial immunity is artificially induced by vaccination. It is also for this reason that the HIV-AIDS establishment has called for an HIV vaccine since 1984.

(14) *All AIDS diseases are consequences of HIV-mediated T-cell deficiency.* Indeed, up to 1992 about 61% of all American AIDS diseases, the microbial diseases such as *Pneumocystis carinii,* candida, tuberculosis, etc. were consequences of Acquired ImmunoDeficiency (Table 1) (Centers for Disease Control, 1993).

However, 39% were neither caused by, nor consistently associated with, immunodeficiency. These include Kaposi's sarcoma, lymphoma, >10% weight loss, and dementia (Table 1). Accordingly, Kaposi's sarcoma and dementia have been diagnosed in male homosexuals whose immune systems were normal (Murray *et al.,* 1988; Spornraft *et al.,* 1988; Gill *et al.,* 1989; Friedman-Kien *et al.,* 1990; Duesberg, 1992; Kaldor *et al.,* 1993; Bacellar *et al.,* 1994).

In 1993, the CDC introduced, once more, a new AIDS definition (Centers for Disease Control and Prevention, 1992). This has shifted the balance of immunodeficiency to non-immunodeficiency AIDS diseases significantly in favour of immunodeficiency diseases, i.e. from 61% to 80% (Table 1) (Centers for Disease Control and Prevention, 1994a). The critical innovation of this new definition was that a healthy person with less than 200 T-cells, but with no clinical disease, would now be registered as an AIDS patient. The new AIDS definition nearly doubled the new AIDS cases, thus adding new life to the sagging curves of the American AIDS statistics (Fig. 1A). However, if one substracts from the 1993 statistics the new AIDS cases with less than 200 T-cells, the ratio of the remaining real immunodeficiency diseases to the non-immunodeficiency diseases is almost the same as in 1992.

Imagine the rationalizations an unprejudiced virologist, who is aware of the heterogeneity of AIDS-defining diseases, must make to accommodate an AIDS virus. Ever since Koch and Pasteur, microbiologists and virologists were taught that a specific microbe or virus would cause a specific disease—e.g. polio, flu, measels, chicken pox, hepatitis, etc.—just like a particular musical instrument would make specific sounds.

To accommodate the AIDS virus, the concept of a specific microbe

Table 1
AIDS-defining diseases
in the U.S. in 1992 and 1993[1]

Immuno-deficiencies	1992 (in %)	1993 (in %)	Non-immuno-deficiencies	1992 (in %)	1993 (in %)
< 200 T-cells	—	79	wasting disease	20	10
pneumonia	42	22	Kaposi's sarcoma	9	5
candidiasis	17	9	dementia	6	3
mycobacterial (including tuberculosis)	12	11	lymphoma	4	2
cytomegalovirus	8	4			
toxoplasmosis	5	2			
herpesvirus	5	3			
	Total = 61[2]	Total = 80[2]		Total = 39	Total = 20

1. The data are from the Centers for Disease Control (Centers for Disease Control, 1993; Centers for Disease Control and Prevention, 1994a).
2. Over 61% and 80% due to overlaps.

causing a specific disease had to be abandoned for the following bewildering scenario: By picking up the AIDS virus from a diarrhea patient, a person would get Kaposi's sarcoma. The Kaposi patient would then be able to cause dementia or pneumonia in others by passing on the diarrhea virus, just as the CDC's sexual contact study had claimed in 1984 (Auerbach *et al.,* 1984). As of 1993, any one of these patients could have also caused a clinically undetectable depletion of T-cells in others, again by passing on their diarrhea, dementia, Kaposi's sarcoma and pneumonia virus.

Moreover, the unprejudiced virologist would have to reconcile this bewildering pathogenic potential of HIV with the fact that HIV is one of the most primitive viruses in terms of genetic information that exist, carrying only 9,000 nucleotides. This is the viral equivalent of a musical instrument that is said to sound like an orchestra, although it only has the repertoire of a bell.

(15) *If HIV is the cause of AIDS, the percent incidence of AIDS diseases will be the same in all risk groups.* However, the percent incidence of AIDS-defining diseases is very different in different risk groups. For example, Kaposi's sarcoma in America and Europe is almost exclusively observed in male homosexuals (Beral *et al.,* 1990). Intravenous drug users have a proclivity for tuberculosis, weight loss, and pneumonia (Duesberg, 1992) and a very high mortality dying at 30 years (Lockemann *et al.,* 1995). Pneumonia and candidiasis are virtually the only AIDS diseases ever diagnosed in hemophiliacs (Duesberg, 1992; Duesberg, 1995b). And bacterial infections other than tuberculosis are almost exclusively diagnosed in babies with AIDS (Centers for Disease Control, 1987; Centers for Disease Control and Prevention, 1992; Duesberg, 1992, see Chapter 6). Thus the percent incidence of an AIDS diseases is very different in different AIDS risk groups.

In view of this, some AIDS researchers cite co-factors of HIV, such as recreational drugs and immunosuppressive transfusions, as explanations for risk group-specific diseases (Evans, 1989; Duesberg, 1992; Ludlam, 1992; Root-Bernstein, 1995a). However, they fail to provide evidence that such cofactors depend on the cofactor HIV to be pathogenic.

The CDC and other mainstream AIDS researchers insist that recreational drugs and transfusions solely enhance the risk to get infected by HIV, rather than playing causative roles in AIDS (Cohen, 1994a). It is for this reason that the CDC refers to drug- or transfusion-risk groups as "exposure categories" (Centers for Disease Control and Prevention, 1994a). In fact, the CDC obscures the existence of risk-group-specific AIDS diseases by reporting only the percent incidence of AIDS diseases in all risk groups combined (Centers for Disease Control and Prevention, 1994a).

It is evident that the HIV-AIDS hypothesis is unable to make even one verifiable prediction—the hallmark of a failed hypothesis.

Even if a hypothesis fails to make valid predictions in terms of established scientific criteria, it could by chance lead to a valid prevention or treatment. But the HIV-AIDS hypothesis has not lead to any public health benefit. Instead it has harmed not only AIDS patients but also healthy persons who are at risk for AIDS or just antibody-positive (see VI).

III. HIV—a harmless passenger virus

Confronted with the evidence that the HIV-AIDS hypothesis has failed to make valid predictions and failed to lead to public health benefits, many agree that HIV may not cause AIDS. But then, they wonder: What does HIV do?

Indeed, all viruses are generally assumed to be pathogenic by an unsuspecting public, because a few of them actually are. Likewise, a whole nation is often stereotyped by the characteristics of a minority. For example the French are considered great lovers and the Italians great singers, because a few of them are great lovers and singers. The same is true for viruses.

In reality, most viruses cause no disease at all. Viruses are not here to kill their hosts, not even to cause disease. Instead, viruses are here for exactly the same reasons we are, to continue their species. This goal can only be achieved by keeping the host species alive, and it is achieved best if every host survives the infection. That is the reason that most viruses never cause a disease in their host. Therefore they are called *passenger viruses*. Passenger viruses are those that take a ride on the host, but demand no more from the host than a passenger demands from an airplane (see Chapter 9).

Since HIV is not the cause of AIDS, the simplest and most plausible HIV hypothesis postulates that HIV is just a passenger virus (Duesberg, 1994a). A passenger virus is defined as follows:

(1) The time of infection is irrelevant to the onset of any disease.

(2) The passenger virus can be either active or passive, either rare or abundant during any disease.

(3) The passenger virus can be entirely absent during any disease.

(4) If the passenger virus is de-repressed by a failing immune system, as for example during a disease, the passenger virus may or may not contribute to the disease. For example HHV-6 (Cone *et al.*, 1994) or cytomegalovirus may contribute their specific pathogenic properties to an immunodeficient patient.

HIV meets all these criteria with regard to its relation to AIDS:

(1) HIV infects at totally unpredictable times prior to or even after the onset of AIDS (see VIII below) or not at all (Duesberg, 1992; Phair *et al.*, 1992; Duesberg, 1993f).

(2) HIV is typically passive and rare during AIDS—hence the notorious difficulties of leading AIDS researchers in isolating HIV from AIDS patients (Duesberg, 1992, see Chapter 6).

(3) There are thousands of HIV-free AIDS cases, e.g. HIV-free homosexuals with Kaposi's sarcoma and HIV-free intravenous drug users with tuberculosis (Duesberg, 1993f, see Chapter 7).

(4) There is no report in the literature that AIDS patients are clinically distinguishable from each other because HIV is active or passive or not present at all (Duesberg, 1993b; Duesberg, 1994a). Thus HIV is a harmless passenger virus, even when it is active in some rare immunodeficient persons (Duesberg, 1993e).

If this is true, there should be many more HIV carriers than AIDS patients. Indeed, there are 1 million healthy HIV-positive Americans (Duesberg, 1992; Duesberg, 1994a) and there are 17 million healthy HIV-positive humans (Merson, 1993; National Institute of Allergy and Infectious Diseases, 1994; World Health Organization, 1995).

Nevertheless, there is some tenuous evidence that HIV can function as an autonomous pathogen, causing a mild flu-like or mononucleosis-like condition, prior to antiviral immunity (Albert *et al.*, 1987; Duesberg, 1987; Kessler *et al.*, 1987; Gaines *et al.*, 1988; Marcus and the CDC Cooperative Needlestick Surveillance Group, 1988; Tindall *et al.*, 1988; Pedersen *et al.*, 1990; Duesberg, 1992; Niu, Stein and Schnittmann, 1993, see Chapters 1, 6). However, in millions of HIV-positives HIV infection has gone unnoticed, because they do not experience a characteristic HIV-disease prior to antiviral immunity—like measles, mumps or flu which all occur prior to immunity against these viral infections.

The rare cases in which HIV infections, prior to antiviral immunity, have been linked with mononucleosis or flu-like symptoms are restricted to prospective studies of male homosexuals at risk for AIDS. These cases could either be coincidences with a common cold or with intoxications from recreational drug use (see below) (Gaines *et al.*, 1988; Tindall *et al.*, 1988; Pedersen *et al.*, 1990) rather than evidence for HIV disease.

IV. HIV—a marker for AIDS risks

Even those who understand all virological arguments against HIV as the cause of AIDS, and for HIV as a passenger virus, have misgivings about dismissing the HIV-AIDS hypothesis, because HIV is more common in AIDS patients than in the healthy population. This sounds like an ominous connection, but only if it is taken out of its trivial microbiological context.

This trivial context is that AIDS risk behavior is synonymous with *collecting microbes.* The common denominator of all AIDS risk groups in America and Europe is that they collect microbes either from unsterile drugs injected with unsterile equipment, or from the thousands of drug-mediated sexual contacts, that are required to transmit HIV sexually, or from transfusions received for the treatment of illnesses (Jaffe *et al.,* 1983; Auerbach *et al.,* 1984; Lauritsen and Wilson, 1986; Haverkos and Dougherty, 1988; Rappoport, 1988; Adams, 1989; Callen, 1990; Lifson *et al.,* 1990; Archibald *et al.,* 1992; Duesberg, 1992; Jones, 1994; Mullis, 1995). This is the reason that numerous uncommon microbes are common not only in AIDS patients but also in healthy persons from AIDS risk groups. For example, the bacteria that cause syphilis, gonorrhea, and tuberculosis, the hepatitis virus, rare strains of herpes virus, putative leukemia virus, genital papilloma virus, and even HIV are all common in AIDS risk groups and AIDS patients but uncommon in the general population (Duesberg, 1992, see Chapter 6). Thus HIV is just one of many microbial markers of AIDS risk behavior. Since AIDS is defined as one of 30 diseases in the presence of HIV, rather than any other microbial or viral marker, the correlation between HIV and AIDS is in theory 100%.

V. The myth of infectious AIDS—unconfirmed

If a hypothesis is unproductive, and unable to make verifiable predictions, the scientific method calls for alternative hypotheses. To find the correct AIDS hypothesis, we need to decide first whether to look for other viruses and microbes or for drugs as causes of AIDS. In other words, we need to know whether AIDS is infectious or not.

There are five classic criteria to define an infectious disease.

In individuals:

(1) The causative microbe/virus is abundant and very active in target tissues during the course of the disease.

(2) The disease follows within days or weeks after infection, because microbes/viruses multiply exponentially with generation times of 0.5 to 48 hrs, unless they are stopped by immunity (see above).

In populations:

(3) The disease spreads, according to Farr's law, exponentially in an un-immunized population within weeks or months, and subsequently fades away as antiviral immunity builds up (Bregman and Langmuir, 1990). The bell shaped curve of a seasonal flu epidemic is the model.

(4) Infectious diseases are equally distributed between the sexes.

(5) Infectious diseases are most commonly observed in those under 20 and over 60 years of age. This is because after birth the immune system builds up a wide repertoire of antimicrobial resistances that is nearly complete at 20, and over 60 the system begins to decline.

But American/European AIDS does not fit one of these criteria:

(1) There is no abundant microbe common to all American AIDS cases. If HIV is present, it is typically rare and hibernating.

(2) If dated from the time of HIV infection, AIDS occurs at entirely unpredictable times ranging from less than 1 year to over 10 years or never. It has now been 10 years since 1 million Americans were found to be HIV-infected. Most of these and 17 million healthy, HIV-positive non-Americans are still waiting for HIV to cause AIDS.

(3) American AIDS has slowly increased over 10 years. Although AIDS affects annually only a small fraction of susceptible persons—less than 100,000 out of a susceptible pool of 250 million Americans—it has has now almost plateaued for 4 years [after adjusting for new additions of diseases to the AIDS definition] (Centers for Disease Control and Prevention, 1994b). Thus AIDS in America has increased steadily over years, just like an occupational disease, as for example lung cancer from smoking. There is no evidence for immunity and no evidence for a bell shaped AIDS curve.

(4) American AIDS is 87% male (Centers for Disease Control and Prevention, 1994c), which is epidemiologically as far from equality between the sexes as the sun is from the earth. A similar sexual bias has been observed early in the epidemic of smoking-related diseases in the 1960s, before women picked up smoking at the same rate as men.

(5) 98% of all American AIDS cases are over 20 and under 60 (Centers for Disease Control and Prevention, 1994c). Only 1% each are under 20 and over 60! Such an age bias is typical of occupational diseases, like bullet wounds for soldiers.

Thus AIDS in America and Europe (Duesberg, 1992) does not meet even one of the criteria of infectious disease.

Indeed, even proponents of the HIV-AIDS hypothesis, such as Jaap Goudsmit from the University of Amsterdam, grant that "AIDS does not have the characteristics of an ordinary infectious disease. This view is incontrovertible" (Goudsmit, 1992). The AIDS epidemiologists Eggers and Weyer from the University of Cologne state that "the spread of AIDS does not behave like the spread of a disease that is caused by a single sexually transmitted agent" (Eggers and Weyer, 1991). To reconcile AIDS with infectious disease they "simulated a cofactor [that] cannot be identified with any known infectious agent." The epidemiologists Anderson and May from the University of London had to invent "assortative scenarios" for different AIDS risk groups to match AIDS with infectious disease (Anderson and May, 1992).

Until we have scientific evidence, infectious AIDS is just a myth—and, in view of the facts, a very implausible myth indeed.

VI. The HIV-AIDS hypothesis is costly, unproductive and harmful

For 11 years now the world has fought the war on AIDS united by the HIV-AIDS hypothesis. But despite its enormous popularity, the virus-AIDS hypothesis has been a complete failure in terms of public health benefits: no vaccine has been developed that prevents AIDS, no drug that cures AIDS, no policy that stops the spread of AIDS (Benditt and Jasny, 1993; Fields, 1994; Swinbanks, 1994; Wade, 1995).

Whatever the reasons are for the complete failure of the HIV-AIDS hypothesis to produce public health benefits, one thing is clear: it was not for lack of trying. The passionate complaint of Shilts' 1987 book, *And the Band Played On,* that indifference was the only obstacle against a solution of AIDS (Shilts, 1987) has long become profoundly obsolete. Since 1984, an unprecedented $35 billion has been paid by the US taxpayer alone in support of HIV-AIDS research and treatment—more than for all other viral and microbial diseases combined (AIDS Weekly, 1995; Gutknecht, 1995; Henry, 1995; Stone and Cohen, 1995). With all this spending, more research has been done on HIV than on any other virus in history, but absolutely no progress has been made against AIDS. Time, at least, has voted against the HIV-hypothesis. Traditionally, such complete failures are the consequences of a flawed hypothesis.

But the HIV-AIDS establishment does not only cost dearly and fails to produce positive results, it also causes irreparable (1) clinical, (2) educational, and (3) psychological damage:

(1) *Clinical damage.* Worldwide about 200,000 HIV antibody-positive persons are prescribed, every six hours, the highly toxic DNA chain terminator AZT or equivalents like ddI, ddC, and d4T as anti-HIV drugs (Duesberg, 1992; Thomas, 1995). Most of these, ie. 200,000 minus the 50,000 to 80,000 annual AIDS patients in America and Europe, are healthy HIV-positives given AZT to prevent AIDS. Recently these include even unborn American and French children and their HIV-positive mothers, although the risk of such children to pick up HIV from their mothers is only about 25% (The Lancet, 1994; Farber, 1995a).

AZT was designed 30 years ago to kill growing human cells for cancer chemotherapy (Horwitz, Chua and Noel, 1964; Duesberg, 1992). In view of its inevitable toxicity, AZT was approved as an anti-HIV drug only tentatively in 1987 (Kolata, 1987). See the warnings of a non-medical manufacturer, Sigma, on the label of an AZT bottle (Fig. 2). The label points out, with skull and cross bones, AZTs toxicity to the bone marrow, the source of T-cells.

Indeed, AZT therapy of HIV appears harmful and irrational. Since HIV is postulated to cause AIDS by killing T-cells (see above), it is irra-

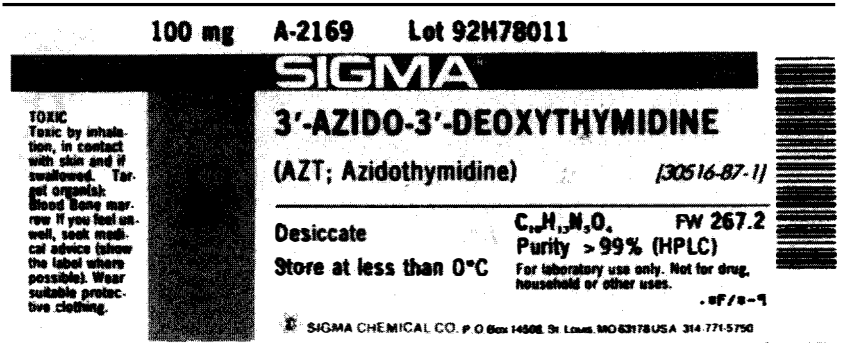

Figure 2 The label on an AZT bottle from the *Sigma Co.* The AZT advisory on the label reads: "TOXIC. Toxic by inhalation, in contact with skin and if swallowed. Target organ(s): Blood bone marrow. If you feel unwell, seek medical advice (show the label where possible). Wear suitable protective clothing.

tional to kill the same HIV-infected cells twice—once with HIV and again with AZT. Moreover, it is harmful to kill numerous uninfected cells with AZT collaterally (Kolata, 1987; Lauritsen, 1990; Nussbaum, 1990; Wyatt, 1994).

Accordingly, AZT has failed to cure even one AIDS patient or to prevent AIDS in HIV-infected persons (Duesberg, 1992; Oddone *et al.*, 1993; Tokars *et al.*, 1993; Bacellar *et al.*, 1994; Goedert *et al.*, 1994; Lenderking *et al.*, 1994; Seligmann *et al.*, 1994, Volberding, 1995, Ho, 1995). Instead, evidence is growing that AZT causes AIDS-defining and other diseases as expected from a chain terminator of DNA synthesis (see below) (Mir and Costello, 1988; Lauritsen, 1990; Duesberg, 1992; Lauritsen, 1992; Bacellar *et al.*, 1994; Cohen, 1994a; Duesberg, 1994a; Goedert *et al.*, 1994; Lewis-Thorton, 1994). Yet this evidence is either denied or belittled by the AIDS establishment as the following examples document:

(i) The observation that "HIV dementia among those reporting any antiretroviral use (AZT, ddI, ddC, or d4T) was 97% higher than among those not using this antiretroviral therapy" is interpreted by its authors with little concern for percentages: "This effect was not statistically significant" (Bacellar *et al.*, 1994).

Goedert *et al.,* explain their stunning results—that HIV-positive hemophiliacs on AZT have 4.5-times more AIDS and have a 2.4-times higher mortality than untreated HIV-positive hemophiliacs—by saying this happened "probably because zidovudine was administered first to those whom clinicians considered to be at highest risk" (Goedert *et al.,* 1994).

(ii) Saah et al. explain their observation that male homosexuals on AZT have a two- to four-fold higher risk of Pneumocystis pneumonia than untreated controls as follows: "Zidovudine was no longer significant after T-helper lymphocyte count was considered, primarily because nonusers had higher cell counts..." (Saah *et al.,* 1995). The fact that an inhibitor of DNA synthesis designed to kill human cells would inhibit lymphocyte growth was not mentioned.

(iii) The blunt result that AZT prophylaxis reduced survival from 3 to 2 years, and caused "wasting syndrome, cryptosporidiosis, and cytomegalovirus infection ... almost exclusively" in AZT-treated AIDS patients, was interpreted like this: "The study of patients who progress from primary HIV infection to AIDS without receiving medical intervention gives insights into the effects of medical intervention on presentation and survival after developing an AIDS defining illness." But the nature of these "insights" was not revealed by the authors (Poznansky *et al.,* 1995).

(iv) The largest test of AIDS prophylaxis with AZT of its kind, the Concorde trial, found a 25% higher mortality in AZT recipients than in untreated controls. In view of this Seligmann *et al.,* reached the conservative conclusion: "The results of Concorde do not encourage the early use of zidovudine [AZT] in symptom-free HIV-infected adults" (Seligmann *et al.,* 1994).

(v) Five years after introducing AZT prophylaxis to several hundred thousands of healthy HIV-positives, Paul Volberding of the University of California at San Francisco, Anthony Fauci of the National Institute of Allergy and Infectious Diseases and over 100 scientific collaborators now publish in the *New England Journal of Medicine*: "Zidovudine ... does not significantly prolong either AIDS-free or overall survival. These results do not encourage the routine use of Zidovudine" (Volberding *et al.*, 1995). In an accompanying editorial "Time to hit HIV,

early and hard" the "Journal" makes the forward recommendation to treat HIV infection with AZT and other experimental drugs before antiviral immunity restricts the virus to chronic latency (Ho, 1995). The article suggests that current AZT prophylaxis is too little too late. This is said although the ineffectiveness of the proposed "early and hard" treatment is known since 1993 (Tokars *et al.*, 1993).

(vi) The occurence of 8 serious birth defects, 8 spontaneous abortions and 8 therapeutic abortions among 104 pregnancies treated with AZT is interpreted as "not proving safety, thus lending tenous support to the use of this drug." (Kumar, Hughes and Khurranna, 1994).

AZT must be considered the most toxic among legal public health threats available to healthy persons, much more toxic than alcohol and tobacco. For this reason I have termed AZT *AIDS by prescription* (Duesberg, 1992, see Chapter 6). Even Burroughs Wellcome, the manufacturer of AZT, makes that same assessment, but expresses it in different words: "It was often difficult to distinguish adverse events possibly associated with zidovudine [AZT] administration from underlying signs of HIV disease..." (Physicians' Desk Reference, 1994).

(2) *Educational damage.* Since HIV, but not drugs, is thought to cause AIDS, the HIV-AIDS establishment educates the public to use "clean needles" for the injection of unsterile (!) street drugs and to wear condoms for sex under the influence of aphrodisiac drugs (Institute of Medicine, 1988; San Francisco Project Inform, 1992; Benditt and Jasny, 1993; National Institute of Allergy and Infectious Diseases, 1994). However, the disregard, in fact explicit dismissal, of drug toxicity by the AIDS establishment (Weiss and Jaffe, 1990; Ascher *et al.*, 1993; Duesberg, 1993d; Maddox, 1993a; Schechter *et al.*, 1993b; Schechter *et al.*, 1993c; Cohen, 1994a) encourages recreational drug use because it eliminates the fear of drug toxicity. A popular joke illustrates this point: "Two junkies are reminded by a friend not to share a syringe full of cocaine. Their response: 'We wear condoms and use a clean needle'."

Yet long-term use of recreational drugs, including cocaine, heroin, amyl- and isobutyl nitrite inhalants, amphetamines, and others has been documented in numerous studies to cause exactly the same diseases that are now blamed on HIV (Haverkos and Dougherty, 1988; Stone-

burner *et al.*, 1988; Lerner, 1989; Duesberg, 1992, see Chapter 6). The list of drug-induced diseases, established long before the discovery of HIV, reads like a catalogue of AIDS-defining diseases: weight loss, fever, dementia, tuberculosis, oral thrush, pneumonia, diarrhea, mouth infections, night sweats, and many others (see below) (Lerner, 1989; Duesberg, 1992).

(3) *Psychological damage.* According to the HIV-AIDS establishment, nearly all HIV-infected, healthy persons are claimed to die from AIDS on average 10 years after infection by HIV (Institute of Medicine, 1988; Garza, Drotman and Jaffe, 1994; National Institute of Allergy and Infectious Diseases, 1994; Thomas Jr., Mullis and Johnson, 1994). In view of this, one million HIV-positive but healthy Americans, and 17 million HIV-positive but healthy humans on this planet (Merson, 1993; National Institute of Allergy and Infectious Diseases, 1994; World Health Organization, 1995), are subjected to a multiplicity of psychological and sociological pressures (Anonymous, 1992; Duesberg, 1992; Schmalz, 1992b; Schmalz, 1992a; Miami Herald, 1994; Yarbo, 1994).

They are given a death sentence by the medical establishment for being HIV-positive; they are denied coverage by health insurance companies; they lose their jobs and social status; they are denied entrance visas to many countries including the U.S.; they are denied employment by the US Army; and worst of all they are pressured to accept the toxic AZT therapy—all of this, only because they have made antibodies against a virus that is presumed to cause AIDS. If they refuse to submit to these pressures, they are charged with *denial* (of the HIV-AIDS hypothesis) by the AIDS establishment (Moss, Osmond and Bacchetti, 1988; San Francisco Project Inform, 1992).

In sum, the public health record of the HIV-AIDS hypothesis in America adds up to a staggering deficit: for $35 billion (Duesberg, 1994b; AIDS Weekly, 1995; Gutknecht, 1995) there is no cure, no vaccine, no effective prevention, hundreds of thousands are subjected to psychological pressures resulting from positive HIV-tests, and several million American drug addicts are denied available information that recreational drugs cause AIDS-defining and other diseases (Drug Strategies, 1995), and about 150,000 are subjected annually to AZT poisoning—many just for being HIV-positive, not for having AIDS (Duesberg, 1992).

VII. The drug-AIDS hypothesis

Given no evidence for infectious AIDS, the reasons for the original "lifestyle hypothesis," and the logic of Sherlock Holmes—that "when you have eliminated the impossible, whatever remains however improbable must be the truth"—AIDS *must be* non-infectious.

In view of this I propose that:

> *All AIDS diseases in America and Europe that exceed their long-established, normal backgrounds are caused by the long-term consumption of recreational drugs and by AZT and its analogs.*
>
> *Hemophilia-AIDS, transfusion-AIDS, and the extremely rare AIDS cases of the general population reflect the normal incidence plus the AZT-induced incidence of these diseases under a new name.*
>
> *African AIDS is a new name for old diseases caused by malnutrition, parasitic infections and poor sanitation* (Duesberg, 1991; Duesberg, 1992; Duesberg, 1994a, see Chapters 6 and 9).

Indeed, the recreational drug use epidemics, that started in America and Europe during the Vietnam war, are the only new health risk of the Western World since World War II. Since its beginnings the drug use and AIDS epidemics in the US and Europe have coincided both epidemiologically and chronologically (Duesberg, 1992). About 33% of all American AIDS patients, nearly all heterosexual AIDS patients, are intravenous drug users (Centers for Disease Control and Prevention, 1994b). Over 60% are male homosexuals who have used psychoactive and aphrodisiac drugs orally such as nitrite inhalants, amphetamines, cocaine and phenylcyclidine (Table 2). Many of these recreational drug users and most of the few AIDS patients who have not used recreational drugs have used AZT and cytotoxic DNA chain terminators as anti-HIV drugs (see below) (Duesberg, 1992; Duesberg, 1994a). Allowing a "latent period of 10 years" for chronic recreational drug use to cause AIDS, the beginning of the American drug use epidemics in the late 1960s and 1970s predicts exactly the origin of AIDS in the 1980s.

Unlike the virus-AIDS hypothesis, the drug hypothesis has a plausible chemical and experimentally testable basis. The recreational drugs postulated to cause AIDS have strong biochemical and psychoactive

Table 2.
Drug use by homosexuals at risk for AIDS

In 1983 the CDC reported the following drug use of 170 male homosexuals, 50 with Kaposi's sarcoma and pneumonia and 120 without AIDS (Jaffe *et al.,* 1983):

96%	nitrite inhalants
35-50%	ethylchloride inhalants
50-60%	cocaine
50-70%	amphetamines
40%	phenylcyclidine
40-60%	LSD
40-60%	metaqualone
25%	barbiturates
90%	marijuana
10%	heroin

In 1987 (Darrow *et al.,* 1987) and again in 1990 (Lifson *et al.,* 1990) the CDC reported the following drug use for a group of 359 homosexual men from San Francisco:

84%	cocaine
82%	alkylnitrites
64%	amphetamines
51%	quaaludes
41%	barbiturates
20%	injected drugs

According to analyses by Duesberg (Duesberg, 1993d), Ellison et al. (Ellison, Downey and Duesberg, 1995), and Craddock (Craddock, 1995) nearly all male homosexual AIDS patients in cohorts from San Francisco (Ascher *et al.,* 1993) and Vancouver (Schechter *et al.,* 1993b) had used nitrites, cocaine, amphetamines and AZT.

	HIV-positives	Drug use	AIDS	healthy
San Francisco	445	100%	215	230
Vancouver	365	>98%	136	229

effects every time they are taken—the reason for their popularity (see Chapter 6). By contrast, HIV is latent, and neither chemically nor clinically detectable in "HIV antibody-positives" with and without AIDS. Despite 11 years of unprecedented research efforts no biochemical evi-

dence has been found in support of the HIV-AIDS hypothesis (Cohen 1995).

The specific toxicity and dosages of recreational and medical drugs used by American and European AIDS risk groups can explain all AIDS diseases (Duesberg, 1992). AIDS drugs are either indirectly toxic, or cytotoxic, or genotoxic and cytotoxic.

(1) *Indirectly toxic.* Cocaine, amphetamines and heroin are indirectly immunotoxic. All three function as catalysts in the human body. Cocaine and heroin are natural compounds and amphetamines are synthetic adrenalins first developed in Germany during World War II to suppress fatigue and anxiety in pilots and tank commanders (Weil and Rosen, 1983).

Indirect toxicity is the result of malnutrition and insomnia which in turn are consequences of drug-induced suppression of appetite and fatigue (Layon *et al.,* 1984; Lerner, 1989; Pillai, Nair and Watson, 1991; Duesberg, 1992; Larrat and Zierler, 1993; Mientjes *et al.,* 1993; Sadownick, 1994). These problems are compounded by poverty due to the enormous costs of illicit drugs. Direct, long-term pathogenic effects of cocaine and heroin have not been studied owing to the general disregard of drug toxicity (Duesberg, 1992).

(2) *Cytotoxic and genotoxic.* Nitrite inhalants are cytotoxic, and thus are immunotoxic in animals and humans (Goedert *et al.,* 1982; Haverkos and Dougherty, 1988). A recreational dose of 1 ml per day (Haverkos and Dougherty, 1988; Duesberg, 1992) corresponds to about 15 ppm in a 75 kg-person, and corresponds to 10^{7} nitrite molecules for everyone of the 10^{14} cells in the human body. The cytotoxicity of nitrites on the epithelial tissues of the lung are enhanced by the toxins of cigarette smoke, which also suppresses the immunesystem (Nieman *et al.,* 1993).

In addition nitrite inhalants are among the best established mutagens and carcinogens (National Research Council, 1982; Lewis, 1989; Winter, 1989; Mirvish *et al.,* 1993). In view of the toxicity of nitrite inhalants, a prescription requirement was instated by the US Food and Drug Administration in 1969 (Newell *et al.,* 1985a), and because of an "AIDS link" (Cox, 1986) the sale of nitrites was banned by the U.S. Congress in 1988 (Public Law 100-690) (Haverkos, 1990) and by the

"Crime Control Act of 1990" (Duesberg, 1992). Moreover, the US Food and Drug Administration limits nitrites as food preservatives to less than 200 ppm, because of direct toxicity and because "they have been implicated in an increased incidence of cancer" (Lewis, 1989, National Research Council, 1982).

(3) *Genotoxic—cytotoxic.* AZT, ddI and other DNA chain terminators are directly toxic by killing all growing cells, in particular the fastest growing ones—the hematopoietic and epithelial cells (Fig. 2), (Merck Research Laboratories, 1992; Chiu and Duesberg, 1995). In addition, AZT prevents mitochondrial DNA synthesis in non-growing cells, such as neurons or muscles, and can be carcinogenic by mutating cells (Pluda *et al.,* 1990; Duesberg, 1992; Parker and Cheng, 1994).

The key to the drug hypothesis is that only long-term consumption causes irreversible AIDS-defining diseases. Occasional or short-term recreational drug use causes reversible diseases or no diseases at all. With drugs, *the dose is the poison.* Yet, most studies investigating the effects of recreational drugs are concerned with their short-term psychoactive rather with their long-term clinical effects (Duesberg, 1992). For example, it takes 20 years of smoking to *acquire* irreversible lung cancer or emphysema, and 20 years of drinking to *acquire* irreversible liver cirrhosis. In contrast to drugs, infectious agents are self-replicating toxins. By multiplying exponentially in the body infectious agents may generate sufficient doses of toxic substances to cause diseases within days or weeks.

Since currently no experiments are being done in America to test the drug hypothesis, I have evaluated the drug-AIDS hypothesis on the basis of its predictions. In contrast to the HIV-AIDS hypothesis, the drug hypothesis can predict all parameters of American/European AIDS.

IX. The drug-hypothesis predicts the American/European AIDS epidemic—completely

(1) *AIDS is restricted to intravenous and oral users of recreational drugs and of AZT, because drugs cause AIDS.*

Since 1981 94% of all American AIDS cases have been from risk groups who had used such drugs (Centers for Disease Control and Pre-

vention, 1994c). About one-third of these were intravenous drug users (Centers for Disease Control, 1993) and two-thirds were male homosexuals (Centers for Disease Control and Prevention, 1994c; Centers for Disease Control and Prevention, 1994a) who had used oral recreational drugs and AZT (Duesberg, 1992; Ascher *et al.,* 1993; Duesberg, 1993c; Duesberg, 1993a; Duesberg, 1993d; Parke, 1993; Schechter *et al.,* 1993b). HIV-positive hemophiliacs and transfusion recipients also receive AZT as an antiviral drug (Duesberg, 1992; Duesberg, 1995b). (However, a small percentage of hemophiliacs annually develop a specific subset of AIDS-defining immunodeficiency diseases, mostly pneumonia and candidiasis, only from the long-term transfusion of foreign proteins that contaminate commercial factor VIII (Duesberg, 1992; Duesberg, 1995b, see Chapter 11). European AIDS also correlates with drug consumption (Duesberg, 1992, see Chapter 6).

(2) *American/European AIDS predominantly affects adult males, because they are the predominant users of recreational drugs and AZT.*

The CDC reports that 87% of all American AIDS patients are males (Centers for Disease Control and Prevention, 1994c). This number is the sum of the following constituents: The National Institute on Drug Abuse and the Bureau of Justice Statistics report that over 75% of *hard,* recreational drugs are consumed intravenously by males (Duesberg, 1992, see Chapter 6).

According to the federally supported Drug Strategies program "women account for the fastest-growing population in jails and prisons, in large part because of drug offenses" (Drug Strategies, 1995). Therefore the CDC reports that women are now the fastest growing AIDS risk group (Centers for Disease Control, 1994; Centers for Disease Control and Prevention, 1994a).

The CDC and independent investigators report that nearly all male homosexuals with AIDS and at risk for AIDS are long-term users of oral drugs such as nitrite inhalants, ethylchloride inhalants, amphetamines, cocaine, and others to facilitate sexual contacts, particularly anal intercourse (Lifson *et al.,* 1990; Duesberg, 1992; Ascher *et al.,* 1993; Duesberg, 1993d; Schechter *et al.,* 1993a; Schechter *et al.,* 1993c). The drug use of male homosexuals with AIDS or at risk for AIDS reported

by the CDC (Jaffe *et al.*, 1983; Darrow *et al.*, 1987; Lifson *et al.*, 1990) and others (Ascher *et al.*, 1993; Duesberg, 1993d; Schechter *et al.*, 1993c; Ellison, Downey and Duesberg, 1995) as of 1983 is listed in Table 2. Ostrow reported that nitrite inhalant use in a cohort of over 5000 male homosexuals from Chicago, Baltimore, Los Angeles and Pittsburgh showed a "consistent and strong cross-sectional association with ... anal sex" (Ostrow, 1994). In addition, many HIV-positive homosexuals are prescribed AZT as an antiviral drug (Duesberg, 1992; Duesberg, 1993d; Ellison, Downey and Duesberg, 1995).

Since intravenous drug users, who are 75% male, make up one-third of all AIDS patients, and male homosexuals make up almost two-thirds of all American AIDS patients, the drug hypothesis explains why 87% of all American AIDS patients are males.

(3) *Pediatric AIDS coccurs because of maternal drug addiction.*

Indeed about 80% of pediatric AIDS cases in America and Europe are children born to mothers who were intravenous drug users during pregnancy (see below (5) and (8)), (Mok et al., 1987; European Collaborative Study, 1991; Duesberg, 1992). The remainder reflects the normal low incidence of AIDS-defining diseases among newborns.

(4) *American AIDS is new and increasing steadily, because the American drug epidemic is new and increasing steadily.*

In the U.S. recreational drug use is epidemiologically new, as it has increased over the last decades from statistically undetectable levels to epidemic levels at about the same rate as AIDS (Duesberg, 1992).

For example, cocaine consumption increased 200-fold from 1980 to 1990, based on cocaine seizures that increased from 500 kg in 1980 to 100,000 kg in 1990 (Duesberg, 1992, see Chapter 6). During the same time cocaine-related hospital emergencies increased from 3,296 cases in 1981, to 80,355 cases in 1990, and to 119,843 in 1992 and to over 120,000 in 1993 (Duesberg, 1992; Meddis, 1994; Drug Strategies, 1995) (Fig. 1B).

In the last three years, the increase of cocaine consumption has slowed down at the expense of increases in heroin consumption, which were accompanied by increases in heroin-related hospital emergencies (Gettman, 1994; Meddis, 1994; Drug Strategies, 1995). Heroin-related

hospital emergencies doubled, from over 30,000 in 1990 to over 60,000 in 1993 (Fig. 1B)(Drug Strategies, 1995).

Amphetamine consumption has increased 100-fold from 1980 to 1990 (Bureau of Justice Statistics, 1991). Non-scientific reports describe new upsurges in the consumption of amphetamines (Sadownick, 1994) and the "gay drug" (nitrite inhalants) (Mirken, 1995) among male homosexuals. According to a recent report from the National Institute on Drug Abuse and the CDC, "nitrite use has increased in the 1990s in gay men in Chicago and San Francisco" after a decline in the 1980s (Haverkos and Drotman, 1995).

Drug offenders are now the "largest and fastest-growing category in the Federal prisons population, accounting for 61% of the total, compared with 38% in 1986." The number of Federal drug offenders increased from about 5,000 in 1980 to about 55,000 in 1993. In 1993, between 60 and 80% of the 12 million prisoners in the US had been on illicit drugs (Drug Strategies, 1995).

The German "Rauschgiftbilanz" reports an 11.2% increase in the consumption of illicit recreational drugs in 1994 compared to 1993 (Rauschgiftbilanz 1994, 1995).

Consider a grace period of about 10 years to achieve the dosage needed to cause irreversible disease, and you can date the origin of AIDS in 1981 as a consequence of the drug use epidemic that started in America in the late 1960s during the Vietnam War. Indeed, AIDS increased from a few dozen cases annually in 1981 to about 100,000 in 1993 (Fig. 1A) (Centers for Disease Control and Prevention, 1994c). Note the parallelisms between the spread of AIDS and the spread of cocaine and cocaine-related hospital emergencies since 1981 (Fig. 1A and B), and the contrast with the non-spread of HIV, the hypothetical cause of AIDS, since 1984 (Fig. 1A). Thus both, the newness and the increase of the AIDS epidemic are predictable by the drug-AIDS hypothesis.

The growth of the epidemic has been accelerated by AZT. Since its introduction in 1987, AZT is now prescribed to about 200,000 HIV-positives worldwide (Duesberg, 1992; Thomas, 1995).

(5) *Only a small fraction of drug users develop AIDS, because only the highest cumulative drug doses cause irreversible diseases.*

The cumulative total of 401,749 American AIDS cases since 1981 that were reported in June 1994 (Centers for Disease Control and Prevention, 1994c) have been recruited from a much larger reservoir of drug users. There are currently between 3 (Drug Strategies, 1995) and 8 million cocaine addicts (Duesberg, 1992) and 0.6 million heroin addicts in the US (Drug Strategies, 1995). In 1980, 5 million Americans had used nitrite inhalants. In 1989, 100 million doses of amphetamines were consumed in the U.S. (Duesberg, 1992).

According to a 1994-survey of the National Institute on Drug Abuse, "more than 5 percent (221,000) of the 4 million women who give birth each year use illicit drugs during their pregnancy." (Drug Strategies, 1995). These mothers are the reservoir from which most of the 1017 pediatric AIDS cases reported in the US in 1994 were recruited (Centers for Disease Control and Prevention, 1994b) (see 10).

Unfortunately, scientific documentation of recreational drug use is extremely sporadic and inaccessible, not only because these drugs are illegal, but more importantly because the medical-scientific community is totally uninterested in drugs as a cause of AIDS (see above).

In addition, about 150,000 HIV-positive Americans were on AZT between 1992 and 1995 (Duesberg, 1992; Thomas, 1995). Probably because drug toxicity is generally ignored, there are also no national statistics available on how many HIV-positive Americans are on AZT and other anti-HIV drugs, that, like AZT, are designed to kill human cells (Duesberg, 1992).

The small percentage of AIDS patients among the many American drug users reflects the highest lifetime dose of drug use, just like the lung cancer and emphysema patients reflect the highest lifetime tobacco dose among the 50 million smokers in the U.S. The long "latent period of HIV" is a euphemism for the time needed to accumulate the drug dosage that is sufficient for AIDS. Indeed it takes about 10 years of injecting heroin and cocaine to develop weight loss, tuberculosis, bronchitis, pneumonia and other drug-induced diseases (Layon *et al.,* 1984; Schuster, 1984; Savona *et al.,* 1985; Donahoe *et al.,* 1987; Espinoza *et al.,* 1987; Weber *et al.,* 1990).

The time lag from initiating a habit of inhaling nitrites to *acquire* Kaposi's sarcoma has been determined to be 7 to 10 years (Newell *et*

al., 1985a; Beral *et al.,* 1990; Lifson *et al.,* 1990; Duesberg, 1992). Blaming Kaposi's sarcoma on HIV after inhaling carcinogenic nitrites for 10 years is like blaming lung cancer and emphysema on a "slow" virus after smoking two packs of cigarettes a day for 20 years.

AZT, at the currently prescribed high doses of 0.5 to 1.5 grams per person per day, causes many of the above described AZT-specific diseases faster than recreational drugs, i.e. within weeks or months after administration (Duesberg, 1992; Lewis-Thorton, 1994).

(6) *Risk group-specific AIDS diseases occur, because of risk group-specific drugs.*

Group-specific drug use explains the following risk-group-specific AIDS diseases:

(i) *Kaposi's sarcoma specific for male homosexuals.* Kaposi's sarcoma as an AIDS diagnosis is 20 times more common among homosexuals who use nitrite inhalants than among AIDS patients who are intravenous drug users, or hemophiliacs (Haverkos and Dougherty, 1988; Beral *et al.,* 1990). Due to the carcinogenic potential, nitrites were originally proposed as causes of Kaposi's sarcoma (Marmor *et al.,* 1982; Haverkos *et al.,* 1985). "Aggressive and life-threatening" Kaposi's sarcoma particularly pulmonary Kaposi's sarcoma, is exclusively observed in male homosexuals (Sloand, Kumar and Pierce, 1993; Meduri *et al.,* 1986; Garay *et al.,* 1987; Gill *et al.,* 1989). Since the lungs are the primary site of exposure to nitrite inhalants, the evidence that up to 32% of Kaposi's sarcomas of homosexual men can be diagnosed as pulmonary Kaposi's sarcoma (Gill *et al.,* 1989; Irwin and Kaplan, 1993), lends additional support to the nitrite-Kaposi's sarcoma hypothesis. Pulmonary Kaposi's sarcoma has never been described by Moritz Kaposi, nor anywhere else prior to the AIDS epidemic (Kaposi, 1872).

It appears that the nitrite-induced AIDS Kaposi's sarcoma and the classic Kaposi's sarcomas are entirely different cancers under the same name. The "HIV-associated" Kaposi's sarcomas observed in male homosexuals are "aggressive and life-threatening" (Sloand, Kumar and Pierce, 1993), fatal within 8–10 months after diagnosis, and often located in the lung (Meduri *et al.,* 1986; Garay *et al.,* 1987; Gill *et al.,* 1989; Irwin and Kaplan, 1993). The classic "indolent and chronic" Kaposi's sarcomas are diagnosed on the skin of the lower extremities and hardly

progress over many years (Meduri *et al.,* 1986; Drotman and Haverkos, 1992; Cohen, 1994a). Meduri *et al.* point out that the "pulmonary involvement by the neoplasma has been an unusual clinical finding" in the Kaposi's sarcomas of male homosexuals compared to all "classic" Kaposi's sarcomas (Meduri *et al.,* 1986). Nevertheless, the distinction between classic and AIDS Kaposi's sarcoma is hardly ever emphasized and may have escaped many observers due to the "difficulty in premortem diagnosis," because "pulmonary Kaposi's sarcoma was indistinguishable from opportunistic pneumonia ..." (Garay *et al.,* 1987).

The immunotoxicity and cytotoxicity of nitrites also explains the proclivity of male homosexual nitrite users for pneumonia, which is the most common AIDS disease in the U.S. and Europe (Haverkos and Dougherty, 1988; Duesberg, 1992) (Table 1) (Chapter 6). Moreover the immunotoxins and cytotoxins of cigarette smoke explain, why in two groups of otherwise matched HIV-positive male homosexuals cigarette smokers developed pneumonia twice as often as non-smokers over a period of 9 months (Nieman *et al.,* 1993).

(ii) *High mortality of intravenous drug users.* Intravenous drug users suffer from long-term malnutrition and insomnia, which are primary causes of immunodeficiency worldwide (Seligmann *et al.,* 1984). This explains the tuberculosis, pneumonia, and weight loss that are typical of these risk groups (Layon *et al.,* 1984; Stoneburner *et al.,* 1988; Pillai, Nair and Watson, 1991; Duesberg, 1992; Mientjes *et al.,* 1993). Injection of unsterile drugs combined with immunodeficiency also cause septicemia and endocarditis that are common in AIDS patients who are intravenous drug users (Duesberg, 1992). As a result, intravenous drug users only achieve a very low average age. A German study found the average age at death to 29.6 years for HIV-free and 31.5 years for HIV-positive addicts (Lockemann *et al.,* 1995); and an American study showed that both HIV-positive and negative intravenous drug users died from the same diseases (Stoneburner *et al.,* 1988).

(iii) *Low birth weight and mental retardation of AIDS babies.* 80% of American/European babies with AIDS are born to mothers who were intravenous drug users during pregnancy; they acquire low birth weight, mental retardation and immunodeficiency through maternal drug use (Duesberg, 1992; Drug Strategies, 1995). The B-cell deficiencies and

certain bacterial infections—that are both only considered AIDS-defining in children—are also specific expressions of their acquired immunodeficiency (Centers for Disease Control, 1987; Centers for Disease Control and Prevention, 1992; Duesberg, 1992).

(iv) *Anemia and wasting of AZT recipients.* Anemia, leukopenia, pancytopenia, diarrhea, weight loss, hair loss, impotence (Duesberg, 1992), hepatitis (Freiman *et al.,* 1993), and pneumocystis pneumonia (Saah *et al.,* 1995) that are observed in recipients of AZT and other DNA chain terminators, are predictable consequences of the cytotoxicity of these drugs (see Chapter 6). In addition, non-renewal of mitochondrial DNA causes muscle atrophy, hepatitis, and dementia; and carcinogenic activity causes cancers such as lymphoma in AZT recipients (Pluda *et al.,* 1990; Duesberg, 1992; McLeod and Hammer, 1992; Freiman *et al.,* 1993; Bacellar *et al.,* 1994; Parker and Cheng, 1994; Physicians' Desk Reference, 1994). Compared to untreated controls AZT recipients die 2.4-times more often (Goedert *et al.,* 1994), 25% more often (Seligmann *et al.,* 1994), or live only 2 years instead of 3 years with AIDS (Poznansky *et al.,* 1995).

(7) *Non-correlations between HIV and AIDS, because drugs, not HIV, cause AIDS.*

(i) *Long-term survivors or "non-progressors."* Persons infected by HIV for more than the 10-year-latent-period-from-HIV-to-AIDS who are studied by HIV researchers are termed long-term survivors and more recently "non-progressors" (Scolaro, Durham and Pieczenik, 1991; Learmont *et al.,* 1992; Cao *et al.,* 1995). David Ho et al. recently gave a key to long-term survival, "none had received antiretroviral therapy" (Cao *et al.,* 1995). Likewise Alvaro Munoz reported that not one of the long-term survivors of the largest federally funded study of male homosexuals at risk for AIDS, the MACS study, had used AZT (Munoz, 1995). And several survey studies document that in addition to abstaining from antiviral drugs long-term survivors are those who have given up or never taken recreational drugs (Wells, 1993; Gavzer, 1995; Root-Bernstein, 1995b).

Indeed, the vast majority of HIV-positives are long-term survivors! Worldwide, they number 17 million, including 1 million HIV-positive

but healthy Americans and 0.5 million HIV-positive but healthy Europeans (Merson, 1993; World Health Organization, 1995). Most of these have been HIV-positive for at least 10 years now, because their numbers have not changed since the time between 1984 to 1988, when the epidemic of HIV-testing began in the respective countries (Duesberg, 1992).

Only about 6% (or 1,025,073) of these 17 million HIV-positives have developed AIDS diseases since AIDS statistics are kept (World Health Organization, 1995). Since no more than 6% of HIV-carriers worldwide have developed AIDS in 7 to 10 years, the annual AIDS risk of an HIV-carrier is less than 1% per year. However, even this low figure is not corrected for the normal occurence of the 29 AIDS-defining diseases in HIV-free controls. There is no evidence that HIV-positive people who are not drug users have a higher morbidity or mortality than HIV-free controls (Duesberg, 1995a, see Chapter 10).

(ii) *Intravenous drug users and male homosexuals losing their T-cells prior to HIV infection.* Prospective studies of male homosexuals using psychoactive and sexual stimulants have demonstrated that their T-cells may decline prior to infection with HIV. For example, the T-cells of 37 homosexual men from San Francisco declined steadily prior to HIV infection for 1.5 years from over 1200 to below 800 per µl (Lang *et al.,* 1989). In fact, some had fewer than 500 T-cells 1.5 years before seroconversion (Lang *et al.,* 1987). Although recreational drug use was not mentioned in these articles, other studies of the same cohort of homosexual men from San Francisco described extensive use of recreational drugs including nitrites (Darrow *et al.,* 1987; Moss, 1987; Ascher *et al.,* 1993; Duesberg, 1993d; Ellison, Downey and Duesberg, 1995). Likewise 33 HIV-free male homosexuals from Vancouver, Canada, had "acquired" immunodeficiency prior to HIV infection (Marion *et al.,* 1989). Again this study did not mention drug use, but in other articles the authors reported that all men of this cohort had used nitrites, cocaine and amphetamines (Archibald *et al.,* 1992; Duesberg, 1993f; Schechter *et al.,* 1993c).

The largest study of its kind reported that about 450 (16% of 2795) HIV-free, homosexual American men of the MACS cohort from Chicago, Baltimore, Pittsburgh and Los Angeles had acquired immuno-

deficiency, having less than 600 T-cells per µl, prior to HIV infection (Kaslow *et al.,* 1989). Many HIV-positive and -negative men of this cohort had essentially the same degree of lymphadenopathy: "Although seropositive men had a significantly higher mean number of involved lymph node groups than seronegative men (5.7 compared to 4.5 nodes, po.005), the numerical difference in the means is not striking" (Kaslow *et al.,* 1987). According to previous studies on this cohort 71% of these men had used nitrite inhalants, in addition to other drugs (Kaslow *et al.,* 1987); 83% had used one drug, and 60% had used two or more drugs during sex in the previous six months (Ostrow *et al.,* 1990).

Another study of the same cohort observed that the risk of developing AIDS correlated with the frequency of receptive anal intercourse prior to and after HIV infection (Phair *et al.,* 1992). Other studies have shown that receptive anal intercourse correlates directly with the use of nitrite vasodilaters (Haverkos and Dougherty, 1988; Duesberg, 1992; Parke, 1993).

Thus in male homosexuals at risk for AIDS, AIDS often precedes infection by HIV, not vice versa. Since the cause must precede the consequence, drug use remains the only group-specific choice to explain "acquired" immunodeficiencies prior to HIV. If male homosexuality were to cause immunodeficiency, about 10% of the adult American male population should have AIDS (Duesberg, 1992; Seidman and Rieder, 1994).

Prospective studies of intravenous drug users also document T-cell losses prior to infection by HIV. For example, among intravenous drug users in New York "The relative risk for seroconversion among subjects with one or more CD4 [T-cell] count <500 cells/µl compared with HIV-negative subjects with all counts >500 cells/µl was 4.53." (Des Jarlais *et al.,* 1993). A similar study from Italy showed that a low number of T-cells was the highest risk factor for HIV infection (Nicolosi *et al.,* 1990). Again, a decrease in T-cells is a risk factor for HIV infection, and not vice versa.

This confirms the hypothesis that HIV is a marker of drug consumption, rather than the cause of AIDS (see IV): the more drugs are consumed intravenously or for sex, the higher is the risk of HIV infection (Duesberg, 1992).

(iii) *HIV-free AIDS.* One summary of the AIDS literature describes over 4,621 clinically diagnosed AIDS cases who were not infected by HIV (Duesberg, 1993f, see Chapter 7). Additional cases are described that were not in this summary (Kaslow *et al.,* 1987; Lang *et al.,* 1987; European Collaborative Study, 1991; Weiss *et al.,* 1992; Ellison, Downey and Duesberg, 1995; Moore and Chang, 1995). They include intravenous drug users, male homosexuals using aphrodisiac drugs like nitrite inhalants, and hemophiliacs developing immune suppression from long-term transfusion of foreign proteins contaminating factor VIII (Duesberg, 1993f; Duesberg, 1995b).

Each of these non-correlations between HIV and AIDS are predicted by the hypothesis that recreational drugs and other non-contagious risk factors cause AIDS.

(8) *Discontinuation of drug use either stabilizes or cures AIDS and other diseases—even in HIV-positives.*

(i) *AZT.* Ten out of 11 HIV-positive, AZT-treated AIDS patients recovered cellular immunity after discontinuing AZT in favor of an experimental vaccine (Scolaro, Durham and Pieczenik, 1991). Two weeks after discontinuing AZT, 4 out of 5 AIDS patients recovered from myopathy (Till and MacDonnell, 1990). Three of four AIDS patients recovered from severe pancytopenia and bone marrow aplasia 4-5 weeks after AZT was discontinued (Gill *et al.,* 1987).

(ii) *Heroin/cocaine.* The incidence of AIDS diseases among HIV-positive intravenous drug users over 16 months was 19% (23/124) and only 5% (5/93) among those who stopped injecting drugs (Weber *et al.,* 1990). The T-cell counts of HIV-positive intravenous drug users from New York dropped 35% over 9 months, compared to HIV-positive controls who had stopped injecting (Des Jarlais *et al.,* 1987).

(iii) *Recreational drugs and AZT.* The health of male homosexuals is stabilized or even improved by avoiding recreational drugs. For example in August 1993 there was no mortality during 1.25 years in a group of 918 British HIV-positive homosexuals who had "avoided the experimental medications on offer" and chose to "abstain from or significantly reduce their use of recreational drugs, including alcohol" (Wells, 1993). Assuming an average 10-year latent period from HIV to AIDS,

the virus-AIDS hypothesis would have predicted at least 58 (918/10 x 1.25 x 50%) AIDS cases among 918 HIV-positives over 1.25 years. Indeed, the absence of mortality in this group over 1.25 years corresponds to a minimal latent period from HIV to AIDS of over 1,148 (918 x 1.25) years. On July 1, 1994 there was still not a single AIDS case in this group of 918 HIV-positive homosexuals (J. Wells, London, personal communication).

The T-cells of 29% of 1,020 HIV-positive male homosexuals and intravenous drug users in a clinical trial even increased over 2 years (Hughes *et al.,* 1994). These HIV-positives belonged to the placebo arm of an AZT trial for AIDS prevention and thus were not treated by AZT. It is probable that under clinical surveillance the 29% whose T-cells increased, despite HIV, have given up or reduced immunosuppressive recreational drug use in the hope that AZT would prevent AIDS.

(iv) *AIDS babies, born to drug-addicted mothers, recover after birth.* HIV-positive babies, born to mothers who were intravenous drug users during pregnancy, provide the best examples for the prediction that termination of drug use prevents, or cures AIDS—despite the presence of HIV. For example, Blanche *et al.* have observed for three years 71 HIV-positive newborns who had shared intravenous drugs with their mothers prior to birth. Ten of these children developed encephalopathy and AIDS-defining diseases of which 9 died during their first 18 months of life. The study points out that the risk of a newborn to develop AIDS was related "directly with the severity of the disease in the mother at the time of delivery." Based on the severity of their symptoms about 60% of the children were treated prophylactically, but apparently briefly with AZT "for at least one month," and 50% were treated with sulfa-drugs (Blanche *et al.,* 1994). Despite HIV, 61 of the 71 HIV-positive children either developed only "intermittent" diseases from which they recovered during their first 18 months or developed no disease at all during the 3 years of observation. The T-cells of these children increased after birth from low to normal levels—despite the presence of HIV.

A very similar picture emerges from a collaborative European study of HIV-positive newborns (The European Collaborative Study, 1994) . The study reports that about 20% of the HIV-positive children had died or developed long-term AIDS during the first year after birth, and

another 20% during the second and third year. About 10% of the children were "treated with zidovudine [AZT]" before 6 months of age and 40% by 4 years (The European Collaborative Study, 1994). But over 60% of congenitally-infected children proved to be healthy up to 6 years after birth—despite the presence of HIV. Most of these had experienced transient AIDS diseases, such as pneumonia, bacterial infections, candidiasis and cryptosporidial infection during the first year after birth.

Although this study does not even mention the health and health risks of the mothers, previous reports from the European Collaborative Study group have documented that "nearly all children were born to mothers who are intravenous drug users" (Mok *et al.,* 1987; Duesberg, 1992). In 1991, the European Collaborative Study group reported that 80% of the children with pediatric AIDS were born to mothers who were intravenous drug users (European Collaborative Study, 1991). The 1991-study further points out that "children with drug withdrawal symptoms" were most likely to develop diseases, and that children with no withdrawal symptoms but "whose mothers had used recreational drugs in the final 6 months of pregnancy were intermediate" in their risk to develop diseases (European Collaborative Study, 1991).

According to the HIV hypothesis every infected baby should have developed AIDS and progressively lost T-cells, and according to an HIV plus cofactor hypothesis, at least all those with intermittent diseases should have progressed to AIDS. This was not observed.

According to the drug hypothesis, the AIDS risk of the children is a function of the drugs consumed. Those who received the highest doses of drugs before birth would have acquired irreversible diseases and those who acquired diseases from sublethal thresholds would be able to recover after cessation of maternally administered drugs. Indeed, both, the European Collaborative Study group and Blanche *et al.* show that the majority of children gained T-cells and recovered from transient diseases after discontinuation of maternal drug input—despite the presence of HIV. The childrens risk for AIDS was related "directly with the severity of the disease in the mother" (Blanche *et al.,* 1994), which is an expression for the extent of drug consumption by the mother.

Moreover, the harm of maternal drug consumption to sick babies

was compounded after birth, because "prophylactic treatment [with] ... sulfamethoxazale and zidovudine [AZT] was started earlier and was more frequent among the 16 children born to mothers with class IV disease (AIDS)" (Blanche *et al.*, 1994). (The Blanche study did include mothers with AIDS who were not intravenous drug users). The European Collaborative Study group reports that 10 to 40% of HIV-positive children were treated with AZT.

It follows that discontinuation of recreational and antiretroviral drug use stabilizes and even cures AIDS in HIV-positive persons.

Likewise the T-cells of HIV-positive hemophiliacs increase after removal of immunosuppressive foreign proteins from their factor VIII therapy (Duesberg, 1995, see Chapter 11), and the T-cells of African HIV-positive tuberculosis patients increase after "standard anti-TB treatment" and improved nutrition (Martin *et al.*, 1995).

In sum, the drug-AIDS hypothesis correctly predicts all aspects of American/European AIDS, while the HIV-hypothesis predicts none.

X. A possible solution at last

Testing the drug hypothesis should have a very high priority in AIDS research, because this hypothesis makes verifiable predictions (Cohen, 1994a; DeNoon, 1995). Drug toxicity could be tested experimentally in animals, and in human cells in tissue culture. In addition, drug toxicity could be tested epidemiologically in humans who are addicted to recreational drugs or are prescribed AZT. Such tests could be conducted at a fraction of the cost that is now invested in the HIV hypothesis.

If the drug hypothesis proved to be correct, AIDS would be an entirely preventable disease. Here is how:

(1) AZT use would be banned immediately.

(2) AIDS from illicit recreational drugs would be reduced or prevented by education against drug use. (Hemophilia AIDS would be prevented by the use of pure factor VIII (Chapter 10)).

(3) AIDS therapy would be achieved by termination of recreational drug use and treating AIDS diseases for their specific causes, e.g. tuberculosis with antibiotics, Kaposi's sarcoma with conventional cancer

therapy, and weight loss with good nutrition—rather than treating each of these unrelated diseases with the same cell-killer AZT.

In addition to saving about 100,000 lives per year from AIDS, the drug hypothesis could save the American tax payer up to $20 billion annually. Currently the federal government spends annually $7.5 billion on AIDS treatment, research and education (AIDS Weekly, 1995; Gutknecht, 1995). And the Federal drug budget currently costs $13 billion, mainly for supply control, interdiction, methadone treatment and "education" (Drug Strategies, 1995).

But neither AIDS education nor drug education ever target the health effects of long-term drug use. They focus on the legal and social consequences of drug use and on the effects of drug use on transmission of HIV via unsafe sex and without "clean needles." Instead of studying the unknown, and warning against the known health hazards of recreational drugs, the medical establishment turns a blind eye to drug toxicity in its single-minded pursuit of HIV with safe sex and clean needles (Project Inform, 1992; Ascher *et al.,* 1993; Cohen, 1994a). The clean-needle program of the AIDS-establishment would appear to encourage rather than discourage intravenous drug use. Reflecting this state of mind, *Science* recently rejected the drug-AIDS hypothesis, quoting a drug researcher that "Heroin is a blessedly untoxic drug" (Cohen, 1994a) and described nitrite inhalant-AIDS links as another "hatched" theory (Cohen, 1994b).

The failure to warn against the health risks of drug addiction is certainly one of the reasons that "drug use among young people has risen substantially for the first time in more than a decade" (Drug Strategies, 1995). Nitrite use continues to remain popular and has even increased recently, particulary among male homosexuals (Ascher *et al.,* 1993; Duesberg, 1993d; Mansfield and Owen, 1993; Parke, 1993; Schechter *et al.,* 1993b; Schechter *et al.,* 1993c; Bethell, 1994; Gorman, 1994; Hodgkinson, 1994; Lauritsen, 1994; Sadownick, 1994; Vollbrechtshausen, 1994; Brandley, 1995; Haverkos and Drotman, 1995, Mirken, 1995). There is no report that nitrite bans are ever enforced or that nitrite warnings are taken seriously (Bethell, 1994, Mirken, 1995). And the number of intravenous drug-AIDS patients has increased steadily for

years in America (Centers for Disease Control and Prevention, 1994b; Drug Strategies, 1995)—probably because drug control in America is "primarily focused on supply control efforts" (Drug Strategies, 1995).

However, if AIDS and drug education were based on the health consequences of long-term drug use, it would be as successful as the federal anti-smoking program. Based on education that smoking causes lung cancer, emphysema and heart disease, smoking has dropped in the US from 42% of the adult population in 1965 to 25% in 1995 (Associated Press, 1995b).

The solution of AIDS could be as close as a very testable, very affordable, and very practicable alternative hypothesis.

Acknowledgments

I thank Ruhong Li for searching the AIDS literature and assistance with computer programs, Prof. Phil Johnson, School of Law UC Berkeley, for many references and critical commentary, Russell Schoch for critical review of the manuscript, and Siggi Sachs for preparation of, and review of the manuscript, and Claus Koehnlein (Kiel, Germany) and Colman Jones (Toronto, Canada) for critical information. This investigation was supported in part by the Council for Tobacco Research, USA, and private donations from Thomas Boulger (Redondo Beach, Calif., USA), Glenn Braswell (Los Angeles, Calif., USA), Dr. Richard Fischer (Annandale, Va., USA), Dr. Peter Paschen (Hamburg, Germany), Ruth Sackman, president of the Foundation for the Advancement in Cancer Therapy (New York, USA).

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