Low CD4+ T lymphocyte counts: A variety of causes and their implications to a multifactorial model of AIDS

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Abstract

Low CD4+ T lymphocyte counts (CD4 counts) are associated with a variety of conditions, including many viral infections, bacterial infections, parasitic infections, sepsis, tuberculosis, coccidioidomycosis, burns, trauma, intravenous injections of foreign proteins, malnutrition, over-exercising, pregnancy, corticosteroid use, normal daily variation, psychological stress, and social isolation. It is also possible that anti-HIV medications can lower CD4 counts when used for long periods, and the short term rise in CD4 counts that is associated with their use may be due to a variety of factors that are unrelated to any anti-HIV activity. Finally, there are a number of people who are completely healthy and who have low CD4 counts for no apparent reason. This paper presents a brief review of several studies documenting low CD4 counts in people who are experiencing these conditions. The low CD4 counts caused by some of these conditions often fall below 200 per cubic millimeter, which is the level needed to diagnose acquired immunodeficiency syndrome (AIDS) in someone who was previously positive for antibodies to the human immunodeficiency virus (HIV-positive). In addition to the diagnosis of AIDS, CD4 counts are regularly used to make treatment decisions in people diagnosed HIV-positive, such as when to start antiretroviral medications and when to begin preventative antibiotics.

Because many of the conditions that cause low CD4 counts are common in people diagnosed HIV-positive, caution is advised regarding the use of CD4 counts to make treatment and diagnostic decisions. This is made more urgent since some of the conditions, like psychological stress, are greatly increased when people are told that their CD4 counts are low, which may compound the problem and cause the CD4 count to fall even further. Psychological stress and social isolation are also created by the diagnosis, HIV-positive, and by the diagnosis of AIDS, which may have chronic effects on the CD4 count. Finally, the widely accepted argument that HIV specifically targets CD4+ T lymphocytes is also called into question, because it appears that low CD4 counts are a common reaction to many kinds of physical and psychological stressors. Other alterations in immune system parameters which are thought to be specific to HIV are also replicated extremely well by the conditions to be reviewed, making it impossible to distinguish any effects attributed to HIV that could not also be caused by these other factors. When several of these factors are combined, as is often the case in people diagnosed HIV-positive, extremely low CD4 counts may be a natural result.

Introduction

Low CD4 T-cell counts are considered to be a marker of the progression of HIV infection and AIDS, and have been called the 'hallmark' of HIV (Balter 1997). Since HIV was first claimed to be the cause of AIDS in 1984, the CD4 count has been widely used to make treatment and diagnostic decisions, but the use of the CD4 count has been controversial, and recommendations regarding how to use them have changed many times over the years (Goldman 2000, Hughes et al. 1998, Choi et al 1993).

In addition to low CD4 counts, the CD4/CD8 ratio is also considered a marker of disease progression in HIV and AIDS, and is often found to be inverted. An 'inverted' ratio simply means
that there are less CD4 cells than CD8 cells, resulting in a ratio of less than 1. CD8 cells are often increased, especially in less advanced stages of AIDS, and this combination of lowered CD4 counts and increased CD8 counts are commonly thought to occur only in people diagnosed HIV-positive. Another finding that is common in people diagnosed HIV-positive is reduced lymphocyte activity and function, as measured by their responsiveness to foreign antigens. This can result in a state of "anergy", where people's skin fails to respond when antigens are injected under it. As this paper will demonstrate, all of these changes are common in a wide variety of conditions that commonly occur to people diagnosed HIV-positive.

There are two major arms of the immune system, one which works through antibodies, which are produced by B-cells and plasma cells, and the other that works through direct cellular action and which relies heavily on CD4+ T-cells. The first is called antibody-mediated or humoral immunity, and the second is called cell-mediated immunity. It is the cell-mediated arm of the immune system that is found to be profoundly suppressed in people diagnosed with AIDS. The antibody-mediated arm of the immune system, however, is usually hyperstimulated in the early stages, with "increasing levels of humoral antibodies and plasma cells" (Fox 1996). The fact that antibody levels are increased is what allows the HIV antibody screening tests to use serum that has been diluted 400 times, unlike other antibody tests that usually use straight, undiluted serum (Abbott Laboratories 1997). In these early stages the lymph nodes may grow in size and be chronically enlarged. In late stages, however, both the cell-mediated and antibody-mediated arms of the immune system begin to fail, and lymph node atrophy results. The only measurement commonly used in clinical practice, however, is the CD4 count, as the following treatment and diagnostic recommendations demonstrate (Cecil Textbook of Medicine, Goldman 2000):

- "Over the years, the recommendations of when to begin therapy for HIV have fluctuated back and forth, and a prior trend to treat most patients with fewer than 500 cells/mm3 with zidovudine (AZT) was modified by the results of a large randomized study (the Concorde Trial) showing that early AZT therapy did not yield improvement in survival." (Goldman 2000, page 1939)

- When the CD4 count in someone diagnosed HIV-positive is found to be below 200, AIDS is diagnosed. This method currently accounts for over half of all AIDS diagnoses, and so is highly significant (CDC 1999).

- There are two approaches regarding when to start antiretroviral therapy. The more aggressive approach recommends starting when the CD4 count falls below 500, and the second approach is to wait until it is below 350 unless the viral load is also above 20,000 copies per ml. The more aggressive approach is more commonly used in the United States, and many clinicians will even start antiretroviral medications immediately in all patients, regardless of the patient's CD4 counts.

- To prevent pneumocystis carinii pneumonia (PCP), antibiotics should be started if the CD4 count is found to be below 200. The most commonly used combination is sulfamethoxazole/trimethoprim (SMX/TMP), commonly referred to by its brand name, Bactrim.

- To prevent fungal infections, the antifungal medication fluconazole should be started if the CD4 count is below 200.

- To prevent mycobacterium avium complex (MAC) infection, the antibiotics clarithromycin, azithromycin, or rifabutin should be started if the CD4 count is below 100.

- To prevent cytomegalovirus (CMV) infection, oral gancyclovir can be started, although no CD4 level or other guideline is given.
Recent media reports have stated that new recommendations from the National Institute of Health will be presented in February, 2001, calling for a halt to the widespread practice of starting antiretroviral medications immediately, regardless of the patient's health status or CD4 count (Garrett 2001). This marks a retreat from the "hit hard, hit early" approach advocated by David Ho and others since 1996 when protease inhibitor combination therapy was begun. The change is being recommended, according to the reports, because the toxicities of the drugs and the difficulty in staying on them for long periods of time were underestimated.

While most people know about the reports of lowered CD4 levels in people diagnosed HIV-positive, which continue to receive widespread press coverage, other reports concerning lowered CD4 counts in people who are HIV-negative have been widely ignored. These reports show that CD4 counts commonly fall extremely low, especially if a person suffers from certain conditions. These conditions include a variety of viral illnesses, bacterial infections, parasitic infections, sepsis, septic shock, multiple organ system failure, tuberculosis, coccidioidomycosis, burns, trauma, transfusions, malnutrition, over-exercising, pregnancy, normal daily variation, psychological stress, and social isolation. In addition to lowered CD4 counts, other immune system changes occur that are also identical to those seen in people diagnosed HIV-positive, including reduced CD4/CD8 ratios, increased CD8 cells, reduced lymphocyte function, anergy, increased antibody levels, atrophy of lymphoid organs, and general suppression of cell-mediated immunity. These effects can take weeks or months to return to normal, and, if there are recurrent infections or if multiple factors are present, the low CD4 count could take much longer than this to correct, or may even stay low indefinitely. Finally, the drugs used to treat HIV commonly cause a dose dependent immunosuppression, as well as other side effects that can easily be blamed on HIV, and this has been made clear by strongly worded warnings from the drugs' own manufacturers. Several studies that examine these effects will be reviewed here, and studies will be emphasized if they reveal either lowered absolute CD4 counts, lowered CD4 percentages, or a reduced CD4/CD8 ratio, since these are most often thought to be specific to HIV and AIDS.

1) Low CD4 counts in the intensive care unit

In 1995, Feeney et al. looked at CD4 counts in 102 consecutive intensive care unit (ICU) patients who were admitted for a variety of reasons, all of whom were HIV negative. The patients suffered from 34 different illnesses, with the most common being myocardial infarction (heart attack), severe bleeding, renal failure, trauma, and chronic pulmonary disease. 30% of these patients had CD4 counts less than 300, and 41% had CD4 counts less than 400. The authors do not discuss how many had counts below 200, the level resulting in a diagnosis of AIDS, or exactly how many had counts below 500, the level at which antiretroviral medications would be started in someone who has been diagnosed HIV-positive. They also did not find that low CD4 counts were linked with a poor prognosis. Here are the author's comments on their findings.

Our results demonstrate that acute illness alone, in the absence of HIV infection, can be associated with profoundly depressed lymphocyte concentrations. Although we hypothesized that this depression would be directly related to the severity of illness, this was not seen in our results. The T-cell depression we observed was unpredictable and did not correlate with severity of illness, predicted mortality rate, or survival rate. This study was consistent with prior studies that have shown similar decreases in T-cell counts in specific subsets of acutely ill patients. These subsets included patients with bacterial infections, sepsis, septic shock, multiple organ system failure,
tuberculosis, coccidioidomycosis, viral infections, burns, and trauma patients. Most of these studies reported decreases in lymphocyte populations, some of which were severe and included CD4/CD8 ratio inversions...

In the largest study to date of hospitalized patients, Williams et al (1983) evaluated T-cell subsets in 146 febrile patients with serious acute infections... with 19 of 45 patients having a CD4 count of less than 300 per microliter.

We also found that CD4 counts were linearly related to total lymphocyte concentrations, as Blatt et al. (1991) reported in HIV-positive patients. (Feeney et al. 1995, pages 1682-1683)

These researchers did not find that low CD4 cell counts were good measures of prognosis, although some other reports differ in this regard.

2) Low CD4 counts in Various Human Infections

2a) Pneumonia, pyelonephritis, abscesses, infected wounds, cellulitis, and sepsis

In 1983, about one year before HIV was first mentioned as a possible cause of AIDS, Williams et al. published a study showing severely reduced CD4 counts in 146 consecutive people with serious acute infections who were admitted to their hospital in New Mexico. This article was referred to in the article by Feeney et al. that was reviewed above. The infections included pneumonia, acute pyelonephritis, abscesses, infected wounds, cellulitis, deep tissue infections, and sepsis.

The authors only provide average CD4 counts for the majority of patients, except for a graph on page 811 that plots the CD4 counts for all 45 pneumonia patients. This reveals that 31 of 45 (69%) had CD4 counts less than 500 cells/mm3, 19 of 45 (42%) had counts below 300, 13 of 45 (29%) had counts below 200, 6 of 45 (13%) had 100 or less, and 2 of 45 (4%) had values less than 50. The average CD4 count for all the people with pneumonia was 574. Although CD8 cells were mildly reduced, the CD4/CD8 ratio was often inverted as seen in AIDS, and the authors caution against using CD4/CD8 ratios to evaluate AIDS patients: "we caution that because infection itself often results in helper-suppressor ratios of less than 1.0, ratios alone cannot be used to define the presence of profound acquired immunodeficiency" (Williams et al. 1983, page 815).

They provide tables with clinical information and CD4 counts for 9 patients with soft tissue infections (STI) and 12 patients with sepsis/deep infections, all of whom had multiple T-cell abnormalities. Brief descriptions of all the cases from these tables who had CD4 counts less than 200 follow:

- a 25 year-old female with "disseminated varicella", CD4 count of 58, "rapid septic course, death".

- a 41 year-old male with Group A hemolytic streptococcal sepsis, CD4 count of 150, "rapid progression, ... death".

- a 42 year-old male with E-coli sepsis, CD4 count of 156, "Multiple previous episodes of E-coli bacteremia".

- a 38 year-old female with a submandibular abscess, CD4 count of 183, "Gram-positive organism, short 5-day hospital stay".
- a 46 year-old man with peritonitis, CD4 count of 205, who was on long-term peritoneal dialysis.

- a 58 year-old female with infected decubitus ulcers, CD4 count of 189, "prolonged 4-month hospital stay, ... E-coli and pseudomonas organisms".

- 75 year-old female with a common duct stone and ascending cholangitis, CD4 count of 139, "multiple positive blood culture results".

These case examples are notable in that some of them sound very similar to people who die of AIDS, such as the 25 year old female who died of disseminated varicella with a CD4 count of only 58 cells/mm3. Others, such as the 38 year old female with an abscess and CD4 count of 189 who was released after a "short 5-day hospital stay" suggest that many people with extremely low CD4 counts can achieve quick recoveries. It is also remarkable that 30% of people with pneumonia, which is a very common illness in people diagnosed HIV-positive, had CD4 counts below 200, and 70% had counts below 500. These authors did find some correlation between severity of illness and CD4 counts; patients with sepsis who recovered also had gradual increases in CD4 counts, while those that died had counts that remained low.

2b) Low CD4 counts in malaria

Malaria is caused by parasites from the plasmodium species, and is extremely common in Africa and in many tropical areas. In 1999 a letter was published documenting severely lowered CD4 counts in African patients with malaria (Chirenda 1999). The author examined the CD4 count in 78 patients with malaria who were HIV-positive, and 19 who were HIV-negative. He was surprised to find that more HIV-negative malaria cases had severely lowered CD4 counts than did the HIV-positive cases, on average, with 8 of 19 (42%) HIV-negative cases being below 200, while only 31 of 78 (40%) HIV-positive cases had CD4 counts below 200. Seven HIV-negative malaria cases had CD4 counts below 100. This data comes from Table 1. In addition, 6 HIV-positive patients had normal CD4 counts, and the author states, "One may want to hypothesise that malaria reduces the CD4 count more than HIV infection". The author did not do statistical analyses to test for statistical significance, nor does he mention the general health or nutrition status of the patients, which may have contributed to their severely lowered CD4 counts, as will be reviewed later in this paper.

2c) Low CD4 counts in mononucleosis

Mononucleosis, commonly called 'mono', is a common viral illness, especially in young people of college age, and can last for several months. It is caused by cytomegalovirus (CMV) or Epstein-Barr virus (EBV), and usually results in prolonged cold and flu symptoms, swollen lymph nodes, and fatigue. In 1981 a group of researchers looked at CD4 and CD8 counts in ten consecutive patients with acute CMV mononucleosis, and compared their counts with those of ten healthy volunteers (Carney et al. 1981). The CD4 counts in people with mononucleosis were significantly reduced, with the healthy volunteers having 73% more CD4+ cells per ml than did people with mono, on average. The CD8 cells in people with mono were increased, and the combination of lower CD4 counts and elevated CD8 counts resulted in an inverted CD4/CD8 ratio in every patient. The average ratio was only 0.2, compared to the normal average of 1.7 found in controls. The CD4 counts were measured in nine of the ten patients, and the three with the lowest CD4 counts had 194, 202, and 255 cells/mm3. The authors also found that the T-lymphocytes of people with mononucleosis responded poorly to antigens, showing depressed function. this paper was published three years before HIV was first claimed to be the cause of AIDS.
Five years later, a different set of researchers measured various lymphocyte subsets in acute EBV mononucleosis (Junker et al. 1986). They took 17 consecutive patients who had recently been diagnosed, gave them an immunization designed to activate their B lymphocytes, and then took samples of blood. The immunization makes this study different from any of the other studies to be examined here. They did not find a statistically significant lowering of CD4 counts, but they did find significantly lowered CD4/CD8 ratios due to elevated numbers of CD8 cells, with the ratios falling below 1 as commonly occurs in people diagnosed HIV-positive. They also found increased B-cell activity with excess antibody production. Although this increased antibody production is common in many of the conditions that cause lowered CD4 counts, the authors assume that the increase occurs because EBV infects lymphocytes. It appears more likely that increased antibody production is a normal response to a wide variety of physical and psychological stressors. The authors conclude that "these studies demonstrate that infection with EBV affects both B and T lymphocytes and causes a broad based transient immune deficiency in patients with uncomplicated infectious mononucleosis" (Junker et al. 1986, page 436). The immune deficiency was "transient" but long lasting, with CD4/CD8 ratios gradually returning to normal over the course of 4 to 6 weeks.

2d) Low CD4 counts in sepsis

In 1986, a group of researchers from Osaka, Japan published a study where they examined various lymphocyte subsets in 9 consecutive patients admitted to the ICU with sepsis (Nishijima et al. 1986). They examined their blood at weekly intervals for four weeks. The CD4 counts in these patients were markedly reduced, with averages beginning below 500 and staying there for the entire 4 week study period. They also found T-cell function to be diminished, especially in patients who did not survive, although there was no significant difference in CD4 counts between those that died and those that survived. The CD8 cells were also reduced in these patients, and although in AIDS CD8 elevations are considered more typical, in advanced AIDS cases the CD8 count can also be markedly reduced. Because of the serious and life-threatening nature of sepsis, these patients would be more similar to advanced AIDS, and so their immune system profile is likely to be similar. The authors did not provide individual CD4 counts, nor do they present data showing how many patients have CD4 counts below 200, but having an average below 500 is still highly significant. Antiretroviral medications would be started at this time if they had been diagnosed HIV-positive, according to the most widely followed guidelines.

2e) Low CD4 counts in pulmonary tuberculosis

Tuberculosis is a relatively common infection in people diagnosed HIV-positive, especially when compared to the general population. It is also relatively common in other people who are immunosuppressed, such as alcoholics, the homeless, intravenous drug users (IVDUs), and people who suffer from malnutrition. In 1985 a group of researchers in Indonesia examined the lymphocyte subsets in 26 patients newly diagnosed with pulmonary tuberculosis (TB) (Beck et al. 1985). They undertook the study because of a previous report of lowered CD4 counts in HIV-positive patients with TB in which the authors assumed that the lowered CD4 counts were due to HIV. They found that in HIV-negative TB patients CD4 counts were also significantly lowered, with an average of 748, compared to 1,043 in healthy controls. Because the CD8 cells were slightly increased, they also found significantly lowered CD4/CD8 ratios. Although the effects seen here were not as dramatic as in the studies reviewed previously, with only 5 of 26 patients having CD4 counts less than 500, the authors still felt their findings were highly significant to people diagnosed HIV-positive. Here are some of their comments:
In a study of AIDS, Vieira et al. stated that it was possible, but highly unlikely, that tuberculosis or its treatment could have altered the relative numbers of circulating lymphocytes bearing the markers CD4 and CD8, but they dismissed this possibility because of the severity of the altered CD4/CD8 ratio. We now report the relatively frequent occurrence of moderate CD4 lymphopenia in patients with untreated but otherwise uncomplicated pulmonary TB. (Beck et al. 1985, page 50)

The authors also comment on some similar findings in leprosy, as well as in HIV-negative hemophiliacs:

Moderate reduction in the CD4/CD8 ratio has been reported in lepromatous leprosy, which reverts to normal under effective chemotherapy... It is tempting to speculate that these changes are analogous to those we now report in tuberculosis and that they are a consequence of ongoing immune response to the disease... Interestingly, comparable CD4 lymphopenia has been reported in hemophiliacs treated with factor VIII, from a population apparently free from AIDS, and this change has been attributed to a reaction to transfusion of foreign proteins. (Beck et al. 1985, page 53).

The reports of the effects of factor VIII transfusions on CD4 counts have since been confirmed, as will be presented in section 3.

2f) Nearly all viruses interfere with lymphocyte function

In 1987 a summary article appeared in the Annual Review of Immunology entitled simply, "Viruses Perturb Lymphocyte Functions" (McChesney & Oldstone 1987). This article did not look at CD4 counts, but rather focused on the ability of CD4+ T-cells to proliferate when presented with an antigen. The authors reviewed evidence that a multitude of viruses interfere with the ability of CD4+ T-cells to proliferate. Following are some direct quotes from the text:

Viruses with every type of genomic nucleic acid, encompassing divergent replication strategies, are now known to infect lymphocytes. The list (Table 1) of viruses that infect lymphocytes is not comprehensive, but rather indicates representative viruses from different taxonomic groups. With few exceptions, immunologic dysfunction has been associated with the infections. (McChesney & Oldstone 1987, pages 280-281)

The viruses listed in Table 1, that infect human lymphocytes, are: Hepatitis B virus, Group C adenoviruses, Herpes simplex viruses, Cytomegalovirus, measles, mumps, respiratory syncytial virus (RSV), Vesicular stomatitis virus, Influenza A, Parainfluenza, Rubella, Poliovirus, Lymphocytic choriomeningitis virus, and Human T-cell leukemia viruses I and II.

After a lengthy section focusing on the measles virus, they go on to discuss the class of viruses to which HIV belongs, retroviruses:

Retroviruses of murine (mouse), avian (bird), feline (cat), and human origin are immunosuppressive as well as oncogenic in their hosts. The evidence of depressed cellular and humoral immune responses... is independent of the transforming function of the virus... There is no interspecies restriction, i.e.
both murine and feline retroviruses can suppress mouse and human lymphocyte proliferation in vitro. (McChesney & Oldstone 1987, page 287)

The authors go on to describe that it is not necessary for the entire retrovirus to be introduced, but only some of its proteins, so that the depressed response is apparently a passive one that does not require any action on the part of the viruses being discussed.

A partially purified 15-kd structural protein of a feline retrovirus inhibited the proliferation of feline lymphocytes... The inhibition was dose dependent and occurred when the protein was added as late as day 3 of a 4-day culture. In contrast, another structural protein, p27, was not inhibitory. (McChesney & Oldstone 1987, page 287)

Unfortunately, at least for the purposes of this paper, the authors do not discuss CD4 cells, specifically.

3) Low CD4 counts caused by injections of foreign proteins

3a) CD4 irregularities in hemophilia

Hemophiliaacs were one of the original HIV risk groups. As mentioned above, hemophiliaacs who are HIV-negative have been found to have lowered CD4 counts as well as lowered CD4/CD8 ratios, and it appears that this effect is caused by injections of factor VIII. Antonaci et al (1988) for example, found decreased CD4/CD8 ratios as well is impaired CD4 function in HIV-negative hemophiliaacs, stating in their conclusion that "Our findings clearly indicate an impairment of immune function in hemophiliaacs regardless of HIV infection" (page 318). Similarly, Madhok et al. (1986) found depressed cell-mediated immunity that was independent of HIV status. Their abstract contains the following comments:

There was no difference in skin response between patients positive and negative for the human immunodeficiency virus (HIV). In the whole group, and in seronegative patients (n = 17), there was an inverse relation between exposure to clotting factor and skin response. In seropositive patients (n = 12) no such association was apparent. This study shows 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, page 978)

3b) CD4 irregularities caused by injected drugs

Intravenous drug users (IVDUs) are another group with a high risk of being diagnosed HIV-positive. In an article published in 1987 in the journal, AIDS, lymphocytes were found to be reduced in HIV-positive injection drug users as a direct function of how many injections they received (Des Jarlais et al. 1987). The authors comment in their abstract:

Continued drug injection was associated with the rate of CD4 cell loss... While it is not possible to distinguish the mechanism underlying the relationship between continued drug injection and CD4 cell loss, seropositive IV drug users should be warned that continued injections may lead to increased HIV-related immunosuppression. (Des Jarlais et al. 1987, page 105)
A similar finding in 1991, also published in the journal, AIDS, found that lymphocyte reactivity was much more significantly reduced in IVDUs who injected more frequently, regardless of whether or not they were HIV-positive (Mientjes et al. 1991). Although the CD4 cell function was impaired, no difference was found in CD4 counts due to frequent injecting. They did find that HIV-positive IVDUs had lower CD4 counts than did HIV-negative IVDUs, however. The T-cell reactivity was 40-50% lower in IVDUs who were injecting 3 times a day for the preceding several months when compared to a similar group who had not injected in the preceding months, regardless of their HIV status. The authors write: "We conclude that lymphocyte reactivity is depressed by frequent injecting in both HIV-negative and HIV-positive drug users" (Mientjes et al. 1991, page 35).

As far back as 1980, a report in the Journal of Immunology documented lowered T-lymphocytes in IVDUs from Georgia, Illinois, and Massachusetts (McDonough et al. 1980). The authors found that IVDUs in their study had about half to one third as many T-lymphocytes, expressed as a percentage, as control populations. Although they did not look specifically at CD4+ T-lymphocytes, it has been found that when total T-lymphocytes are reduced, CD4 counts are also normally reduced (Kotze 1998). They discuss previous findings of opiate receptor sites on T-lymphocytes, suggesting that the IV opiates were the cause of the lowered T-cells, but they also recognize other possible contributing factors:

Since most street heroin addiction involves polydrug use including chronic use of marijuana, barbiturates, hallucinogens, and other illicit substances, the hypothesis can be proposed that the depression of T-lymphocyte percentage was caused by another drug or combination of drugs, or by the effect of drug use on the addict's general physical health and nutrition, i.e., the addict milieu. (McDonough et al. 1980, page 2542)

The finding that a wide variety of physical and psychological stressors can lower CD4 counts supports this multifactorial argument, in which general health and nutrition can be significant contributing factors.

Finally, a review paper that was published in 1995 in the journal, Immunopharmacology, had an interesting discussion of the significance of this information for IVDUs diagnosed HIV-positive.

Among the unwarranted side effects of respiratory depression, constipation, and physical dependence are the immunosuppressive qualities, particularly those which affect cell-mediated immunity. The immunosuppressive characteristics of opioid narcotics (e.g., morphine) have recently come into focus with the advent of acquired immune deficiency syndrome (AIDS) and the putative causative agent, human immunodeficiency virus type 1 (HIV-1). Specifically, a vast reservoir of HIV-1-infected individuals exists among drug abusers. Moreover, experimental evidence would suggest narcotic opioids may increase viral load in infected individuals. (Carr et al 1995, page 59).

3c) CD4 Irregularities caused by in utero exposure to opiates

In 1987, a study found that infants exposed to intravenous drugs in utero also have decreased CD4/CD8 ratios and reduced CD4 function, even when they are HIV-negative (Culver et al 1987).
The CD4/CD8 ratio decreased with age in the drug-exposed infants compared with control infants (P less than 0.005). Our data demonstrate that infants of intravenous drug-using mothers have distinct immunologic differences at birth compared with non-drug-exposed infants and that these persist throughout the first year of life. The cause appears unrelated to intrauterine viral infection, suggesting a direct toxic effect of the drugs on fetal immunologic development. (Culver et al. 1987, page 230)

These results show that multifactorial causes of low CD4 counts probably apply to all age groups, including newborns. This is especially true in the United States and in Europe where most newborns who are HIV-positive are born to women who use intravenous drugs. In Africa, malnutrition and other infectious diseases are more likely to contribute, as will be discussed below.

4) Low CD4 counts caused by injuries and burns

Several studies over the years have looked at the effects of severe injuries or burns on CD4 counts. An early report appeared in 1982, in which the authors looked at the percentage of CD4 counts in 30 patients admitted to their hospital's burn center (Antonacci et al. 1982). They found that the severity of the burns was directly correlated with depressed CD4 percentages. Patients with greater than 25% of their body covered with 3rd degree burns had the lowest percentages on admission, 37%, as compared to normals who had 63%. They found a similar pattern with the CD4/CD8 ratio, but do not report on absolute CD4 counts.

In 1984, a group of researchers decided to look at lymphocyte subsets in patients with multiple trauma who had no burns (O'Mahoney et al. 1984). They examined the blood of 31 patients and compared their lymphocyte profile to ten normal controls. The CD4/CD8 ratio was significantly reduced and inverted, with an average of 0.96, compared with 1.82 in controls. They also found reduced lymphocyte proliferation/blastogenesis in response to antigen challenges. While their original report said they found no difference in absolute CD4 counts, they report in a postscript that they were mistaken in this regard: "in looking back now at the data, we feel the CD4 population did change relative to the CD8 population because of an absolute decrease in the number of CD4 cells" (O'Mahoney et al. 1984, page 875). The CD8 cells were slightly increased, as is also seen in people diagnosed HIV-positive.

In 1985, a study was published by some of the same researchers that looked at two groups of patients with severe injuries, a group of 25 patients with burns, and a group of 21 patients with non-thermal injuries (O'Mahoney et al. 1985). Both groups had severely lowered CD4 percentages, which persisted until 50 days post-injury when the study was concluded. They also found that people with lower CD4 percentages were more likely to develop sepsis. Here are some of the author's comments:

The most important abnormality appears to be a reduction in CD4 positive cells in burn patients... A change in the ratio of CD4 to CD8 positive cells soon after injury is due to a reduction in CD4 positive cells, not an increase in CD8 positive cells (O'Mahoney et al. 1985, page 584).

We believe that the more important abnormality in the patients studied is a reduction in T-cell help - both in terms of the number of circulating CD4 positive cells and a reduction in interleukin 2 production seen both in burn and non-thermal injury patients. Interleukin 2 is produced by T-cells, especially CD4 positive cells, and promotes their growth and stimulates clonal expansion.
of T-cell subsets: it is thus crucial in the response to foreign antigen.
(O'Mahoney et al. 1985, page 585).

The final study to be reviewed is also quite old, from 1986, and looked at 20 consecutive patients who had emergency surgery due to major trauma (Polk et al. 1986). This was the only study of trauma victims where absolute numbers of CD4 cells are given, which makes it more significant from the perspective of this paper. Figure 7 on page 289 shows that 6 of 20 (30%) patients had CD4 counts below 200 cells/mm3, and 13 of 20 (65%) had counts below 500. The authors state simply: "Total T-cells represent what is interpreted as a normal and common response to injury... All patients had low total lymphocyte counts on admission and exhibited a further decline on day 3" (Polk et al. 1986, page 287). 10 of the patients also had major infections, and three had minor infections, which may have also contributed to their extremely low CD4 counts. This paper is distinctive in that it attempts to explain a mechanism for the lowered CD4 counts, citing a study supporting the hypothesis that increased cortisol levels are responsible for the decline, and that increased cortisol is also a normal response to injury. They also argue that the reduction in CD4+ lymphocytes probably does not represent cell death, but rather redistribution out of the bloodstream and into the tissues. The argument that cortisol plays a key role in lowered CD4 counts will be encountered again in the section on psychological stress.

5) Low CD4 counts in normal human pregnancy

Several studies have been published on CD4 counts during normal pregnancy. Most recently, Burns et al. published a study in 1996, where they attempted to control for potentially confounding factors like the increased blood volume that normally occurs in pregnancy. They used CD4 percentages because of this variable, and determined that "Our CD4 cell findings for HIV-negative women are consistent with the majority of prior studies, which demonstrate a decline in CD4 levels during normal pregnancy" (Burns et al. 1996, page 1465). They also found that HIV-positive women had a more severe decline which did not correct post-partum as it did in HIV-negative women, although they fail to take into account other factors that can cause lowered CD4 counts. These include any infections that the women may have experienced, the traumatic effects of C-sections which are normally performed on HIV-positive women to prevent neonatal transmission, or the potentially severe psychological stress of worrying if their baby will also be HIV-positive, which can take up to 18 months to determine.

In 1989 a study was published of normal pregnancy which found reduced CD4 percentages in the 1st and 2nd trimester, as well as reduced CD4/CD8 ratios in the 2nd trimester (Castilla et al. 1989). They comment on previous studies looking at a variety of lymphocyte changes during pregnancy, stating simply, "In these studies, variation in the number and proportion of CD4+ lymphocytes is the alteration most frequently reported" (Castilla et al. 1989, page 104). The percentage of CD8+ lymphocytes was unchanged. They also claim that "we have accounted for all the presently known factors that can alter the concentrations of T-cell subsets in blood" (Castilla et al. 1989, page 104), but in fact they did not consider any of the factors described in this paper, such as infections, trauma, overexercising, normal daily variation, or psychological stress. This demonstrates that even clinicians and researchers doing studies that focus specifically on CD4 levels are often unaware of how many different conditions cause low CD4 counts.

The final study to be reviewed here is an early one from 1982 (Sridama et al. 1982). These researchers found reduced absolute CD4 counts, as well as reduced percentages of CD4+ T-cells in 76 women with normal pregnancies. By the third trimester, the pregnant women had an average of only $543 \pm 169$ CD4+ T-cells, compared to $1073 \pm 441$ in non-pregnant women who
served as controls. Both the absolute numbers and the percentages stayed low until several months post-partum, and similar results were obtained for the CD4/CD8 ratio which was also reduced. B-cells were increased which is compatible with the increased antibody levels normally found in human pregnancy, and which are also commonly seen in people diagnosed HIV-positive. This is the only study found of normal pregnancy that provides data on absolute CD4 counts, and the average of 543, with a standard deviation of 169, means that a relatively large percentage of these women had levels lower than 500, the point at which antiretroviral medications would be started in someone diagnosed HIV-positive.

6) Reduced CD4 counts from overexercising

Only one study will be discussed in detail here, which was published in 1992 (Verde et al. 1992). In a controlled trial, ten athletes were asked to over-train for three weeks. Blood samples were taken immediately before starting, at the end of the three weeks, and again three weeks after returning to normal. The researchers found steady declines in the percentage of CD4+ T-cells, with the lowest amount occurring 3 weeks after returning to a normal exercise schedule. The authors also found reductions in the CD4/CD8 ratio, although these had normalized by the 3 week endpoint. Finally, the authors also checked levels before and 5 minutes after acute exercise, and again found reductions in CD4 percentages and in CD4/CD8 ratios, although these normalized by 30 minutes post-exercise. It is interesting that a stress as simple as overexercising for three weeks could cause lowered CD4 counts, and that they did not correct for at least three more weeks after returning to a normal exercise schedule.

Other studies have found increased infections in athletes, especially during periods of heavy training or competition, which suggest the presence of "clinically relevant immune suppression in well trained athletes" (Mackinnon 1997).

7) Low CD4 counts in malnutrition

A number of studies have looked at the immunosuppression that results from malnutrition. Like the other conditions covered in this paper, malnutrition causes severe immunodeficiency with depletion of CD4+ T-cells and reduction of cell mediated immunity. One of the most recent studies is from India, where malnutrition is extremely common (Hegde et al. 1999). The authors found that reduced CD4 counts were a natural physiological effect of malnutrition, and comment that both HIV and malnutrition lead to a state of anergy with failure of cell-mediated immunity. They also point out that HIV usually occurs in conjunction with several other stressors of the immune system: "micronutrient abnormalities, concomitant infections, and genetic factors are some of the compounding co-factors which further contribute to the deterioration of immune functions in AIDS patients" (Hegde et al. 1999, page 318).

A review paper from the Journal of Nutrition in 1996 also compares malnutrition and AIDS, saying that "Protein/energy malnutrition or deficiencies of single nutrients that assist in nucleic acid metabolism generally lead to atrophy of lymphoid tissues and dysfunctions of cell mediated immunity" (Beisel 1996, page 2611S). The author comments on a syndrome of immunosuppression caused by malnutrition which is called "NAIDS", and states that it often occurs in people diagnosed HIV-positive:

Immunological dysfunctions associated with malnutrition have been termed Nutritionally Acquired Immune Deficiency Syndromes (NAIDS). Infants and small children are at great risk because they possess only immature, inexperienced immune systems and very small protein reserves. The combination of NAIDS and common childhood infections is the leading cause of human
mortality. NAIDS can generally be corrected by appropriate nutritional rehabilitation, but from a viewpoint highly important to this Workshop, AIDS and NAIDS are intensely synergistic... Aggressive nutritional support for children with HIV infections could delay, or lessen, the development of NAIDS and avoidance of NAIDS would improve both quality and length of life. (Beisel 1996, page 2611S)

Later in the paper they describe some of the immunological changes and clinical courses often seen in malnutrition, which sound very similar to AIDS.

Generalized, protein energy malnutrition causes widespread atrophy of lymphoid tissues, especially in children. The thymus, spleen, tonsils, and lymph nodes are all affected, with evidence of atrophy being greatest in T-lymphocyte areas of these tissues. ...

Malnutrition, in turn, leads to a variety of immune system dysfunctions, ... which allow infectious diseases to flourish. These closely linked events can initiate a "downhill spiral" or a "vicious cycle" that leads inexorably to death.

Protein energy malnutrition causes a marked repression of cell-mediated immunity and the function of T-lymphocytes. Malnourished children show anergy with loss of delayed dermal hypersensitivity reactions and a decrease or reversal of the CD4/CD8 cell ratio... In contrast, B-lymphocyte numbers and functions appear to be maintained. While existing antibody production is conserved or even increased during malnutrition, antibody responses and antibody affinity are impaired. (Beisel 1996, page 2612S)

The "downhill spiral" of opportunistic infections that "lead inexorably to death" is particularly reminiscent of a description of AIDS. Beisel also reviews similar effects of deficiencies of specific nutrients, such as vitamin A and zinc:

Deficiencies of single essential nutrients with important roles in nucleic acid synthesis and metabolism appear to cause derangements in immunological functions that are quite similar to those seen in protein energy malnutrition ... Both vitamin A and zinc deficiencies are characterized by lymphoid tissue atrophy and depressed cellular immunity ... (Beisel 1996, page 2613S)

To provide an idea of how prevalent the problem of malnutrition is worldwide, he points out that the combination of malnutrition induced immunosuppression and childhood infections "is the leading cause of human mortality, producing more than 10 million deaths per year (i.e. over 25,000 deaths per day)" (Beisel 1996, page 2614S).

Another review paper published one year later, in 1997, made similar arguments about the significance of malnutrition in impairing immunity (Chandra 1997). This is the only paper found that gives percentages of CD4 cells, although absolute CD4 counts are still not provided. Figure 3 on page 462S shows that the percentage of CD4+ T-cells in normal well-nourished children is about 45%, while the percentage in malnourished children is only 25%. Chandra describes the immune system changes seen in malnutrition:
Nutrition is a critical determinant of immune responses and malnutrition the most common cause of immunodeficiency worldwide. Work done in the past 25 years has confirmed that impaired immunity is a critical adjunct factor in malnutrition-associated infections. ... Lymphoid atrophy is a dramatic feature of protein energy malnutrition. ... Delayed hypersensitivity cutaneous responses are markedly depressed. It is not uncommon to have complete anergy to a battery of different antigens. These changes are observed in moderate deficiencies as well. The skin reactions are restored after appropriate nutritional therapy for weeks or months. ... the proportion of helper T-lymphocytes (CD4+ T-cells) is markedly decreased, and the ratio of CD4 to CD8 cells is significantly lower than in well-nourished control subjects. (Chandra 1997, page 460S-461S)

From this review it is seen that not only are the CD4 percentages markedly reduced (from 45% to 25%), but that it takes "weeks or months" of nutritional therapy for the effects of malnourishment to revert to normal.

The final article to be examined is also a review (Harbige 1996). This paper mentions similar findings to the ones already discussed, including lowered CD4+ lymphocytes, decreased T-cell function, and anergy. It also mentions the increase in antibody levels which is also seen in people diagnosed HIV-positive, specifically serum IgG, IgM, IgA, and IgD. In contrast to serum IgA, however, secretory IgA is diminished. The main addition that this paper provides which others did not is the mention of specific infections that are particularly common in people who are malnourished:

Among the many infectious organisms commonly associated with protein energy malnutrition are Paramyxovirus (Measles), Rotaviruses, Mycobacterium tuberculosis, E-coli, Shigella, E-histolytica, and Pneumocystis carinii. (Harbige 1996, page 289)

Two of these organisms, M. tuberculosis and Pneumocystis Carinii, result in the diagnosis of AIDS when they occur in someone who has already been diagnosed HIV-positive. Pneumocystis carinii pneumonia, or "PCP", is perhaps the single infection most commonly associated with AIDS in the United States and Europe, while tuberculosis has always been very common in Africa, and is today considered by some to be a common "AIDS defining" illness there.

This information concerning malnutrition-induced immunodeficiency and opportunistic infections is obviously significant for Africa, where malnourishment is common and where HIV is also thought to be the most prevalent, but it also may be very significant for people in the United States and Europe. Several articles point to malnourishment as a very common problem in AIDS due to decreased nutrient intake or malabsorption (Babameto & Kotler 1997, Keusch & Thea 1993). These problems with nutrient intake can be caused by infections of the oral cavity and gastrointestinal tract, which are quite common in people diagnosed with AIDS.

Antiretroviral medications, which cause diarrhea and/or vomiting in well over half of the people who take them, also have the potential to interfere significantly with nutrient intake. In addition, decreased appetite is one of the standard symptoms of depression, which is common in people diagnosed HIV-positive. Many years ago a "giving-in-giving-up" complex was described that can result in people becoming ill and dying before their disease has progressed. A disease like AIDS, with the hopeless description provided to people diagnosed HIV-positive together with the the social stigma that accompanies it, could be particularly susceptible to this phenomenon (Engle 1968). Here are some quotes from a review that focuses on malnutrition in HIV and AIDS, which was published in Gastroenterology Clinics of North America in 1997:
Malnutrition is a common complication of HIV infection and plays a significant and independent role in its morbidity and mortality. Malnutrition was one of the earliest complications of AIDS to be recognized, and unexplained weight loss is one of the most common initial AIDS defining diagnoses to be given to people who were previously diagnosed HIV-positive. ...

The development of malnutrition in clinical disease generally is believed to be secondary to the underlying disease, and improvement is believed possible only by addressing the underlying disease. Studies have shown, however, that the effects of malnutrition in HIV/AIDS are independent of immune dysfunction per se. ...

Malnutrition associated with HIV infection has far reaching ramifications... Many patients become too debilitated to work steadily and come to rely on public or other assistance. Weight loss is often the initiating event in a vicious cycle of increased fatigue and decreased physical activity, including the ability to prepare and consume food. (Babameto & Kotler 1997, pages 393-394)

The authors do not comment on the emotional burden of HIV/AIDS or how this burden may reduce the person's appetite significantly, which could add strength to the "vicious cycle" described above. Finally, infections of any type put a physical stress on the system which results in loss of weight (Scrimshaw & SanGiovanni 1997). This is because people break down their own tissues to use as fuel, resulting in increased nutrient requirements. A review article that examined this issue states:

Infections, no matter how mild, have adverse effects on nutritional status. The significance of these effects depends on the previous nutritional status of the individual, the nature and duration of the infection, and the diet during the recovery period [all of these factors are often adversely affected in people diagnosed HIV-positive]. Conversely, almost any nutrient deficiency, if sufficiently severe, will impair resistance to infection. (Scrimshaw & SanGiovanni 1997)

Based on the articles examined above, it could easily be argued that food, social support, and financial independence are solutions that should be given a much higher priority when offering aid to poorer nations. They also suggest that food, financial independence, and social support should be a much higher priority for HIV and AIDS programs in wealthy nations, as well.

8) Daily variation of CD4 counts

Only one study concerning the daily, or diurnal, variation in CD4 counts will be reviewed here (Malone et al. 1990). The authors compared the diurnal variation in HIV-positive and HIV-negative people, finding a significant variance in both. They found that greater variations occurred in HIV-negative people, but that both groups followed a pattern that coincides with known daily fluctuations of cortisol, with minimum CD4 levels occurring between 8:00 and 10:00 a.m., and maximums occurring at around 10:00 p.m.. Cortisol has a daily variation with maximums at about 8:00 a.m., and, as will be reviewed later in this paper, cortisol also causes low CD4 and total T-lymphocyte counts. People with lower baseline CD4 counts had much less diurnal variation. A flattening of the normal diurnal variation of cortisol, together with elevated average cortisol levels, is often seen in people under chronic psychological stress, and is also common in people diagnosed HIV positive. Babameto & Kotler (1997) state simply "Endocrine alterations in HIV infection include elevations in serum cortisol and loss of the normal diurnal
periodicity" (page 401). They do not comment on the causes of these altered cortisol levels but chronic psychological stress is a possibility given the stress associated with being diagnosed HIV-positive or diagnosed with AIDS. Malone et al.'s study of CD4 variation found that HIV-negative people had an average variation of 506 cells/mm3 each day, while HIV-positive people had only about 60 cells/mm3 of variation. The authors caution that even this blunted variation is significant, however, stating "3 of 12 HIV-positive patients had CD4+ cell counts below 200 cells/mm3 in the morning but had greater than 200 cells/mm3 in the afternoon" (Malone et al. 1990, page 150). In other words, in the morning they would be diagnosed with AIDS, but if their blood was checked in the afternoon they would just be HIV-positive, albeit with a relatively low CD4 count. They found similar results for total lymphocyte counts, but CD4/CD8 ratios did not have statistically significant changes. The authors conclude that blood draws for CD4 counts should always be done at the same time of day, but they do not comment on relations between the diurnal cycle they observed and the diurnal variation in cortisol.

9) Changes in CD4 counts and lymphocyte function due to psychological stress and social isolation

A large number of studies have looked at the effects of stress on the immune system, and several reviews have been published on this topic (Bonneau 1993, Castle 1995, Herbert 1993, Kennedy 1988, Kiecolt-Glaser 1984, 1991, 1992 Laudenslager 1983, Pariante 1997, Stefanski 1998). These studies have looked at people under chronic stress, such as people suffering from depression, people who were recently divorced or separated, college students during exams, and people who are the primary caregivers of demented family members. There are also a number of studies of animals under stress. Stress causes a state of immunodeficiency characterized by a reduction of the number of T-lymphocytes, with special targeting of CD4, helper T cells. There is also a reduced CD4/CD8 ratio, with a relative increase in CD8, suppressor/cytotoxic T cells. Unfortunately for the purposes of this paper, the vast majority of studies look at lymphocyte function and total T-cell counts. The few studies that have looked at CD4 cells used percentages (Kiecolt-Glaser et al. 1992).

A group of researchers led by Robert Sapolsky has done a great deal of work observing the effects of psychological and social stress on baboons and other primates, with most of their work focusing on the neurotoxicity that is caused by stress, with dementia and loss of neurons in the hippocampus (Sapolsky 1990, 1996). In one study, however, they measured total lymphocyte counts and cortisol levels in a group of baboons that were invaded by a highly aggressive young male baboon, whom they named Hobbs (Alberts et al. 1992). Hobbs was particularly threatening to females in the group, and was apparently attempting to use fear, physical intimidation, and abuse to increase his chances of successful mating. Cortisol levels in the group nearly doubled after Hobbs joined the group, with a slightly greater increase among females. T-lymphocytes plummeted in the group, from a pre-Hobbs level of 67 per 10,000 red blood cells to a level of about 39, a drop of 42%. When looking at only the levels in baboons who were victims of Hobbs' aggression, the levels fell even more steeply, to only 29 per 10,000 RBC's, a drop of 55%.

Interestingly, Hobbs, himself had the lowest number of lymphocytes in the entire group, and the highest cortisol level, suggesting that his behavior may have been taking an even greater toll on his system than it did on the victims of his aggression. Field conditions prevented them from determining the number of lymphocytes per microliter of blood, or from specifically measuring CD4 cells, and the authors comment on their use of lymphocyte counts instead of more sophisticated methods:

Whereas most studies of the effects of stress upon immunity examine functional indices of immune competence (e.g. mitogen stimulation tests,
antibody generation, cytokine responsiveness), our field conditions limited us to this rather crude quantitative measure of numbers of cells. (Alberts 1992 page 174)

It is interesting that these researchers consider T-cell counting to be a crude measure of immune competency. Although the clinicians in this study could not report on CD4 counts, low total lymphocyte counts are associated with low CD4 counts (Kotze 1998), so the findings of this study are likely to indicate that CD4 counts are also lowered.

A review from as far back as 1988 also examined how the immune system was affected by stress, with the following comments regarding CD4 helper T-cells (Kennedy et al. 1988):

Data are given which document immunosuppressive effects of commonplace, short-term stressors, as well as more prolonged stressors, such as marital disruption and caring for a relative with Alzheimer's disease. Immune changes included both quantitative and qualitative changes in immune cells, including changes in herpes virus latency, decreases in the percentages of T-helper lymphocytes and decreases in the numbers and function of natural killer cells. These effects occurred independently of changes in nutrition. Psychological variables, including loneliness, attachment and depression were related to the immune changes. The data are discussed in a framework in which quality interpersonal relationships may serve to attenuate the adverse immunological changes associated with psychological distress, and may have consequences for disease susceptibility and health.’ (Kennedy et al. 1988, page 77).

Another review, published in 1993, performed a meta-analysis of all studies that looked at psychological stress and the immune system (Herbert & Cohen 1993). In their discussion they mention their findings regarding CD4 helper T-cells:

In terms of cell numbers, stress is reliably associated with a ... lower number of circulating B cells, helper cells, cytotoxic cells, and large granular lymphocytes. Stress is also reliably associated with a lower percent of lymphocytes that are T cells, helper T cells, and cytotoxic T-cells. (Herbert & Cohen 1993, page 373)

The last review to be discussed here looked at short-term stressor effects and made similar comments to the two reviews above, again focusing on CD4 percentages instead of absolute CD4 counts:

The immunological changes observed following short-term stressors are very similar to those that have been described following epinephrine injections: increased percentages of natural killer cells, decreased blastogenesis in response to mitogens (decreased lymphocyte function), and decreased percentages of CD4 cells. Total T cells and monocytes did not change. (Kiecolt-Glaser et al. 1992, page 680)

This quote mentions epinephrine injections, but cortisol injections also produce similar effects on the immune system. Secretion of these hormones is the most commonly proposed mechanism for the immunosuppression that occurs during states of acute or chronic psychological stress. One of the major changes during times of stress is an outpouring of the hormones epinephrine and cortisol, which lead to a dramatic reduction in the number of T-lymphocytes.
The strength of the correlation between decrease in T-cells and excess cortisol is so strong that low T-cells is one of the diagnostic criteria for identifying excess cortisol. Here are some quotes on this topic from a basic textbook of physiology (Guyton 1996).

Almost any type of physical or mental stress can lead within minutes to greatly enhanced secretion of ACTH and consequently cortisol as well, often increasing cortisol secretion as much as 20-fold (Guyton 1996, p.966).

Cortisol suppresses the immune system, causing lymphocyte production to decrease markedly. The T lymphocytes are especially suppressed. (Guyton 1996, p.964)

Cortisol decreases the number of eosinophils and lymphocytes in the blood; this effect begins within a few minutes of injection of cortisol and becomes marked within a few hours. Indeed, a finding of lymphocytopenia or eosinopenia is an important diagnostic criterion for overproduction of cortisol by the adrenal gland. Likewise, the administration of large doses of cortisol causes significant atrophy of all the lymphoid tissue throughout the body... This occasionally can lead to fulminating infection and death from diseases that would otherwise not be lethal, such as fulminating tuberculosis in a person whose disease had previously been arrested (Guyton 1996, p.965).

It is interesting that this description of 'fulminating infection and death from diseases that would otherwise not be lethal' sounds very similar to a description of AIDS. Cecil's Textbook of Medicine also discusses the specific lowering of CD4 counts that corticosteroids cause:

A significant T lymphocytopenia occurs with a selective egress from the circulation of CD4+ "helper-inducer" T cells, whereas CD8+ "cytotoxic-suppressors" T cells are relatively resistant to these effects (see Chapter 270). B lymphocytes are less susceptible to glucocorticosteroid-induced effects than T cells, with little alteration in intravascular number or composition. ... A variety of lymphocyte functions, including activation, proliferation, and differentiation, are sensitive to glucocorticosteroids. Although glucocorticosteroids do not affect T-cell activation, down-regulation of RNA synthesis decreases proliferation. ... Unlike T cells, B-lymphocyte function is only modestly affected by glucocorticosteroids. Within 1 month of glucocorticosteroid therapy, reduction in serum immunoglobulins is noted because of increased catabolism. Antibody responses to injected antigens are not impaired. (Goldman 2000, page 111)

This sounds exactly like what is described in AIDS, with selective lowering of CD4 counts, normal or increased CD8 counts, and normal or increased antibody titers in the early stages. The similarity is so striking that one cannot help but wonder if factors that increase cortisol, such as chronic and severe psychological stress, could be major players in the immunosuppression observed in AIDS. What is even more curious, however, is that cortisol analogues are often used in people diagnosed with AIDS to treat conditions such as *pneumocystis carinii* pneumonia, a topic that will be discussed in the next section, entitled "Immunosuppression caused by drugs used in the treatment of people diagnosed HIV-positive".

There is a disease which is characterized by long-term hypersecretion of cortisol, called Cushing's syndrome or Cushing's disease. Cecil Essentials of Medicine describes the physical manifestations of Cushing's disease, many of which are also common in AIDS:
Regardless of the etiology, hypercorticolism results in central obesity, carbohydrate intolerance, muscle wasting, and osteoporosis. Obesity is centripetal, manifested typically by a "buffalo hump", increased supraclavicular fat pads, and moon facies... Depression occurs often, and, rarely, patients may be frankly psychotic. (Andreoli et al. 1993)

Muscle wasting, depression, and dementia-associated psychosis are all relatively common findings in people diagnosed with AIDS. Cushing's disease also causes immunodeficiency (Britton et al. 1975) and dementia with loss of cortical neurons (Starkman et al. 1992), both of which are characteristic of people diagnosed with AIDS. It is also interesting that the redistribution of fat described here is a common side effect seen in HIV-positive patients after long-term protease inhibitor use, with the same "buffalo hump" and central obesity, which has been referred to as a "protease paunch". Early osteoporosis has also been recently found to be another common adverse effect of these medications.

Multiple studies have found that people diagnosed HIV positive have chronically elevated cortisol levels, suggesting that the low CD4 T-cells in people diagnosed with AIDS could be at least partly caused by elevated cortisol (Azar 1993, Christeff 1988, 1992, Coodley 1994, Lewi 1995, Lortholary 1996, Membreno 1987, Norbiato 1996, Norbiato 1997, Verges 1989). It is important to note, however, that chronic stress can induce immune suppression even when cortisol and epinephrine are not elevated (Bonneau 1993, Keller 1983), so that the mechanisms by which stress affects health and immunity are not completely understood.

In 1998, a group of researchers put the stress-cortisol hypothesis to the test by checking CD4 counts and cortisol levels in people who were randomly assigned either to a bereavement support group intervention or to a wait-list control (Goodkin et al. 1998). The intervention consisted of 10 weekly support group meetings, and blood samples continued to be taken periodically for a total of 6 months. Some of the group members were HIV-positive, and the authors stratified their data according to HIV status. They found that CD4 counts were increased in people receiving the support group intervention as compared to controls, and that these increases correlated with reduced levels of the stress hormone cortisol. Here is their description of the results:

In HIV-negative intervention subjects, the CD4 cell count increased 112 cells/mm3, while that in HIV-negative control subjects decreased 88 cells/mm3, for a difference of 200 cells/mm3 between treatment and control groups. In treated HIV-positive individuals, the CD4 cell count was stable, within laboratory error over the entire six months. However, that in HIV-positive controls decreased 61 cells/mm3. Both (statistical tests) demonstrated a statistically significant intervention effect on the CD4 cell count. (Goodkin et al. 1998, page 387)

Results like these may help to explain why socially isolated people, when compared to people with high levels of social support, have been found in over eight studies to have between double and triple the death rates from all causes (Berkman 1979, House 1988, Ornish 1997). A recent study found that people diagnosed HIV positive were two to three times more likely to 'progress to AIDS' if they were socially isolated and under high levels of stress (Leserman et al. 1999). Here is a brief quote from the abstract of their paper:

Faster progression to AIDS was associated with more cumulative stressful life events (p=0.002), more cumulative depressive symptoms (p=0.008), and less cumulative social support (p<0.0002). ... At 5.5 years, the probability of getting AIDS was about two to three times as high on those above
the median on stress or below the median on social support. ... (Leserman et al., page 397)

This study was not able to assess the impact of the stress of living with the diagnosis, HIV-positive, nor can any study that is ethically designed. It is not unreasonable, however, to infer that the stress of the diagnosis is a strong contributor to immunosuppression in people diagnosed HIV-positive, and even a contributor to mortality.

In addition to the cortisol hypothesis, another mechanism has been presented in a paper in the journal, Medical Hypothesis (Shallenberger 1998). The author presents a multifactorial model of AIDS in which the immune system becomes overbalanced towards antibody-mediated immunity (AMI) when it is chronically stressed. He does not feel that HIV is necessary to create this imbalance, and cites similar evidence to what has been cited here. When AMI becomes dominant, the cytokines released by this arm of the immune system (interleukins 4 and 10) naturally suppress the other arm, called cell-mediated immunity (CMI). CMI uses CD4+ cells in abundance, and when it is suppressed the CD4 count will drop. If the AMI dominance is maintained long enough it can become pathological and be very difficult to reverse, eventually leading to failure of both AMI and CMI, according to Shallenberger. His arguments are supported by the fact that people who are diagnosed HIV-positive invariably have high levels of antibodies, even when their CD4 counts have dropped significantly. Shallenberger carefully documents that evidence of this phenomenon occurs in all the risk groups for HIV, whether or not they are HIV positive, including hemophiliacs, male homosexuals, IVDUs, and transfusion recipients. This AMI dominance mechanism could still be mediated, at least in part, by excess cortisol secretion, but the author does not discuss the cortisol hypothesis in his paper.

10) Immunosuppression caused by drugs used in the treatment of people diagnosed HIV-positive

Many drugs regularly used to treat people diagnosed HIV-positive have severe immunosuppressive effects, as well as other serious adverse effects. These include corticosteroids, AZT, other drugs in the same class as AZT, certain antibiotics, and protease inhibitors. People diagnosed HIV-positive take these drugs indefinitely, which increases the risks of adverse effects significantly.

Corticosteroids, as described above, cause an immunosuppression that is extremely similar to the immunosuppression that is claimed to be caused by HIV, with lowered CD4 counts and sparing of CD8 cells as well as sparing of antibody production. In spite of this, corticosteroids are commonly used in people diagnosed HIV-positive to treat conditions like Pneumocystis carinii pneumonia, as the following quote from Cecil's Textbook of Medicine demonstrates:

The major breakthrough in the search for more effective therapies for Pneumocystis has been the irrefutable evidence that mortality for severe episodes can be reduced nearly twofold by use of corticosteroids within 72 hours after beginning specific anti-Pneumocystis therapy. (Goldman 2000, page 1882)

Thus corticosteroids have been found to reduce mortality from what is perhaps the most common serious infection in people diagnosed with AIDS, and at the same time they cause the exact same immunosuppression that is supposedly allowing Pneumocystis to flourish. This seeming contradiction is very difficult to explain, at least if it is true that low CD4 counts are truly the primary problem in people diagnosed HIV positive.

Other medications used to treat people diagnosed HIV-positive, such as AZT and protease inhibitors, also have immunosuppressive effects. AZT, also called Retrovir or
zidovudine, continues to be the most commonly used drug in people diagnosed HIV-positive. Up until 1996 it was used alone as a monotherapy, and it was given at a dose that is about triple the dose used today. In 1996 it began to be used in combination with other drugs such as protease inhibitors, and the dose was reduced significantly. Many other drugs that are often used in combination with AZT use the same basic mechanism as AZT and have similar toxicities, including ddi, ddC, 3TC and d4T. The most severe effect of AZT is a lowering of the number of neutrophils, which are the most numerous cells of the immune system, as well as lowering eosinophils, basophils, red blood cells, and platelets. The elimination of neutrophils, eosinophils, and basophils, which are all critically important cells of the immune system, is called "granulocytopenia". If the number of neutrophils is lowered, this is called "neutropenia". If someone suffers from granulocytopenia, they also by definition suffer from neutropenia. Neutropenia and granulocytopenia are also common complications of cancer chemotherapy. The clinical course of severe neutropenia, as described in the basic pathology textbook, *Pathologic Basis of Disease* (Robbins et al. 1994), describes what happens to people with severe neutropenia.

**CLINICAL COURSE:** The symptoms and signs of neutropenias are those of bacterial infections. ... In severe agranulocytosis with virtual absence of neutrophils, these infections may become so overwhelming as to cause death within a few days. (p.631).

This sounds quite similar to a description of AIDS. Later stages of HIV infection are often associated with neutropenia as well as low CD4 counts. This may be why many of the AIDS defining diseases are bacterial infections, which are not considered typical infections in people suffering from low CD4 counts and a specific loss of cell-mediated immunity. Robbins (1994) uses italics to highlight the following statement about neutropenia: "the most severe forms of neutropenias are produced by drugs" (Robbins et al 1994, page 630). This is especially true when the drugs are given for long periods, as is true in people diagnosed HIV-positive.

While AZT and other drugs used in combination therapy do not cause low CD4 counts in the short term, it is probable that long term use will also lower CD4 counts significantly, especially if it is given for long periods. This finding has been ignored because the original study of AZT's toxicity to CD4 lymphocytes claimed that very high concentrations, much higher than concentrations used in clinical practice, were needed before CD4+ lymphocytes were affected. What is not mentioned in the Physician's Desk Reference is that AZT has been found in five studies performed afterwards to be equally toxic to CD4+ T lymphocytes. These later studies found that AZT was toxic to CD4 lymphocytes at about the same dosage that is given to people diagnosed HIV-positive (Duesberg 1992).

Glaxo Wellcome puts the following warning in bold-faced, capital letters at the start of the section in the 1999 Physician's Desk Reference that describes AZT.

**ETROVIR (ZIDOVUDINE) MAY BE ASSOCIATED WITH SEVERE HEMATOLOGIC TOXICITY INCLUDING GRANULOCTYPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS ALSO BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY SIMILAR TO THAT PRODUCED BY HUMAN IMMUNODEFICIENCY VIRUS. (PDR 1999).**

An earlier version of the Physician's Desk Reference, published in 1992 made the connection even clearer:
It is often difficult to distinguish adverse events possibly associated with Zidovudine administration from underlying signs of HIV disease or intercurrent illness. (PDR 1992)


Because of the complexity of this disease state, it is often difficult to differentiate between the manifestations of HIV infection [sic] and the manifestations of zidovudine (AZT). In addition, very little placebo controlled data is available to assess this difference. (United States 1996, pages 3032-3034)

Granulocytopenia means a deficiency of the most numerous cells of our immune system, which in turn leads to opportunistic infections that can become "so overwhelming as to cause death within a few days" (Robbins et al 1994, page 631). Thus, AZT, by its maker's own admission, can attack a person's own immune system, which is the very thing that HIV is supposedly attacking.

In an article in the journal, *Nature Medicine* in 1998, the author argues that the initial rise in CD4 count after starting on antiretroviral medications does not represent any decreased killing of CD4+ T lymphocytes, but rather represents shifting of available cells out of the tissues and into the bloodstream (Roederer 1998). The increased T-cell count created by the use of AZT was shown to have no bearing on survival in the best and most well-controlled study available on AZT, the Concorde Study (1994). The Concorde study, which was originally published in the *New England Journal of Medicine* in 1992, found that people who were given AZT earlier died faster even thought their CD4 counts were higher, although the difference in death rates were not statistically significant (Henderson et al. 1992). Recent evidence shows that AZT and several protease inhibitors specifically inhibit microbes that commonly cause infections in people diagnosed HIV-positive. Protease inhibitors, for example, inhibit *Pneumocystis carinii* and *Candida albicans*, two of the most common infections found in people diagnosed HIV-positive (Cassone 1999, Atzori 2000). AZT inhibits many different strains of bacteria, including *Enterobacter*, *Shigella*, *Salmonella*, *Klebsiella*, *Citrobacter*, and *E-coli*, and AZT also acts synergistically with commonly used antibiotics such as Bactrim (PDR 1999). Unfortunately, the antimicrobial effects may be short lived as the following statement indicates: "Limited data suggests that bacterial resistance to zidovudine (AZT) develops rapidly" (PDR 1996, page 1158). It is possible that these drugs may inhibit many other microbes as well, but studies looking at their effects on most microbes have not been done. The finding that they attack microbes may explain the rises in CD4 counts that people on these drugs experience in the short term, since infections with these microbes are associated with extremely low CD4 counts even in the absence of HIV infection. As bacterial resistance develops in the microbes and they again flourish, however, the CD4 count would naturally begin to fall. It is also possible that the immunosuppressive effects of long-term administration of anti-HIV medications could bring the CD4 count down along with the other white cells.

An example of a study that documented the toxic effects that AZT has on healthy people's immune systems was published in the *Annals of Hematology* in 1994 (Schmitz et al. 1994). AZT was given to 14 health care workers who had been exposed to HIV-contaminated blood through needle sticks and similar accidents. This type of study is important because the toxicity observed cannot be blamed on HIV, as is quite likely to happen in people diagnosed HIV-positive. None of the 14 workers actually became HIV-positive as a result of their needle stick, which is not surprising since the likelihood of contracting HIV is estimated at about 1 in 333, which is even less than the probability of finding someone who is HIV-positive when randomly picking from the general population. Fully half of the 14 workers had to quit the drug
because of severe toxic effects, and the study was stopped early because of these effects. Only 11 of the 14 people could continue to take the drug for more than four weeks. Neutropenia developed in 36% (4 of 11) of the people who completed 4 weeks of AZT treatment. The three people who could not make it to four weeks dropped out due to "severe subjective symptoms". What is truly remarkable in this study is that these side effects developed in only 4 weeks, while patients diagnosed HIV-positive often stay on AZT and other similar drugs for years.

Other drugs commonly used with people diagnosed HIV-positive have similar immunosuppressive effects. Didanosine (ddI or Videx), is listed in the Physician's Desk Reference (1999) as causing granulocytopenia in 25% of children who had normal values to begin with, and in 62% of children whose values were already abnormal. In adults, 8% experienced "serious" levels of granulocytopenia, compared to 15-19% in patients treated with AZT. Perhaps more significantly, between 13% and 16% experienced serious levels of "leukopenia", which involves reductions of all white blood cells including lymphocytes. The most serious adverse effects of didanosine, as well as lamivudine (3TC or Epivir), stavudine (d4T or Zerit), and zalcitabine (ddC or Hivid), which are all in the same class of drugs as AZT, however, are dose dependent peripheral neuropathy and pancreatitis. Although these effects are unlikely to be blamed on HIV, pancreatitis is a life threatening condition. In Phase 1 trials of didanosine pancreatitis occurred in 9% of people given doses in the range currently used, and it occurred in 27% of people given higher doses. Peripheral neuropathy was even more common, occurring in 51% of people on the higher dose and 34% of people in the dose range commonly used today.

Finally, the drug used to treat and prevent CMV retinitis, gancyclovir, has serious immunosuppressive effects, with a similar bold faced warning in the PDR to what was seen in the section on AZT:

"THE CLINICAL TOXICITY OF (GANCICLOVIR) INCLUDES GRANULOCYTOPENIA, ANEMIA, AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC, AND CAUSED ASPERMATOGENESIS" (Page 2104).

According to current treatment guidelines, gancyclovir is supposed to be started in all people diagnosed HIV-positive if their CD4 counts fall below 100, or if they are diagnosed with CMV retinitis. They are supposed to continue weekly injections of gancyclovir indefinitely, until they die.

An article in the New England Journal of Medicine looked at the muscle wasting, or myopathy, which is caused by AZT, and compared it to muscle wasting that has been presumed to be caused by HIV (Dalakas et al. 1994). Their comments in the abstract indicate a major problem:

We conclude that long-term therapy with Zidovudine can cause a toxic mitochondrial myopathy, which... is indistinguishable from the myopathy associated with primary HIV infection... (Dalakas et al 1994, page 1098).

Robbin's text on pathology also contains sections on mitochondrial myopathy, stating that this kind of muscle wasting results in severe weakness. Because it is also associated with neurological symptoms such as dementia, according to Robbins, mitochondrial myopathies "may also be classified as mitochondrial encephalomyopathies" (Robbins et al. 1994, page 1290). Encephalomyopathy, in lay language, means widespread damage to the brain and spinal cord.

Although most retrospective studies have not found AZT to be associated with "HIV dementia, retrospective studies are uncontrolled and thus open to many confounding variables and biases. One of the better controlled studies did find that "HIV dementia" was twice as likely
to happen in people taking AZT. In this study, published in the journal *Neurology* (Bacellar et al 1994), the authors state:

> Among subjects with CD4+ cell counts < 200/mm3, the risk of developing HIV dementia among those reporting any antiretroviral use (AZT, ddI, ddC, or d4T) was 97% higher than among those not using this antiretroviral therapy. (page 1895)

Because the authors include only people with low CD4 counts in their comparison, it is less likely that people took AZT because they were already sick. They go on to discuss peripheral neuropathy, which is a degeneration of sensory nerves:

> In addition, the findings of our analysis seem to confirm previous observation of a neurotoxic effect of antiretroviral agents. Numerous studies have linked the use of ddI, ddC, and d4T to the development of toxic sensory neuropathies, usually in a dose-response fashion. (page 1895).

These studies are but a sample of the evidence that suggest that AZT and other anti-HIV drugs used as monotherapy or as parts of protease inhibitor cocktail regimens are causing a variety of AIDS-like symptoms which are being blamed on HIV.

11) Unexplained low CD4 counts and "Idiopathic CD4 T Lymphopenia"

In 1992 the Centers for Disease Control (CDC) in Atlanta introduced a new condition characterized by unexplained low CD4 counts in the absence of HIV infection. They called this syndrome "idiopathic CD4 T lymphopenia" (ITL). Bird (1996) provides an excellent summary of this condition, which he calls "Non-HIV AIDS" or "Non-HIV associated immunodeficiency". He concludes that it is distinct from HIV associated immunodeficiency, but he overlooks a number of key points. Several of these points will be reviewed in detail.

Although Bird (1996) does consider the effects of infections on CD4 counts, he fails to take into account most of the conditions reviewed in this paper, such as malnutrition, trauma, burns, intravenous injections of foreign proteins, over-exercising, pregnancy, corticosteroid use, normal daily variation, psychological stress, and social isolation. He also fails to point out that infections alone could easily explain the low CD4 counts found in people diagnosed HIV-positive, who often experience chronic or recurring infections of various types. In addition, malnutrition, injections of foreign proteins, and chronic severe psychological stress are all common in people diagnosed HIV-positive.

It appears that one of Bird's major purposes in writing his paper was to refute the positions of several researchers who question the significance of HIV in causing AIDS. These arguments were being reinvigorated by the discovery of people with low CD4 counts who were HIV negative. Following are the primary positions which Bird attempts to refute:

1) AIDS is multifactorial with multiple causes. This has been argued by many clinicians and researchers such as Joseph Sonnabend, who has been working with people diagnosed HIV-positive since before HIV was first claimed to cause AIDS (Sonnabend 1984).

2) HIV needs cofactors to become active, a position advocated by the discoverer of HIV, Luc Montaignier, and others (Grau 1998).
3) Other factors are the only significant ones, and HIV is an opportunistic virus that does not cause AIDS or immunosuppression of any kind. This stance is maintained by a number of prominent researchers including Peter Duesberg, the retrovirologist who first mapped out the genetic code of retroviruses, and David Rasnick, who holds a number of patents in protease inhibitor research (Duesberg & Rasnick 1998).

Although Bird's paper is thorough in many ways, he overlooks much of the information presented above, and also contradicts itself several times. In the beginning of his paper, he presents a description of how the occurrence of "non-HIV AIDS" was first discovered and made public:

The unexpected announcement of the Eighth International AIDS Conference, that the US CDC in Atlanta was investigating a series of reported cases of AIDS in which HIV did not seem to be implicated, rekindled many of these issues. At this conference the possibility was discussed that many AIDS cases might not be caused by HIV. (Bird 1996, pages 171-172)

The majority of cases classified as non-HIV AIDS or CD4+ lymphopenia have been detected following investigation of clinical signs which suggest cellular immunodeficiency. The patients have presented with a history of severe or recurrent infections with intracellular pathogens or virus-associated malignancies which, even before the description of AIDS, were recognised as being highly suggestive of underlying deficiency of cell-mediated immunity. Indeed, it was this constellation of clinical features ... that clearly identified a new clinical entity of AIDS. (Bird 1996, page 173)

After this comparison which reveals just how similar the two conditions are, he goes on to make a similar admission regarding pneumocystis carinii pneumonia:

Indeed, pneumocystis carinii was first identified as a pathogen amongst severely malnourished (and thus immunodeficient) populations in continental Europe immediately following the Second World War. (Bird 1996, page 173)

Bird does not mention that malnutrition is characterised by exactly the same type of immunodeficiency seen in AIDS, with low CD4 counts, increased immunoglobulins, and severely depressed cell-mediated immunity. He also does not mention how common malnutrition is in people diagnosed HIV-positive (Babameto & Kotler 1997, Keusch & Thea 1993). After these statements describing the similarities between non-HIV associated immunodeficiency and AIDS, he makes several statements in an attempt to distinguish the two. These will be addressed individually.

He states that "the condition (non-HIV associated immunodeficiency) remains exceptionally rare" (Bird 1996, page 176). Even considering only malnutrition, which has a state of immunodeficiency that is very similar to what is seen in AIDS, this statement appears questionable. As outlined above, malnutrition is the leading cause of immunodeficiency worldwide, can be caused by repeated infections, and is very common in people diagnosed with AIDS regardless of their financial status. Other conditions that are associated with very low CD4 counts, such as sepsis, pneumonia, and mononucleosis, are also quite common. Sepsis causes over 100,000 deaths per year in the United States alone, affects young and old alike, and is characterized by markedly lowered absolute CD4 counts, as outlined previously.

Another statement that attempts to distinguish between non-HIV AIDS and HIV-induced AIDS is that "most non-HIV immunodeficiency cases have normal or low immunoglobulin levels and also have low CD8 counts" (Bird 1996, page 175). Nearly all of the conditions outlined
above were characterized by lowered or inverted CD4/CD8 ratios, showing that CD8+ T-cells at the very least are affected much less than CD4 cells. In many of the conditions discussed above, especially infections, CD8+ T-cells are usually either significantly elevated or normal. Bird himself admits this later in his paper:

Low CD4 counts have been reported as a transient or long-lasting feature of a number of acute and chronic infectious diseases. However, in most cases the effect is to lower the percentage of CD4+ cells as a result of increased CD8 cells, rather than as a consequence of absolute reduction of CD4 cells. (Bird 1996, page 179)

Here he not only admits that CD8 cells are often elevated in a wide variety of common human infections, but also makes another serious misstatement regarding CD4 counts. The studies reviewed in this paper clearly show that absolute numbers of CD4+ T-cells are commonly reduced in various human infections, often severely so, in spite of Bird's claim to the contrary. While it is true that CD8 counts were reduced in septic patients, this reduction is often seen in very advanced stages of AIDS, and sepsis is an extremely serious condition which is more comparable to advanced stages of AIDS than it is to earlier stages. Although most studies reviewed did not discuss immunoglobulin/antibody levels, which Bird says are "low or normal" in non-HIV AIDS, malnutrition, which is perhaps the most common condition that occurs in people diagnosed with AIDS, is characterized by increased antibody levels, as described previously. Bird also does not consider that in late stages of AIDS a complete immune collapse is often seen, with lowered CD4, CD8, and immunoglobulin levels, so the use of these parameters to attempt to distinguish non-HIV and HIV acquired immunodeficiency is not particularly reliable.

Bird also states "whereas some cases (of non-HIV associated immunodeficiency) have had a fulminant and fatal outcome, others have been associated with longer term survival associated with stabilisation or reversal of the immunodeficiency" (page 175). Even if a minority of people with non-HIV associated immunodeficiency experience a "fulminant and fatal outcome", however, this is enough to suggest that possible causes of this outcome should be carefully studied. The information obtained from such a study has the potential to provide a great deal of help to people diagnosed HIV-positive, especially considering the studies reviewed above which show how common the conditions associated with low CD4 counts are in this population. Even Bird's stance that "longer term survival" somehow distinguishes them is questionable, however. Long term survival and reversals of CD4 counts are also very common in people diagnosed HIV-positive, although people with progressive downhill courses have received more attention. The average time between a diagnosis of HIV-positive and diagnosis of AIDS is estimated at about ten years, which was based on studies conducted when an opportunistic infection had to be present to diagnose AIDS, i.e. low CD4 counts could not be used for the diagnosis. Between 5 and 15% of people diagnosed HIV-positive never even show immunological abnormalities (Learmont et al. 1992, Ashton et al. 1998, Walton 1999). Finally, at the time of Bird's writing (1996), non-HIV AIDS had only been recently discovered so the potential for a long term outcome could not be determined accurately. Protracted courses with increases and decreases of CD4 counts have always been a common occurrence, even before the introduction of protease inhibitors.

Another statement of Bird's attempts to explain why non-HIV associated immunodeficiency was clustered around AIDS risk groups:

Although groups at risk of HIV infection appear to be over-represented amongst the early case reports, these almost certainly represent an ascertainment
bias. ... Many of these cases, had they occurred in the general population, might otherwise have escaped detection. (Bird 1996, page 176)

The problem with this line of reasoning is that it also applies equally well to HIV and AIDS, because HIV tests were only routinely given to people in the identified risk groups. It is likely that a very high percentage of people who die of sepsis, multiple trauma, pneumonia, tuberculosis, and malnutrition would qualify for a diagnosis of AIDS based on their clinical and immunologic picture. Indeed, the only obvious difference between them is the result that they have on the HIV antibody tests. Thus a similar ascertainment bias appears to be present in the exclusive focus on HIV. A similar problem exists with Bird's next point regarding non-HIV associated immunodeficiency:

The other issue that needs to be considered is whether the low CD4 counts reported in individual patients could be secondary to their particular infections rather than responsible for them. (Bird 1996, page 177)

The problem here is that people diagnosed HIV-positive are even more likely than others to have lowered CD4 counts "secondary to their individual infections", so this is a very poor distinguishing feature. In Bird's own words, as cited previously, "The patients (with non-HIV AIDS) have presented with a history of severe or recurrent infections ... which, even before the description of AIDS, were recognised as being highly suggestive of underlying deficiency of cell-mediated immunity. Indeed, it was this constellation of clinical features ... that clearly identified a new clinical entity of AIDS" (Bird 1996, page 173). In fact the very definition of AIDS, according to the CDC, includes the presence of any one of about 25 different infections in someone who was previously diagnosed HIV-positive (Goldman 2000). Recurrent infections, especially if other conditions such as severe psychological stress are present, could result in a lowered CD4 count that may stay low indefinitely. the fact that Bird overlooks this possibility is even more unusual because he later admits that low CD4 counts can be long-lasting even from a single infection.

Since CD4 depletion in the blood (after an infection) can persist for long periods, the current CDC definition (of idiopathic CD4 T lymphopenia) is unsatisfactory. I propose that a period of at least 6 months is added to the requirement for consecutive low CD4 counts to rule out short-term secondary effects of infection. (Bird 1996, page 177)

While a six month waiting period would certainly be an improvement, it does not address the possibility that a person could easily suffer another infection within the six month follow-up period, especially if they are prone to recurrent infections. In addition, Bird fails to take into account any of the non-infectious conditions associated with low CD4 counts, which are also quite common. In summary, all of the distinctions Bird attempts to make between non-HIV AIDS and HIV associated AIDS are either weak or nonexistent, which leaves open the possibility that non-HIV AIDS and HIV associated AIDS can be caused by the same factors. Identifying and helping people overcome these non-HIV factors could be more effective than the current practice which focuses solely on trying to eliminate HIV.

Bird also introduces another aspect of CD4 counting which may explain why people initially believed that the low CD4 counts found in people diagnosed HIV positive were a new and unique entity. He points out that the tests that are used to measure CD4 counts were developed at about the same time as AIDS cases were first being identified. This meant that researchers did not know much about CD4 counts, nor did they know that most of the conditions
being used to diagnose them with AIDS, such as severe and chronic infections, are strongly associated with low CD4 counts, as are many other conditions that they were experiencing.

Sporadic cases of apparent late-onset cellular immunodeficiency, associated with opportunistic infections, have appeared as case reports over the years. Because the emergence of HIV-associated AIDS coincided with the introduction of T-cell specific monoclonal antibodies which permitted the identification and quantitation of human CD4-positive T lymphocytes, no T-lymphocyte surface marker results are available on many of the earlier cases. (Bird 1996, page 172)

Individual T-cell populations could not be quantified before 1978 (Bird 1996, page 173)

The first AIDS cases were identified in 1979, together with the extremely low CD4 counts that were thought to be the cause of their chronic infections. Because the tests used to measure CD4 counts were only developed the year before, in 1978, it is very likely that the assumption that HIV was causing the death of CD4 cells was made prematurely, before any clinicians or researchers had enough experience or knowledge about CD4 counts to make accurate decisions about their significance. Studies since that time on low CD4 counts have been widely ignored unless they focused on people diagnosed HIV-positive, creating the illusion that low CD4 counts are somehow specific to HIV and AIDS. This illusion may have allowed HIV to be falsely credited with creating immunodeficiency while other factors that are more significant are being ignored.

DISCUSSION

This review is extremely limited in scope, and many of the studies presented here use different measures of immune function, making it difficult to perform accurate comparisons. Nevertheless, it is remarkable that so many different conditions are associated with profoundly reduced CD4 counts, as well as reduced CD4 percentages, reduced measures of lymphocyte function, and reduced CD4/CD8 ratios. The fact that HIV-negative people with many common conditions like mononucleosis, pregnancy, and pneumonia can have levels below those needed to diagnose AIDS suggests that the common use of CD4 counts to make diagnostic and treatment decisions should be carefully reappraised, especially since most clinicians are apparently unaware of how serious these influences are. It is also apparent that the syndrome of AIDS, with extremely low CD4 counts and severe or fatal infections, is also fairly common in people diagnosed HIV-negative, and is likely to be present in between 40 and 70 percent of people admitted to intensive care units with severe acute or chronic infections (Feeney et al 1995, Williams et al. 1983). In people who die of their infections this percentage may be even higher.

Low CD4 counts and other immunosuppressive effects are associated with so many different physical and psychological stressors that it is possible that these other factors are the primary ones causing immunosuppression in many people diagnosed HIV-positive. Following is a brief list of factors commonly present in "high-risk" groups that could explain or contribute to a low CD4 count:

1) In Africa, malnutrition, a variety of endemic infectious diseases, psychological stress, and social ostracism could all be strong factors in causing an acquired immunodeficiency.
2) In the United States and Europe, AIDS is still primarily confined to the original risk groups, male homosexuals, IV drug users, and hemophiliacs, all of whom regularly experience many of the conditions described:

a) Male homosexuals suffer from societal rejection which causes psychological stress and social isolation. When AIDS first appeared, several events had made the social isolation of male homosexuals painfully clear; a successful campaign to repeal gay rights in Miami Dade County was being led by Anita Bryant, and the first elected official in the United States who was openly gay, Harvey Milk, was assassinated. Ironically, over the years the phenomenon of AIDS may have helped significantly to reduce this social ostracism and hatred, albeit in the context of a widespread human tragedy.

b) The small subset of gay men in whom AIDS first appeared were engaging in a type of party atmosphere which involved multiple partners, late nights, and the regular use of alcohol and recreational drugs, possibly as a way to cope with the societal rejection they were experiencing. Many people in this group suffered from recurrent or chronic sexually transmitted diseases, as well as general ill health.

c) IV drug users live in conditions of psychological stress and social isolation, and also often suffer from malnutrition. Injections of foreign proteins are a daily routine, and opiates have also been shown to cause immunosuppression. IV drug users have always had high rates of infectious diseases including cellulitis, tuberculosis, pneumonia, and non-healing ulcers.

d) Hemophiliacs need regular transfusions of factor VIII, which introduces a number of foreign proteins and impurities into their bloodstream. The quality of the Factor VIII has steadily improved over the years, as has their health and life expectancy, but in spite of this they still have chronic health problems and their life expectancy is still greatly reduced when compared to the normal population.

e) Corticosteroids, which are cortisol analogues, are often used as treatments in people diagnosed HIV-positive, especially in Western nations, for illnesses such as pneumocystis carinii pneumonia (PCP).

3) The very diagnosis, HIV-positive, carries a substantial burden of psychological stress and social isolation, which is made even worse when the CD4 count is found to be reduced, or when "full blown" AIDS is diagnosed.

It would be helpful to see studies of CD4 counts in even more common illnesses like influenza, and to see studies that try to determine when the CD4 counts begin to fall. If the CD4 counts were low before experiencing the conditions presented, the CD4 count could have caused the condition. The low counts in burn and trauma victims, however, argue in favor of the hypothesis that the conditions themselves caused the low CD4 counts, as it is difficult to argue that such a high percentage of people had low CD4 counts before the trauma was experienced. The studies reviewed here show that the CD4 counts can stay low for weeks or months, and this effect would be magnified if many factors were present at once, or if several conditions occurred in sequential order. Because of this, repeated findings of low CD4 counts over time could also be a common finding.
Studies looking at the mechanisms that cause low CD4 counts could also be helpful. The hypotheses presented in some of the articles reviewed above regarding mechanisms include increased cortisol, antibody-mediated immune dominance, and malnutrition. It is possible that several of these could operate simultaneously, as well, or that they could occur sequentially in a cascade. All of the factors presented here, from infections to psychological stress, could combine in causing immunosuppression, and many of them could be much more easily treated than current methods of treating HIV, which rely on long-term use of medications with a number of serious adverse effects.

Finally, the results described here cast doubt on the original claims that HIV specifically targets CD4+ T lymphocytes. It could be instead that many or all of the conditions reviewed here operate under the same mechanism. The search for a new infectious agent began around 1979, when clinicians found extremely low CD4 counts in a few young male homosexuals who were dying of multiple infections. The ensuing international scientific search resulted in Robert Gallo’s claim that HIV was the cause, in particular because it infected CD4+ lymphocytes (Gallo et al. 1984). Based on the results reviewed in above, however, it is very possible that the low CD4 counts in those early cases were simply a result of the opportunistic infections that were present, not because of any new agent that targeted CD4+ T-cells. This argument is strengthened by the continued difficulty in determining a mechanism for how HIV destroys CD4+ T-cells. The mechanisms originally proposed by Gallo have had to be abandoned, and new hypotheses have also experienced several major revisions over the years. A conference in 1997 determined that the cause was still unknown (Balter 1997), and recent articles seriously discredit the reigning hypothesis that the immune system destroys its own CD4+ T lymphocytes (Roederer 1998). A quote from the article by Balter (1997) which describes the conference on the causes of low CD4 counts, follows:

> It might be said that AIDS researchers know the virus that causes the disease, HIV, inside and out. They have isolated its proteins, sequenced its genome, and identified the receptors it uses to dock onto the CD4 T lymphocytes that are the viruses primary target. Yet the central mystery of AIDS remains unresolved: How does the virus cause the severe loss of CD4 T-cells, which wrecks the immune system, that is the hallmark of the disease? (Balter 1997, page1399)

One argument that is commonly used to support the claim that HIV specifically targets CD4+ cells is that when anti-HIV medications are given, the CD4 count rises. As described above in the section describing the immunosuppressive effects of anti-HIV medications, however, protease inhibitors and AZT specifically inhibit a variety of microbes that commonly create infections in people diagnosed HIV-positive (PDR 1999, Cassone 1999, Atzori 2000). This finding may explain some of the rise in CD4 counts that people on these drugs experience, but there are also other important factors to consider such as the tremendous psychological relief that these drugs provide for those who take them. The introduction of protease inhibitors was accompanied by widespread media acclaim, and this may help them generate a powerful psychological effect that relieves much of the stress that is associated with the diagnosis HIV-positive. Because psychological stress lowers the CD4 count, its relief could allow the CD4 count to rise. Once a rise in the CD4 count is seen, for whatever reason, the relief of psychological stress would be strengthened, as would the belief in the power of the anti-HIV drugs.

About 5-15% of people who are diagnosed HIV-positive do not go on to show any immunological abnormalities at all, even after ten or more years (Learmont et al. 1992, Ashton et al. 1998, Walton 1999). In addition, only about 50% of people diagnosed HIV-positive will be diagnosed with AIDS in the first ten years after their diagnosis, a period which has been called
the latent phase of the virus. Perhaps, by focusing on AIDS as a multifactorial illness, this latent phase can be extended indefinitely in more and more people. Further research that focuses on some of the many factors reviewed in this paper may reveal why these long-term nonprogressors appear to stay healthy in spite of being diagnosed HIV-positive, and may help increase the percentage of people who succeed in doing so.

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