DO WE KNOW THE CAUSE(S) OF AIDS?

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The reason for inventing a new theory is to drive us out of the hypotheses in which we hitherto have taken refuge into the state of thoroughly conscious ignorance which is the prelude to every real advance in science.
        - J. C. MAXWELL

Some of the most interesting questions in science are those that appear to have answers so obvious that no one thinks to ask them. Few people, for example, would doubt at this moment in time that we know the cause of the immunosuppression in AIDS. But do we? How do we know that we do? While many people will consider such methodological questions pointless (after all, virtual unanimity exists that HIV is the cause), it is nonetheless true that data can be interpreted only in light of theory, and that the same data may take on different meanings according to different theories. For example, consider data showing that a beach ball falls more slowly than a lead ball in earth's atmosphere at sea level. Aristotle would have considered this observation to be evidence supporting the theory that heavy objects fall faster than light ones. Galileo would have denied that Aristotle was right and declared the experiment irrelevant to an understanding of falling bodies because it was not performed in a vacuum. And a modern aeronautical engineer trained within the Galilean tradition would nonetheless find the experiment very informative - not about the law of falling bodies, but about aerodynamics. Thus, data become facts only within certain theoretical frameworks that predetermine what is to be observed and how it is to be interpreted. In the case of AIDS, we must therefore understand that when we say that HIV causes immunosuppression in AIDS, this statement presupposes a whole series of theoretical and methodological assumptions about how etiologies are established and

what we mean by causation. In consequence, data showing that HIV is highly correlated with AIDS and that it

infects a specific set of T—cells that are compromised in AIDS patients are insufficient to prove that HIV causes the immunosuppression in AIDS if these data can be shown to have a reasonable alternative meaning within a different theoretical framework. The question is whether such an alternative theoretical framework exists.

The history of science repeatedly demonstrates that the key to finding such alternatives clearly lies in not accepting anything at face value. Assumptions need to be questioned skeptically and systematically. We must assure ourselves that our innate tendencies toward scientific positivism have not misled us in our theorizing by focusing our attention on what we observe rather than on what we expect to see and do not. Hypotheses must be invented that can cause us to rethink the meaning of our data or set new boundary conditions on the validity of our observations. We must search for phenomena that we may be missing by prematurely accepting the theory that HIV causes immunosuppression in AIDS.

In short, questions of methodology will be as important to defining and solving the problem of AIDS as are clinical observation and laboratory experiment. How do we know what we know? What are the limitations of that knowledge? Many physicians and biologists may find this approach questionable. Theory, after all, is not held in high esteem in the biomedical sciences. And yet, to say that a disease agent causes a disease -that is to say, to establish an etiology- is to work as a theoretician as much as to work as an empiricist, and I believe that reference to the founders of modern germ theory -Louis Pasteur, Robert Koch, and their peers- surely verifies the point. It is, therefore, just as important to know how we justify the conclusion that a disease agent causes disease as it is to discover new disease agents.

Moreover, the adventure of searching for the unobvious and overlooked aspects of AIDS surely has the potential benefit of allowing us to examine how we know what we know about AIDS and how complete that knowledge is. It also holds out the possibility of surprise. What if HIV cannot be demonstrated convincingly to be the cause of AIDS? What if as yet untested alternatives

still exist despite the apparent confluence of
scientific data and opinion? Surely, given the threat
of AIDS and the billions of dollars for research being
devoted to its cure, it is worth a skeptical look at
the HIV theory. We cannot afford -literally, in terms
of human lives, research dollars, and manpower
investment- to be wrong. Unfortunately, we may be.

Most investigators believe that acquired
immunodeficiency syndrome (AIDS) is caused solely by
human immunodeficiency virus (HIV) [1, 2]. However,
several puzzling facts cast doubt on this conclusion:
about 5 percent of AIDS patients tested for HIV
seroconversion never display signs of HIV infection,
and less than 50 percent of all AIDS patients have been
tested for seroconversion [3]; seroconversion may not
indicate active infection but, rather, a successful
immunological response to HIV, at least in some cases
[4-7]; a single T-lymphotropic virus cannot explain the
simultaneous immunosuppression of T-cells, natural
killer cells, B-cells, and macrophages that
characterizes the immune system of AIDS patients [4-7];
several other immunosuppressive viruses and bacteria
are as highly correlated with the syndrome as is HIV
[8]; Koch's postulates have not been satisfied, nor
have chimpanzees infected with HIV displayed any of the
typical symptoms of AIDS [6-7]; and seroconversion
following HIV exposure is so varied (anything from
seroconversion after a single, unprotected sexual
contact with an HIV carrier to no seroconversion after
hundreds of unprotected encounters) that even HIV
proponents are admitting that there must exist some "as
yet unexplained biologic variation in transmissibility
or susceptibility" to HIV infection [9]. Indeed,
between 30 and 100 hemophiliacs may use the same lot of
clotting factor concentrates, and yet there are no
reported cases of more than one hemophiliac developing
AIDS from an AIDS-donor-contaminated lot [10-11].

Furthermore, there is a logical problem that is
often overlooked by uncritical HIV proponents: AIDS
patients all die of previously identified diseases, not
of HIV infection per se. That is why AIDS is a
syndrome, not a distinct disease entity. Thus, the
putative role of HIV is solely to cause the

immunosuppression that sets the stage for subsequent fatal opportunistic infections. But before we can accept HIV as the sole cause of immunosuppression characteristic of AIDS patients, it is necessary to assure ourselves that alternative explanations of the data do not exist. After all, theories, just like experiments, need controls; for just as experimental artifacts are reproducible, so can a theory explain existing data and yet, as Aristotle's theory of falling bodies demonstrates, still not be the best explanation. In the present context we must, therefore, before accepting HIV as the sole cause of the immunosuppression typifying AIDS, demonstrate directly that HIV actually does cause immunosuppression in animals or human beings and also assure ourselves that other immunosuppressive agents cannot explain the etiology of AIDS. In other words, we must determine that the HIV theory is necessary and sufficient to explain AIDS and that no other theory is necessary or sufficient. Are there, for example, individuals who are immunosuppressed whose sole infection is HIV? If so, then we can assure ourselves that HIV is sufficient to cause immunosuppression. Do AIDS patients in general have any identified immunosuppressive risks other than HIV? If so, are these sufficient to explain the immunosuppression associated with AIDS in the absence of HIV, or not?

Existing data do not, as yet, allow us to establish HIV as the unequivocal cause of immunosuppression in AIDS. No nonhuman animal other than the chimpanzee appears to be infected by HIV, and HIV-infected chimpanzees do not display long-term immunological abnormalities [6, 7]. Moreover, all AIDS patients do have multiple, wellestablished causes of immunosuppression prior to, concomitant with, subsequent to, and sometimes in the absence of, HIV infection. These immunosuppressive agents are of seven basic types: chronic or repeated infectious diseases caused by immunosuppressive microorganisms; recreational and addictive drugs; anesthetics; antibiotics; semen components; blood; and malnutrition. While no AIDS patient is likely to encounter all of these agents, all AIDS patients encounter several. Healthy heterosexuals and lesbians rarely encounter more than one. Therefore, the conclusion that HIV is the sole cause of immunosuppression in AIDS, and the sole factor differentiating AIDS patients from non-AIDS

patients, cannot be maintained, and alternative hypotheses remain possible.

Begin by exploring a few immunological factors that have largely been overlooked or ignored in the quest to conquer AIDS. The majority of AIDS patients are gay or bisexual men [12]. Many habits related to their sexual preference translate into immunosuppressive risks. Receptive anal intercourse and "fisting" with multiple partners are the most significant identified risks [13]. These forms of anal sex are often accompanied by rectal bleeding, which probably allows semen to enter the bloodstream. Thus, virtually all gay men who engage in receptive anal intercourse (but not those who are exclusively sperm ''donors'') develop antibodies to semen and sperm antigens [14, 15]. These antibodies have been shown to cross—react with T—lymphocytes [16], which may cause gay men to develop an autoimmune reaction against their own immune systems in which B—cells are pitted against T—cells. Moreover, semen and sperm contain agents that are, in and of themselves, immunosuppressive and act to protect sperm from vaginal and cervical lymphocytes during heterosexual sex [17, 18]. Thus, immunological contact with semen has multiple immunosuppressive effects.

Another immunosuppressive risk factor associated with gay men is abuse of amyl and butyl nitrites as vasodilators and muscle relaxants in order to facilitate anal intercourse and to increase sexual response [19]. Subchronic inhalations of extremely low doses of these volatile nitrites are not immunotoxic but do cause degeneration of the thymus in experimental animals [20]. Acute high doses more akin to those encountered in human use cause natural killer cell suppression and the abnormally low helper T-suppressor T ratio of lymphocytes typical of AIDS patients [21]. Since as much as tenth—millimolar concentrations of nitrites have been observed in the blood of some abusers [22], it is probable that the high—dose results are more representative of nitrite immunotoxicity in habitual and high—dose acute users.

Many gay men, particularly promiscuous ones, also tend to abuse antibiotics, apparently as a prophylactic

or remedial measure against repeated sexually
transmitted diseases [23]. Chronic treatment with most
antibiotics causes T—cell immunosuppression [24, 25],
possibly by depleting trace elements such as zinc,
which is an essential cofactor for enzymes controlling
lymphocyte cloning [26—28]. Gay men typically have
unusually low zinc and selenium serum levels and
abnormally high copper levels as compared with
heterosexual men and women and lesbians [23, 29].

Antibiotics and nitrites taken together represent
yet another risk: nitrites convert virtually all
commonly used antibiotics, including penicillin,
ampicillin, and tetracycline, into potent carcinogens
[30] and produce other mutagenic nitrosation products
in blood [31]. Given the high concentrations of both
compounds that may be present simultaneously,
particularly in patients being treated repeatedly for
sexually transmitted diseases, the reactions producing
these carcinogens become likely. It has been suggested
that nitrite use is correlated with incidence of
Kaposi's sarcoma in gay men [32—34], and perhaps the
combination of nitrites with antibiotics is a causative
agent. (One recent study failed to find any evidence of
HIV or hepatitis B viral DNA in Kaposi's sarcoma tumors
from AIDS patients and isolated cytomegalovirus DNA
from only two of 13 tumors. On the other hand, they
were able to demonstrate polyclonal karyotypic
rearrangements within Kaposi's cells, arguing for a
nonviral mechanism of DNA disruption [35].) The same
mechanism would operate in heterosexuals who abuse
nitrites and antibiotics simultaneously.

Another risk factor for AIDS that is common to most
patients is the presence of multiple, concurrent
infections. Several viral diseases are as highly
correlated with AIDS as is HIV: hepatitis B virus,
herpes simplex virus (HSV), cytomegalovirus (CMV), and
Epstein—Barr virus (EBV). Herpes simplex virus, CMV,
and EBV are all known to reduce the helper T—cell
(T4):suppressor T—cell (T8) ratio that typifies the
AIDS patient's immune system [36—39], and one type of
herpes virus has been shown to act symbiotically to
increase the cytocidal effects of HIV [40]. Both

hepatitis and cytomegalovirus were present in unusual proportions of high-risk populations before the recognition of AIDS [41-43].

Chronic or repeated diseases carry other immunosuppressive risks both in and of themselves or owing to chronic antibiotic treatment. Both acute and chronic hepatitis infections have been shown to adversely affect cell-mediated immune functions [44-45]. Epstein-Barr virus, CMV, influenza virus, and various bacterial diseases including chronic syphilis and tuberculosis, are known to adversely affect B-cell and macrophage function [38, 39, 46], and the World Health Organization lists genital ulcer disease caused by HSV and Treponema pallidum as risk factors in AIDS [47]. Homosexual and bisexual men often suffer from repeated fungal and amoebal infections of the lower intestine ("gay bowel"), which was recognized prior to AIDS [48-49]. Lymphadenopathy also increased significantly in gay males in the decade before the recognition of AIDS [50]. All of these phenomena are evidence that multiple infections preceded the recognition of AIDS in high-risk groups and led to observed immunological abnormalities.

Intravenous drug abuse is the second-highest risk factor associated with AIDS. Intravenous drug abuse has been known to be immunosuppressive since the early 1970s [51] and has been linked for at least 2 decades to susceptibility to unusual infections and neoplasms [52], including CMV infection [53] and multifocal, disseminated tuberculosis [54], both of which are symptoms of AIDS [3]. Moreover, heroin and morphine have been demonstrated to cause immunosuppression of T-lymphocytes both by indirect, brain-mediated pathways [55, 56] and by direct action on the lymphocytes themselves [57-59]. One study of heroin addicts conducted in 1982 [60] found that all had significantly depressed E-rosette formation, which is highly correlated with clinical immunosuppression [61]. The longer the period of addiction, the greater the effect

on T—lymphocyte activity. Moreover, as of 1982, 24 percent had T4:T8 ratios typical of AIDS patients, although retesting of these individuals in 1985 showed that only 12 percent were HIV positive [59]. It may be presumed that the incidence of HIV among this group was significantly lower than 12 percent in 1982 and, therefore, that profound immunosuppression preceded HIV infection. In the same vein, clinicians have reported generalized lymphadenopathy, low-grade fevers, night sweats, Roth spots, and other symptoms typical of AIDS and pre—AIDS among heroin addicts for several decades [62].

Drug abusers also have other immunological risks. Like gay men, they are very likely to transmit a wide variety of immunosuppressive disease agents, including hepatitis, CMV [53], and EBV when they share needles. They are very often malnourished [63, 64], and chronic malnourishment is perhaps the oldest known and most frequent cause of immunosuppression [65, 66]. It is perhaps significant that the most frequent disease concomitant of AIDS in drug abusers is Pneumocystis pneumonia and that all major outbreaks of this pneumonia since World War 11 have been linked directly to malnutrition [67, 68]. Also noteworthy is the fact that weight loss and anorexia are frequent concomitants of AIDS in all risk groups, and that AIDS patients in general display nutrient insufficiencies that are manifested in significantly low levels of zinc and selenium [23, 29]. Deficiencies of each are known to cause immunosuppression in man and experimental animals [26—28, 69—71].

Intravenous drug abusers also share an immunosuppressive risk factor with hemophiliacs and blood transfusion recipients: they receive other people's blood. I am unable to find any data concerning the immunological effects of small doses of untyped blood such as drug abusers might encounter repeatedly by sharing needles; however, it is a well—established principle of immunology that repeated injections of very small amounts of almost any antigen eventually result in suppression of the immune response [72]. (given that these small, repeated blood injections will include a proportion of leukocytes, it is likely that immunosuppression to various HLA types will eventually

occur. This mechanism of immunosuppression has previously been suggested for semen, which also contains small numbers of leukocytes [73].

Anti—HLA alloimmunization has already been observed in multiply transfused patients [74, 75]. Repeated use of anticlotting factors results in abnormal suppressor: helper T—cell ratios even among otherwise healthy hemophiliacs and even in countries like Australia, in which HIV is virtually nonexistent [76—78]. Almost every hemophiliac also contracts hepatitis [79] and presumably various other viral agents that are transmissible in blood, such as CMV and EBV [80, 81]. Moreover, it has been established that even properly typed blood causes profound immunosuppression [79, 82—84]. Physicians have known for over a decade that blood transfusions depress the immune response effectively enough to facilitate the acceptance of organ transplants and to increase significantly the risk of death from cancer [85—89]. This immunosuppression is dose related, and it is therefore significant that the average transfusion—related AIDS patient receives blood from 16 to 21 donors - five or more times that of the average surgery patient (a statistically significant difference) [90, 91]. Although the exact mechanism of transfusion induced immunosuppression is unknown, T—cells are certainly a primary target, and B—cells and macrophages are also involved. Thus, recent studies show that anyone receiving multiple transfusions or blood—derived products such as clotting agents - hemophiliacs, those with sickle—cell anemia [92], trauma patients [93], and surgery patients [94]- are at high risk for developing the lymphadenopathy, low helper T—cell: suppressor T—cell ratio, and low-grade fever associated with AlDS—related—complex (ARC,). These symptoms generally precede HIV seroconversion.

Sketchy data also indicate that the rate of blood transfusions among gay men is significantly higher than among heterosexual men and women and lesbians [23]. The cause is unknown. One possibility is that, since amyl

and butyl nitrites are known to cause methemoglobinemia
(accounting for between 20 and 70 percent of hemoglobin
in some abusers [22]), and in some cases it has been
severe enough to warrant transfusion [95], they may be
the indirect cause. Fisting can also lead to
complications requiring surgery [96].

Patients who require multiple blood transfusions
incur additional immunosuppressive risks. They are on
the operating table an unusually long time. Surgical
trauma is, itself, immunodepressive [94, 95]. So are
anesthetics. The effects of anesthetics are dose

related; and some of their actions on T—cells, B—cells,
and macrophages can last for a month [97, 98]. Most
major surgical patients are given prophylactic doses of
antibiotics and placed on narcotic painkillers like
morphine or one of its derivatives as well, which are
again immunosuppressive. If, on top of this, the blood
they have received is contaminated with any
immunosuppressive viruses, such as EBV or CMV, for
which screening has only recently been initiated,
further immunosuppression may ensue. The more blood
they receive, the more likely they are to incur such an
infection.

Thus far, every group at high risk for AIDS has
been demonstrated to have multiple immunosuppressive
risks other than HIV-save for one group: pediatric AIDS
cases. These cases are of particular importance, since
they are often cited as some of the best evidence that
HIV alone is sufficient to cause AIDS. Anthony Fauci,

for example, has disparaged life—style theories of AIDS
by asking what possible risky behaviors a newborn
infant could indulge in [99]. Also, it is considered

significant bv many investigators that HlV—infected
mothers who show no clinical symptoms of AIDS
nonetheless give birth to children who develop AIDS

during the first years of life [100—102]. The inference
that is often drawn from these data is that HIV is the
only immunosuppressive risk associated with these
infants and thus must be the sole cause of their
immunosuppression. In fact, the mother transfers all of

her life—style risks to the fetus and newborn.

Of the 1,346 AIDS patients under the age of 13
years who were reported to the CDC as of December 31,

1988, 78 percent acquired an HIV infection perinatally, 13 percent from blood transfusions, and 6 percent from blood products used to treat hemophilia. Four percent had no known risk. Sexual abuse and intravenous drug abuse are thought to account for many of the patients without known risk [103].

Among perinatally acquired cases, 73 percent of the mothers have intravenous drug abuse as a risk factor, 7 percent are sexually active with an AIDS or ARC patient, 2 percent acquired HIV infection through blood transfusion, 11 percent are from a country such as Haiti or Uganda in which heterosexual transmission of AIDS (as well as malnutrition and multiple chronic infection) is common, and no data are available for 7 percent [103]. All mothers of AIDS infants for whole immunological data are available have immunological abnormalities [101–103], which undoubtedly put the infant at increased risk for opportunistic infections during the 3 months during which its own immune system becomes functional. In addition to passively acquired immune abnormalities, the majority of infants contracting AIDS are of unusually low birth weight and have unusually small head circumference; many suffer from hepatosplenomegaly; most are premature; and like all very low-birth-weight, microcephalic, and preterm babies, they are immunologically immature and at higher risk for infections of all kinds [100–102, 104].All of these symptoms were found to be typical of infants of intravenous drug abusers a decade or more before AIDS was first diagnosed [105–107].

Most AIDS infants not only have HIV infections but also must be treated for one or more of the following: sexually transmitted diseases, CMV, hepatitis, and a variety of other infectious diseases acquired from their mothers [100– 102, 104]. Moreover, each maternal risk factor translates into an immunosuppressive risk for the child: the child, too, is immunosuppressed by intravenous drug abuse; premature birth is highly correlated with multiple or chronic maternal infections (often sexually transmitted diseases), causing lymphocytes to release prostaglandins, which in turn stimulate uterine contractions [108]; the highest correlate for low-birth-weight infants and infants with

small head circumference is malnutrition in the mother,
which often translates into malnutrition for the infant
[105, 109, 110]; malnutrition and AIDS are both
correlated with unusually low levels of serum selenium

and zinc which lead to immunosuppression [26–29, 111–
112]; and maternal zincaemia can also result in failure
of immune development in breastfed infants who acquired
a nutritional zinc deficit through the milk [113].
Thus, maternal immunodeficiencies, malnutrition, drug
abuse, and infections can all play a role in
determining the immune status of the infant: AIDS
infants, like all other AIDS patients, therefore have
multiple sources of immunosuppression.

It is also important to note that two caveats are
in order in evaluating the data concerning infant AIDS.
The most recent reports indicate that HIV
seropositivity should not be used uncritically (as it
has been in the past) as a marker for infant AIDS,

since many HlV–seropositive infants have been shown to

acquire seropositivity lasting up to 24 months through

their mothers' milk and in the absence of either pre-
or perinatal HIV infection [114]. Thus, some previously
reported cases of infant AIDS might not now qualify as
AIDS cases. This is very important since a significant

number of HIV–seropositive mothers have given birth to

healthy children, and some HlV–seropositive children

never develop any symptoms of ARC or AIDS [100–102,
104]. Both observations argue against HIV as a
sufficient cause of AIDS.

Much is also made by some investigators of the fact

that many HIV–infected mothers of AIDS infants do not,

themselves, show AIDS–related symptomatology during
pregnancy. It is important to stress that all do show
immunological abnormalities, and the majority do go on

to develop AIDS or ARC [100 – 102]. It should therefore

be considered whether pregnancy has some short–term
prophylactic action on AIDS development similar to the
delay in immunological response to fetal antigens such
as Rh factor. This observation could be of use in

developing a treatment for AIDS if the effect is real and if its cause can be isolated.

So, it appears that acquired immunosuppression can be acquired in many ways, and that HIV is, at best, only one of many immunosuppressive factors encountered by all AIDS patients. Moreover, some of these immunosuppressive factors may help to explain aspects of AIDS that the HIV theory leaves murky. Unlike HIV, which in vitro has very specific effects only on a particular subset of T-lymphocytes, most of the immunosuppressive factors just listed affect the T4:T8 ratio and other T-cell subsets, B-cells, and macrophages. These broader immunosuppressive effects explain the clinical and immunological picture of AIDS in ways in which retroviral infection of a single set of T-cells cannot [4-7]. since AIDS patients eventually display abnormalities of virtually all lymphocyte activities. Moreover, all AIDS patients encounter these non-HIV immunosuppressive factors repeatedly before, during, and after HIV infection and, notably, sometimes in the absence of HIV infection. The greater the number of these immunosuppressive factors encountered by a patient, and the more prolonged their exposure to them, the greater the risk of developing AIDS. Logically, then, HIV cannot be singled out as the sole cause of acquired immunosuppression in AIDS.

At this point, we must, it seems to me, elaborate possibilities and determine how they can be compared and tested. Several alternative hypotheses for AIDS etiology must therefore be considered: HIV may cause AIDS only in people previously, concomitantly, or subsequently immunosuppressed by other agents; HIV may not cause AIDS at all but be merely another, difficult-to-acquire, opportunistic organism that accompanies AIDS (this would make HIV no more than a marker infection indicating previous immunosuppression [115]); AIDS may have several distinct etiologies and HIV may or may not be one; or HIV may be necessary to development of AIDS, but these other immunosuppressive agents determine the time course and specific disease symptoms that an individual patient displays.

The last hypothesis bears particular consideration, since one of the characteristics of AIDS that cannot be explained by an exclusive HIV etiology is the fact that different risk groups contract different opportunistic diseases: Kaposi's sarcoma and chronic candidiasis are largely limited to gay men, whereas drug abusers have a significantly higher incidence of Pneumocystis pneumonia [7]. While basic immunology leads one to expect that different immunosuppressive agents will result in the suppression of different Iymphocyte specificities, thus exposing individuals in different risk groups to different opportunistic diseases, a single immunosuppressive agent as HIV cannot explain why AIDS has different manifestations in different individuals.

The possibility that HIV is not sufficient to induce AIDS is further supported by data on the incidence of AIDS among health-care workers and laboratory researchers who handle HlV-contaminated material. The CDC figures show that, of several thousand reported cases of needle sticks, cuts, and other contaminations, only 5 percent have developed HIV seropositivity; and of these, only one individual lacking other identified risk factors has thus far developed AIDS [116, 117]. Since identification of risk requires personal testimony, we can never be sure that a lack of identified risk does not mean simply a lack of candor on the part of the patient, so that this one case may or may not be significant. Certainly it is significant that so few health-care and laboratory workers having subcutaneous contact with HIV have even developed antibody. One possible interpretation of these data are that people with healthy immune systems are as safe from HIV as from the other opportunistic diseases, such as Kaposi's sarcoma or Pneumocystis pneumonia, that characterize AIDS.

Other data seem to support this interpretation. Of four women identified as having been artificially inseminated with HIV-contaminated semen before 1984, all are currently healthy, as are their children and spouses [118]. These data suggest that contact with HIV, and even outright HIV infection, is insufficient to induce AIDS in some (if not most) cases [6, 7, 63, 115].

Alternative hypotheses must therefore be entertained and seriously investigated. These alternative hypotheses may be differentiated on the basis of several sorts of experimental tests. Animals may be pretreated with repeated small doses of untyped blood, multiple transfusions, drugs, anesthetics, antibiotics, semen components, malnutrition, and chronic infections, either singly or in various combinations and over varying periods of time, and then exposed to the various infectious agents that typify AIDS: CMV, Pneumocystis carinii, and so forth. Since most healthy animals have already been shown to be resistant to these disease agents unless previously chemically immunosuppressed [67, 119-122]-that is, after all, why they are known as opportunistic-infection would indicate the sort of profound immunosuppression characteristic of AIDS; HIV would then be demonstrated to be unnecessary for AIDS induction. The possibility that the time course of AIDS is affected by non-HIV immunosuppressive agents, or that HIV is necessary to AIDS induction but requires concomitant immunosuppression to become pathogenic, can be tested in chimpanzees with the same strategy but combining the immunosuppressive regimens with prior, concomitant, or post-HIV infection. The success of any of these experiments would suffice to produce a natural animal model for the various marker diseases characteristic of AIDS, thus satisfying Koch's postulates. Success of any experimental protocol would also provide strong support for one or more of the hypotheses suggested above, while their constant failure could bolster the notion that AIDS is caused solely by HIV or indicate that still further hypotheses are needed.

We must also consider some of the possible implications of these various hypotheses. These implications can aid hypothesis testing. If HIV is not the sole cause of immunosuppression in AIDS, then it follows that HIV seroconversion may not be, in and of itself, an indicator of incipient AIDS. Only in the ongoing presence of the other immunosuppressive agents listed above would HIV positivity indicate incipient AIDS. Alternatively, the rate at which HIV infection develops into AIDS may be determined by the degree to which individuals are acted upon by these other agents.

Seropositive individuals who lack these other risk
factors, or who alter their behavior to eliminate these

ongoing immunosuppressive factors from their life—
style, may have a much higher probability of remaining
healthy, or remain healthy longer, than those
individuals who repeatedly engage in risky behaviors.
Retrospective or prospective studies of existing cases
might be able to validate or falsify this possibility.
Certainly, such a hypothesis would allow the huge

variation in HIV infectivity and the ever—increasing
period from HIV seroconversion to active AIDS to be
explained. If so, behavior modification techniques such
as those used to treat alcohol and nicotine addiction
might be of benefit for those patients at high risk for
AIDS. Nutritional counseling, alternative drug
regimens, and nonsurgical approaches to disease
treatment may turn out to be as effective as antiviral
drugs or vaccinations.

Another implication of the hypotheses elaborated
above is that new types of information will have to be
gathered in new ways if they are to be tested
adequately. What you discover is determined by how and
when you look. Thus, physicians will need to alter the
way in which they gather information from AIDS patients
and the types of questions they ask. We can no longer
rely on the pediatrician to evaluate the newborn infant
infected with HIV-we must collaborate with the
obstetrician infant family practitioner to gather a
complete picture of the previous health care and habits
of the entire AIDS family if we are to reveal the risk
factors that may have brought about the infant's
immunosuppression. It will no longer be sufficient to
collect merely a sexual history of each patient-drug
use, eating habits, and a complete medical history will
he essential, including a history of all medications
and hospital procedures. Nor can we rely on verbal
questions and answers to identify risks. Tests for drug
use, zinc and copper levels, anemia, vitamin

deficiencies, protein—calorie deprivation, and other

measures of nutritional and drug—related metabolic
imbalances will have to become more common and our
understanding of their affects on the immune system
broadened and applied more cogently to discussions of
AIDS.

One final set of implications must also be explored (although space does not permit a full discussion of them here), and these concern why AIDS has emerged as an apparently new phenomenon during the 1980s when the immunosuppressive factors listed have existed, in some cases, for centuries. Suffice it to say that a

significant number of cases fitting the pre—HIV definition of AIDS (1987) do exist in the literature for at least 100 years before 1980 (a few of which have been cited here [53, 54, 123, 124]); intravenous drug abuse, nitrite use, and promiscuous homosexual activity all increased dramatically during the 1970s; and techniques of diagnosis for many rare, opportunistic diseases, such as Pneumocystis pneumonia, in living patients became available only during the 1970s. Finally, the likelihood of infection with the rare opportunistic diseases that constitute AIDS has become probable only since the widespread use of antibiotics and vaccines in the past few decades has allowed immunosuppressed patients to survive previously more prevalent diseases (tuberculosis, smallpox, typhus, typhoid, etc.) that undoubtedly killed such patients in the past. The evidence for these assertions will form the basis of a forthcoming paper.

Let me be clear, in concluding, about just what I am and am not arguing. I am arguing that premature closure of inquiry lays us open to the risk of making a colossal blunder by assuming that the first reasonable answer we achieve is in fact the best answer. It may be; then again, it may not. I am arguing further that, because the standard criteria for establishing etiologies have not been satisfied for AIDS, it is premature to conclude that HIV is "the" cause of

immunosuppression in AIDS [5—7, 63, 115, 125]. Correlations between HIV and AIDS are not sufficient to establish the etiology of AIDS because too many other immunosuppressive agents are also correlated with AIDS and because no AIDS patient has only HIV as his or her sole risk factor. Koch's postulates must be met or some other direct form of experimental proof of disease causation provided.

I am not arguing that HIV cannot cause immunosuppression in AIDS-it may, and some of the experiments suggested above may help to prove that-but the assertion that HIV is the sole or even the primary cause of the immunosuppression in AIDS needs to be

demonstrated by direct experiment, not argued by correlation or assumption. And I am not arguing that we should abandon research on HIV-only that we should investigate other possible modes of immunosuppression that are associated with AIDS as possible causative factors or potentiating agents until such time as these have been demonstrated conclusively either to influence the course of AIDS or not.

And if it turns out that all of the tests of alternative theories of AIDS etiology are negative, then what? Nothing could be more important, for then we will have a much firmer basis upon which to conclude that HIV is the sole cause of AIDS-something that we do not have now. These alternative theories will become the controls for the HIV theory, tested, elaborated, and, if the data so dictate, discarded. Yet the process of testing these alternatives is far from useless. It is in the nature of research that, for every correct theory, dozens of others must be tried and abandoned along the way. For, just as in the evolution of new species by natural selection of random genetic variations, these abandoned theories are a necessary part of the process without which there would be no way to know that the most adaptive possibility was selected [126]. Alternatives-especially unlikely alternatives that cause us to question assumptions and to rethink dogmatic assertions-need to be propounded and tested before we can be sure that our preconceptions have not blinded us to the unexpected. Nature is full of surprises. and the purpose of doing research is to search for them [126-128].

Thus, the question of AIDS etiology must be kept open a bit longer while we assure ourselves that no surprises still await us. I therefore ask, and ask quite seriously, "Do we know the cause(s) of AIDS?" I believe that we all stand to gain new insights and deeper knowledge of AIDS if we take the question of causation seriously and realize that theory and methodology will be as important to understanding this syndrome as data. We must therefore heed not only what fits our cherished beliefs about AIDS, but data that do not [129], and alternative hypotheses [130] that challenge our assumptions. These are the crucibles of science.*

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