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# Foreign-protein-mediated immunodeficiency in hemophiliacs with and without HIV

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**Abstract**

Hemophilia-AIDS has been interpreted in terms of two hypotheses: the foreign-protein-AIDS hypothesis and the Human Immunodeficiency Virus (HIV)-AIDS hypothesis. The foreign-protein-AIDS hypothesis holds that proteins contaminating commercial clotting factor VIII cause immunosuppression. The foreign-protein hypothesis, but not the HIV hypothesis, correctly predicts seven characteristics of hemophilia-AIDS: 1) The increased life span of American hemophiliacs in the two decades before 1987, although 75% became infected by HIV — because factor VIII treatment, begun in the 1960s, extended their lives and simultaneously disseminated harmless HIV. After 1987 the life span of hemophiliacs appears to have decreased again, probably because of widespread treatment with the cytotoxic anti-HIV drug AZT. 2) The distinctly low, 1.3–2%, annual AIDS risk of hemophiliacs, compared to the higher 5–6% annual risk of intravenous drug users and male homosexual aphrodisiac drug users — because transfusion of foreign proteins is less immunosuppressive than recreational drug use. 3) The age bias of hemophilia-AIDS, i.e. that the annual AIDS risk increased 2-fold for each 10-year increase in age — because immunosuppression is a function of the lifetime dose of foreign proteins received from transfusions. 4) The restriction of hemophilia-AIDS to immunodeficiency diseases — because foreign proteins cannot cause non-immunodeficiency AIDS diseases, like Kaposi's sarcoma. 5) The absence of AIDS diseases above their normal background in sexual partners of hemophiliacs — because transfusion-mediated immunotoxicity is not contagious. 6) The occurrence of immunodeficiency in HIV-free hemophiliacs — because foreign proteins, not HIV, suppress their immune system. 7) Stabilization, even regeneration, of immunity of HIV-positive hemophiliacs by long-term treatment with pure factor VIII. This shows that neither HIV nor factor VIII plus HIV are immunosuppressive by themselves. Therefore, AIDS cannot be prevented by elimination of HIV from the blood supply and cannot be rationally treated with genotoxic antiviral drugs, like AZT. Instead, hemophilia-AIDS can be prevented and has even been reverted by treatment with pure factor VIII.

## 1. The drug- and hemophilia-AIDS epidemics in America and Europe

About 30 previously known diseases are now called AIDS if they occur in the presence of antibody against human immunodeficiency virus (HIV) (Institute of Medicine, 1988; Centers for Disease Control and Prevention, 1992). These diseases are thought to be consequences for an *a*cquired *i*mmuno *d*eficiency *s*yndrome and hence are grouped together as AIDS (Institute of Medicine, 1988). From its beginning in 1981, AIDS has been restricted in America and Europe to specific risk groups (Centers for Disease Control, 1986; World Health Organization, 1992b). Currently, over 96% of all American AIDS cases come from AIDS risk groups, rather than from the general population (Centers for Disease Control, 1993). These include over 60% male homosexuals who have been long-term oral users of psychoactive and aphrodisiac drugs, 33% mostly heterosexual, intravenous drug users and their children, 2% transfusion recipients, and about 1% hemophiliacs (Duesberg, 1992a; Centers for Disease Control, 1993). Altogether, about 90% of all American and European AIDS patients are males (World Health Organization, 1992a; Centers for Disease Control, 1993).

Each risk group has specific AIDS diseases. For example, Kaposi's sarcoma is almost exclusively seen in male homosexuals, tuberculosis is common in intra-

venous drug users, and pneumonia and candidiasis are virtually the only AIDS diseases seen in hemophiliacs (Duesberg, 1992a).

In view of these epidemiological and clinical criteria, American and European AIDS has been interpreted alternatively as an infectious and a non-infectious epidemic by the following hypotheses:

1) *The virus-AIDS hypothesis.* This hypothesis postulates that all AIDS is caused by the retrovirus HIV, and thus an infectious epidemic. The inherent danger of a transmissable disease quickly promoted the HIV hypothesis to the favorite of 'responsible' health care workers, scientists and journalists (Booth, 1988). For example, a columnist of the *New York Times* wrote in July 1994 that all non-HIV AIDS science is 'cruelly irresponsible anti-science' (Lewis, 1994). And the retrovirologist David Baltimore warned in *Nature* 'There is no question at all that HIV is the cause of AIDS. Anyone who gets up publicly and says the opposite is encouraging people to risk their lives'. (Macilwain, 1994).

Moreover, the U.S.' Centers for Disease Control (CDC) have favored the HIV-AIDS hypothesis from the beginning (Centers for Disease Control, 1982; Shilts, 1985; Centers for Disease Control, 1986; Booth, 1988; Oppenheimer, 1992), because – according to Red Cross official Paul Cumming in 1983 — 'the CDC increasingly needs a major epidemic to justify its existence' (Associated Press, 1994). Indeed, there has been no viral or microbial epidemic in the U.S. and Europe since polio in the 1950s. All infectious diseases combined now account for less than 1% of morbidity and mortality in the Western World (Cairns, 1978). And the control of infectious diseases is the primary mission of the CDC.

2) *The drug-AIDS hypothesis.* This hypothesis holds that AIDS in the major risk groups is caused by group-specific, recreational drugs and by anti-HIV therapy with cytocidal DNA chain terminators, like AZT, and is thus not infectious (Lauritsen & Wilson, 1986; Haverkos & Dougherty, 1988; Duesberg, 1991, 1992a; Oppenheimer, 1992). The drug-AIDS hypothesis was favored by many scientists, including some from the CDC, before the introduction of the HIV-AIDS hypothesis in 1984 (Marmor *et al.*, 1982; Mathur-Wagh *et al.*, 1984; Haverkos *et al.*, 1985; Mathur-Wagh, Mildvan & Senie, 1985; Newell *et al.*, 1985; Haverkos & Dougherty, 1988; Duesberg, 1992a; Oppenheimer, 1992).

3) *The foreign-protein-hemophilia AIDS hypothesis.* This hypothesis holds that hemophilia-AIDS is caused by the long-term transfusion of foreign proteins contaminating factor VIII and other clotting factors and thus not infectious. This hypothesis also preceded the virus hypothesis and has coexisted with it, despite the rising popularity of the HIV hypothesis (see Section 3).

The infectious and non-infectious AIDS hypotheses indicate entirely different strategies of AIDS prevention and therapy. Here we analyze the cause of hemophilia-AIDS in the lights of the HIV-AIDS hypothesis and the foreign-protein-AIDS hypothesis. The hemophiliacs provide the most accessible group to test AIDS hypotheses of infectious versus non-infectious causation. This is because the time of infection via transfusion can be estimated more accurately than HIV infection from sexual contacts, and because the role of treatment-related AIDS risks can be controlled and quantitated much more readily than AIDS risks due to the consumption of illicit, recreational drugs.

## 2. The HIV-AIDS hypothesis

The HIV hypothesis claims that AIDS began to appear in hemophiliacs in 1981 (Centers for Disease Control, 1982) because (i) hemophiliacs were accidentally infected via transfusions of factor VIII contaminated with HIV since the 1960s, when widespread prophylactic factor VIII treatment began (but no longer after 1984 when HIV was eliminated from the blood supply) and because (ii) AIDS is currently assumed to follow HIV infection on average only after 10 years (Centers for Disease Control, 1986; Institute of Medicine, 1988; Chorba *et al.*, 1994). Indeed, about 15,000 of the 20,000 American hemophiliacs, or 75%, are HIV antibody-positive from transfusions of HIV-contaminated clotting factors received before HIV was detectable (Tsoukas *et al.*, 1984; Institute of Medicine and National Academy of Sciences, 1986; Sullivan *et al.*, 1986; McGrady, Jason & Evatt, 1987; Institute of Medicine, 1988; Koerper, 1989). Contamination of factor VIII with HIV reflects the practice, developed in the 1960s and 1970s, of preparing factor VIII and other clotting factors from blood pools collected from large numbers of donors (Aronson, 1983; Koerper, 1989; Chorba *et al.*, 1994).

The HIV hypothesis claims that 2,214 American hemophiliacs developed AIDS-defining diseases between 1982 and the end of 1992 because of HIV (Centers for Disease Control, 1993). However, this corresponds only to a 1.3% annual AIDS risk, i.e. 201 cases per 15,000 HIV-positive hemophiliacs per year. (Note that the non-age adjusted annual mortality of an American with a life expectancy of 80 years is 1.2%). Further, the HIV-AIDS hypothesis claims that the mortality of hemophiliacs has increased over 2-fold in the 3-year period from 1987 to 1989 compared to periods from 1968 to 1986, although infection with HIV via transfusions had already been halted with the HIV-antibody test in 1984 (Chorba *et al.*, 1994).

HIV is thought to cause immunodeficiency by killing T-cells, but paradoxically only after the virus has been neutralized by antiviral immunity, and only on average 10 years after infection (Institute of Medicine, 1988; Duesberg, 1992a; Weiss, 1993). However, HIV, like all other retroviruses, does not kill T-cells or any other cells *in vitro*; in fact, it is mass-produced for the HIV antibody test in immortal T-cell lines (Duesberg, 1992a). Moreover, the basis for the 10-year latent period of the virus, which has a generation time of only 24–48 h, is entirely unknown (Duesberg, 1992a; Weiss, 1993; Fields, 1994). It is particularly paradoxical that the loss of T-cells in hemophiliacs over time does not correspond to viral activity and abundance. No T-cells are lost prior to antiviral immunity, when the virus is most active (Duesberg, 1993a; Piatak *et al.*, 1993). Instead, most T-cells are lost when the virus is least active or latent in hemophiliacs (Phillips *et al.*, 1994a) and other risk grous (Duesberg, 1992a; 1993a, 1994; Piatak *et al.*, 1993; Sheppard, Ascher & Krowka, 1993), namely after it is neutralized by antiviral immunity (a positive HIV-antibody test). Indeed, there are healthy, HIV-antibody positive persons in which 33 to 43 times more cells are infected by latent HIV than in AIDS patients (Simmonds *et al.*, 1990; Bagasra *et al.*, 1992; Duesberg, 1994). Even Gallo, who claims credit for the HIV-AIDS hypothesis (Gallo *et al.*, 1984), has recently acknowledge: 'I think that if HIV is not being expressed and not reforming virus and replicating, the virus is a dud, and won't be causing the disease . . . nobody is saying that indirect control of the virus is not important . . . ' (Jones, 1994).

There is also no explanation for the profound paradoxes that AIDS occurs only after HIV is neutralized and that antiviral immunity does not protect against AIDS, although this immunity is so effective that free virus is very rarely detectable in AIDS patients (Duesberg, 1990, 1992a, 1993a; Piatak *et al.*, 1993). The high efficiency of this antiviral immunity is the reason that leading AIDS researchers had notorious difficulties in isolating HIV from AIDS patients (Weiss, 1991; Cohen, 1993).

All of the above associations between HIV and AIDS support the hypothesis that HIV is a passenger virus, instead of the cause of AIDS (Duesberg, 1994). A passenger virus differs from one that causes a disease in three criteria:

1) The time of infection by the passenger virus is unrelated to the initiation of the disease. For example, the passenger may infect 10 years prior to, or just immediately before, initiation of the disease — just as HIV does in AIDS.
2) The passenger virus may be active or passive during the disease, i.e. the primary disease is not influenced by the activity of the passenger virus or the number of virus-infected cells, as is the case for HIV in AIDS.
3) The disease may occur in the absence of the passenger virus. In the case of AIDS, over 4621 HIV-free AIDS cases have been clinically diagnosed (Duesberg, 1993b; see also Section 4.6).

Therefore, HIV meets each of the classical criteria of a passenger virus — exactly (Duesberg, 1994).

Moreover, since HIV is not active in most AIDS patients, and often more active in healthy carriers than in AIDS patients (Duesberg, 1993a, 1994; Piatak *et al.*, 1993), and since AIDS patients with and without HIV are clinically identical (Duesberg, 1993b), HIV is in fact only a harmless passenger virus. It is harmless, because it does not contribute secondary diseases to AIDS pathogenicity, as for example pneumocystis pneumonia, candida or herpes virus do. These microbes each cause typical AIDS-defining opportunistic infections. But HIV does not appreciably affect the pathogenicity of AIDS as HIV-free and HIV-positive AIDS cases are clinically indistinguishable (Duesberg, 1993b, 1994). Likewise, there is no clinical distinction between AIDS cases in which HIV is active and those in which it is totally latent and restricted to very few cells (Duesberg, 1993a; Piatak *et al.*, 1993).

Thus, despite enormous efforts in the last 10 years, there is no rational explanation for viral pathogenesis, and the virus-AIDS hypothesis stands unproved (Weiss & Jaffe, 1990; Duesberg, 1992a; Weiss, 1993; Fields, 1994). Above all, the hypothesis has failed to make any verifiable predictions, the acid test of a scientific hypothesis. For example, the predicted explosion of

AIDS into the general population, or among female prostitutes via sexual transmission of HIV, or among health care workers treating AIDS patients via parenteral transmission did not occur (Duesberg, 1992a, 1994).

As yet, the hypothesis is supported only by circumstantial evidence, i.e. correlations between the occurrence of AIDS and antibodies against HIV in AIDS patients (Blattner, Gallo & Temin, 1988; Institute of Medicine, 1988; Weiss & Jaffe, Weiss, 1993). However, because AIDS is defined by correlation between diseases and antibodies against HIV (Institute of Medicine, 1988), the relevance of the correlation argument for AIDS etiology has been challenged (Duesberg, 1992a, 1993b, 1994; Thomas Jr., Mullis & Johnson, 1994). States Mullis, at a *London Sunday Times* Nobel Laureate lecture in 1994, 'Any postgraduate student who had written a convincing paper demonstrating that HIV 'causes' AIDS would ... have published 'the paper of the century' . (Dickson, 1994).

In view of the circularity of the correlation argument, the apparent transmision of AIDS to hemophiliacs via transfusion of HIV-infected blood or factor VIII has been cited as the most direct support for the virus-AIDS hypothesis (Blattner, Gallo & Temin, 1988; Institute of Medicine, 1988; Weiss & Jaffe, 1990; Weiss, 1993). However, the HIV-hemophilia-AIDS hypothesis is weakened by the extremely long intervals between infection and AIDS, averaging between 10 years (Institute of Medicine, 1988) and 35 years, (Duesberg, 1992a; Phillips *et al.*, 1994b) compared to the short generation time of HIV which is only 24 to 48 h (see Section 4.2). During such long intervals other risk factors could have caused AIDS diseases, particularly in hemophiliacs who depend on regular transfusions of clotting factors for survival. The fact that HIV is typically not more active, and often even less active, in those who develop AIDS than in those who are healthy, further weakens the HIV-hemophilia-AIDS hypothesis (see above).

## 3. The foreign-protein-hemophilia-AIDS hypothesis

Before the introduction of the HIV-AIDS hypothesis, but after the introduction of prophylactic long-term treatment of hemophilia with blood-derived clotting factors had begun, numerous hematologists had noticed immunodeficiency and corresponding opportunistic infections in hemophiliacs. Several of these had advanced the foreign-protein-hemophilia-AIDS hypothesis, which holds that the long-term transfusion of foreign proteins contaminating commercial factor VIII, and possibly factor VIII itself, is the cause of immunosuppression in hemophiliacs. Indeed, until recently most commercial preparations of factor VIII contained from 99% to 99.9% foreign, non-factor VIII proteins (Brettler & Levine, 1989; Mannucci *et al.*, 1992; Seremetis *et al.*, 1993; Gjerset *et al.*, 1994). According to the foreign-protein hypothesis immunodeficiency in hemophilia patients is proportional to the lifetime dose of foreign proteins received (Menitove *et al.*, 1983; Madhok *et al.*, 1986; Schulman, 1991).

Long before HIV had been discovered, it was known empirically that 'transfusion of patients undergoing renal transplantation is associated with improved graft survival and it has been suggested that transfusion is immunosuppressive in an as yet unidentified way'. (Jones *et al.*, 1983). The authors had cited this empirical knowledge to explain immunosuppression in eight, and Pneumocystis pneumonia in six British hemophiliacs (Jones *et al.*, 1983). A multicenter study investigating the immune systems of 1,551 hemophiliacs, treated with factor VIII from 1975 to 1979, documented lymphocytopenia in 9.3% and thrombocytopenia in 5% (Eyster *et al.*, 1985). Further, the CDC reported AIDS-defining opportunistic infections in hemophiliacs between 1968 and 1979, including 60% pneumonias and 20% tuberculosis (Johnson *et al.*, 1985). An American hematologist commented on such opportunistic infections in hemophiliacs, including two candidiasis and 66 pneumonia deaths that had occurred between 1968 and 1979, '...it seems possible that many of the unspecified pneumonias in hemophiliacs in the past would be classified today as AIDS' (Aronson, 1983).

In 1983, Gordon from the National Institutes of Health noted that all hemophiliacs with immunodeficiency identified by the CDC had received factor VIII concentrate. While acknowledging the possibility of a 'transmissible agent', Gordon argued that 'repeated administration of factor VIII concentrate from many varied donors induces a mild disorder of immune disregulation by purely immunological means, without the intervention of infection'. (Gordon, 1983). Froebel *et al.* also argued against the hypothesis that immunodeficiency in American hemophiliacs was due to a virus, and suggested that it was due to treatments with factor VIII because 'Scottish patients with hemophilia, most of whom had received no American factor

VIII concentrate for over two years, were found to have immunological abnormalities similar to those in their American counterparts...' (Froebel *et al.*, 1983). Already in 1983 Menitove *et al.* described a correlation between immunosuppression of hemophiliacs and the amount of factor VIII received over a lifetime; the more factor a hemophiliac had received the lower was his T4/T8-cell ratio. Their data were found to be 'consistent with the possibility that commercially prepared lyophilized factor VIII concentrates can induce an AIDS-like picture...' (Menitove *et al.*, 1983). Also in 1983, Kessler *et al.* proposed that ' Repeated exposure to many blood products can be associated with development of T4/T8 abnormalities' and 'significantly reduced mean T4/T8 ratios compared with age and sex-matched controls' (Kessler *et al.*, 1983).

After the introduction of the HIV-AIDS hypothesis in 1984, Ludlam *et al.* studied immunodeficiency in HIV-positive and HIV-negative hemophiliacs and proposed 'that the abnormalities [low T4 to T8 cell ratios] result from transfusion of foreign proteins' (Carr *et al.*, 1984). Likewise, Tsoukas *et al.* concluded 'These data suggest that another factor, or factors, instead of, or in addition to, exposure to HTLV-III [old term for HIV] is required for the development of immunedysfunction in hemophiliacs' (Tsoukos *et al.*, 1984).

In 1985 even the retrovirologist Weiss reported 'the abnormal T-lymphocyte subsets are a result of the intravenous infusion of factor VIII concentrates per se, not HTLV-III infection' (Ludlam *et al.*, 1985). Likewise, the hematologists Pollack *et al.* deduced that, 'Derangement of immune function in hemophiliacs results from transfusion of foreign proteins or a ubiquitious virus rather than contracting AIDS infectious agent' (Pollack *et al.*, 1985). The 'AIDS infectious agent' was a reference to HIV, because in 1985 HIV was extermely rare in blood concentrates outside the U.S., but immunodeficiency was observed in Israeli, Scottish, and American hemophiliacs (Pollack *et al.*, 1985). A French AIDS-hemophilia group also observed '...allogenic or altered proteins present in factor VIII ...seem to play a role of immunocompromising agents'. They stated that 'A correlation between treatment intensity and immunologic disturbances was found in patients infused with factor VIII preparations, irrespective of their positive or negative LAV [HIV] antibody status' (AIDS-Hemohilia French Study Group, 1985). Likewise, Hollan *et al.* reported in 1985 'an immunodeficiency independent of HTLV-III infection' in Hungarian hemophiliacs (Hollan *et al.*, 1985).

In 1986, Madhok *et al.* arrived at the conclusion that 'clotting factor concentrate impairs the cell mediated immune response to a new antigen in the absence of infection with HIV' (Madhok *et al.*, 1986). Moreover, Jason *et al.* from the CDC observed that 'Hemophiliacs with immune abnormalities may not necessarily be infected with HTLV-III/LAV, since factor concentrate itself may be immune suppressive even when produced from a population of donors not at risk for AIDS' (Jason *et al.*, 1986). Sullivan *et al.* deduced from a comprehensive study of hemophiliacs that 'hemophiliacs receiving commercial factor VIII concentrate experience several stepwise incremental insults to the immune system: alloantigens in factor VIII concentrate [etc.] ...' (Sullivan *et al.*, 1986).

In 1987, Sharp *et al.* commented that 'Five out of 12 such patients had a mild T4 lymphocytopenia, and this may have been related to parenteral administration of large quantities of protein'. (Sharp *et al.*, 1987). And Aledort observed that 'chronic recipients ... of factor VIII, factor IX and pooled products ... demonstrated significant T-cell abnormalities regardless of the presence of HIV antibody' (Aledort, 1988). Brettler and Levine proposed in 1989 that 'Factor concentrate itself, perhaps secondary to the large amount of foreign-protein present, may cause alterations in the immune systems of hemophiliac patients' (Brettler & Levine, 1989). And even Stehr-Green *et al.* from the CDC conceded that foreign proteins were at least a cofactor of HIV in immunosuppression: 'Repeated exposure to factor concentrate ... could also account for more rapid progression of HIV infection with age'. (Stehr-Green *et al.*, 1989).

Although Becherer *et al.* claimed in 1990 that clotting factor does not cause immunodeficiency, they showed that immunodeficiency in hemophiliacs increases with both the age and the cumulative dose of clotting factor received during a lifetime (Becherer *et al.*, 1990). Likewise, Simmonds *et al.* observed in 1991 that even among HIV-positive hemophiliacs 'The rate of disease progression, as assessed by the appearance or not of AIDS symptoms or signs within five years of seroconversion, was related ... to the concentration of total plasma IgM before exposure to infection...' (Simmonds *et al.*, 1991). The hematologist Prince noted in a review from 1992 that 'When serum samples from these [immunodeficient hemophilia] patients were tested for antibodies to HIV-1, it was found that a sizable group of hemophilia patients, usually 25% to 40%, were seronegative for HIV-1', and '... all found marked anergy, lack of response, in HIV-

seronegative concentrate recipients. Taken together, these findings were interpreted as evidence that clotting factor concentrates suppressed the immunocompetence of recipients...' (Prince, 1992).

In 1991, Schulman concluded that "immunosuppressive components in F VIII concentrates" cause immunodeficiency not only in HIV-positive but also in HIV-negative hemophiliacs (Schulman, 1991). Schulman had observed reversal of immunodeficiency and thrombocytopenia in HIV-positive hemophiliacs treated with purified factor VIII, and that immunity "was inversely correlated with the annual amount of factor VIII infused" (Schulman, 1991).

At the same time several groups have reported that T-cell counts are stabilized, or even increased in HIV-positive hemophiliacs treated with factor VIII free of foreign proteins (de Biasi *et al.*, 1991; Hilgartner *et al.*, 1993; Seremetis *et al.*, 1993; Goedert *et al.*, 1994) (see also Section 4.7). And in 1994, the editor of *aids News*, published by the Hemophilia Council of California, granted foreign proteins the role of a cofactor of HIV in hemophilia AIDS with an editorial "Factor concentrate is a Co-factor" (Maynard, 1994).

According to the foreign-protein hypothesis, antibodies against HIV and against other microbes would merely be markers of the multiplicity of transfusions received (Evatt *et al.*, 1984; Pollack *et al.*, 1985; Brettler *et al.*, 1986; Sullivan *et al.*, 1986; Koerper, 1989). Since HIV has been a rare contaminant of blood products, even before 1984, only those who have received many transfusions would become infected. The more immunosuppressive transfusions a person has received, the more likely that person is to become infected by HIV and other microbes contaminating factor VIII (see Section 4.6). For example, only 30% of hemophiliacs who had received less than 400 units factor VIII per kg per year were HIV-positive, but 80% of those who had received about 1000 units, and 93% of those who had received over 2100 units per kg per year were HIV-positive (Sullivan *et al.*, 1986).

## 4. Predictions of the foreign-protein- and HIV-AIDS hypotheses

Here we compare the HIV- and the foreign-protein-AIDS hypotheses in terms of how well their predictions can be reconciled with hemophilia-AIDS:

4.1 *Mortality of hemophiliacs with and without HIV.* The virus-AIDS hypothesis predicts that the mortality of HIV-positive hemophiliacs will be higher than that of matched HIV-free counterparts. Considering the high, 75%-rate of infection of American hemophiliacs by HIV since 1984, one would expect that the median age of all American hemophiliacs would have significantly decreased and that their mortality increased. The HIV-AIDS hypothesis predicts that in 1994, at least one 10-year-latent-period after most American hemophiliacs were infected, over 50% of the 15,000 HIV-positive American hemophiliacs would have developed AIDS or died from AIDS (Institute of Medicine, 1988; Duesberg, 1992a). But despite the many claims that HIV causes AIDS in hemophiliacs (Centers for Disease Control, 1986; Institute of Medicine, 1988; Weiss & Jaffe, 1990; Chorba *et al.*, 1994), there is not a single controlled study showing that the morbidity or mortality of HIV-positive hemophiliacs is higher than that of HIV-negative controls matched for the lifetime consumption of factor VIII.

Instead, the mortality of American hemophiliacs has decreased and their median age has increased since 75% were infected by HIV. The median age of American hemophiliacs has increased from 11 years in 1972, to 20 years in 1982, to 25 years in 1986, and to 27 years in 1987, although 75% had become HIV antibody-positive prior to 1984 (Institue of Medicine and National Academy of Sciences, 1986; Koerper, 1989; Stehr-Green *et al.*, 1989). Likewise, their median age at death has increased from about 40 to 55 years in the period from 1968 to 1986 (Chorba *et al.*, 1994).

Contrary to the HIV-AIDS hypothesis, one could make a logical argument that HIV, instead of decreasing the life span of hemophiliacs, has in fact increased it. A more plausible argument suggests that the life span of American hemophiliacs has increased as a consequence of the widespread use of factor VIII that started in the late 1960s (see above). As predicted by the foreign-protein hypothesis, the price for the extended life span of hemophiliacs by treatment with commercial factor VIII was immunosuppression due to the long-term parenteral administration of large quantities of foreign protein (see Section 4.2). Prior to factor VIII therapy, most hemophiliacs died as adolescents from internal bleeding (Koerper, 1989).

However, a recent CDC study reports that the mortality of American hemophiliacs suddenly increased 2.5-fold in the period from 1987 to 1989, after it had remained almost constant in the period from 1968 to 1986 (Chorba *et al.*, 1994). Since American hemophiliacs became gradually infected via the introduction in the 1960s of pooled factor VIII treatments until

1984, when HIV was eliminated from the blood supply (see above), one would have expected first a gradual increase in hemophilia mortality and then a rather steep decrease. The increase in mortality would have followed the increase of infections with a lag defined by the time that HIV is thought to require to cause AIDS. The presumed lag between HIV and AIDS has been estimated at 10 months by the CDC in 1984 (Auerbach *et al.*, 1984) and at 10 years by a committee of HIV researchers, including some from the CDC, in 1988 (Institute of Medicine, 1988). Therefore the sudden increase in hemophilia deaths in 1987 is not compatible with HIV-mediated mortality. Hemophilia mortality should have gradually decreased after 1984, when HIV was eliminated from the blood supply, depending on the lag period assumed between infection and AIDS. Even if the lag period from HIV to AIDS were 10 years, the mortality of hemophiliacs should have significantly decreased by 1989, 5 years after new infections had been stopped.

An obvious explanation for the chronological inconsistency between infection of hemophiliacs with HIV since the 1960s and the sudden increase in their mortality 20 years later is the introduction of the cytotoxic DNA chain terminator AZT as an anti-HIV drug in 1987. AZT has been recommended and prescribed to symptomatic HIV carriers since 1987 (Fischl *et al.*, 1987; Richman *et al.*, 1987) and to healthy HIV carriers with lower than 500 T-cells since 1988 (Volberding *et al.*, 1990; Goldsmith *et al.*, 1991; Phillips *et al.*, 1994b). Approximately 200,000 HIV antibody-positives with and without AIDS diseases are currently prescribed AZT worldwide (Duesberg, 1992a). According to a preliminary survey of hemophiliacs from a national group, Concerned Hemophiliacs Acting for Peer Strenght (CHAPS), 35 out of 35 HIV- positive hemophiliacs asked had taken AZT, and 20 out of 35 who had taken AZT at some time were currently on AZT (personal communication, Brent Runyon, executive director of CHAPS, Wilmington, N.C.).

The DNA chain terminator AZT was developed 30 years ago to kill growing human cells for cancer chemotherapy. Because of its intended toxicity, chemotherapy is typically applied for very limited periods of time, i.e. weeks or months, but AZT is now prescribed to healthy HIV-positives indefinitely, despite its known toxicity (Nussbaum, 1990; Volberding *et al.*, 1990). Indeed, AZT has been shown to be toxic in HIV-positives and proposed as a possible cause of AIDS diseases since 1991 (Duesberg, 1991, 1992c, 1992a, 1992b). Recently, the European 'Concorde trial' (Seligmann *et al.*, 1994) and several other studies have shown that, contrary to earlier claims, AZT does not prevent AIDS (Oddone *et al.*, 1993; Tokars *et al.*, 1993; Lenderking *et al.*, 1994; Lundgren *et al.*, 1994). The Concorde trial even showed that the mortality of healthy, AZT-treated HIV-carriers was 25% higher than that of placebo-treated controls (Seligmann *et al.*, 1994). Likewise, an American multicenter study showed that the death risk of hemophiliacs treated with AZT was 2.4 times higher, and that their AIDS risk was even 4.5 times higher than that of untreated HIV-positive hemophiliacs (Goedert *et al.*, 1994). Thus, the widespread use of AZT in HIV-positives could be the reason for the sudden increase in hemophilia mortality since 1987.

The AZT-hemophilia-AIDS hypothesis and the foreign-protein-AIDS hypothesis both predict that hemophilia-AIDS would stay constant or increase as long as unpurified factor VIII is used and AZT is prescribed to HIV-positive hemophiliacs. By contrast, the HIV-AIDS hypothesis predicts that hemophilia-AIDS should have decreased with time since 1984 when HIV was eliminated from the blood supply. The HIV hypothesis further predicts that AIDS should have decreased precipitously since 1989 when AZT was prescribed as AIDS prevention to inhibit HIV.

But the decrease in hemophilia-AIDS predicted by the HIV-AIDS hypothesis was not observed. Instead, the data confirm the AZT-/foreign-protein-AIDS hypotheses: The CDC reports 300 hemophilia AIDS cases in 1988, 295 in 1989, 320 in 1990, 316 in 1991 , 316 in 1992 and, after broadening the AIDS definition as of January 1993 (Centers for Disease Control and Prevention, 1992), 1096 in 1993 (Centers for Disease Control, 1993; Centers for Disease Control and Prevention, 1994; and prior *HIV/AIDS Surveillance* reports).

4.2 *Annual AIDS risk of HIV-positive hemophiliacs compared to other HIV-positive AIDS risk groups.* The HIV-AIDS hypothesis predicts that the annual risk of HIV-positive hemophiliacs would be the same as that of other HIV-infected risk groups. One could in fact argue that it should be higher, because the health of hemophiliacs is compromised compared to AIDS risk groups without congenital health deficiencies.

By contrast, the foreign-protein-AIDS hypothesis makes no clear prediction about the annual AIDS risk of hemophiliacs compared to drug-AIDS risk groups, because the relative risks have not been studied and are hard to quantitate.

By the end of 1992, 2,214 American hemophiliacs with AIDS were reported to the CDC (Centers for Disease Control, 1993; Chorba *et al.*, 1994). Since there are about 15,000 HIV-positive American hemophiliacs, an average of only 1.3% (201 out of 15,000) have developed AIDS annually between 1981 and 1992 (Tsoukas *et al.*, 1984; Hardy *et al.*, 1985; Institute of Medicine and National Academy of Sciences, 1986; Sullivan *et al.*, 1986; Stehr-Green *et al.*, 1988; Goedert *et al.*, 1989; Koerper, 1989; Morgan, Curran & Berkelman, 1990; Gomperts, De Biasi & De Vreker, 1992). But after the inclusion of further diseases into the AIDS syndrome (Institute of Medicine, 1988), and the introduction of AZT as an anti-HIV drug, both in 1987, the annual AIDS risk of American hemophiliacs appears to have stabilized at 2%, e.g. about 300 out of 15,000 per year until 1993 when the AIDS definition was changed again (Centers for Disease Control, 1993) (see Section 4.1).

Hemophilia-AIDS statistics from Germany are compatible with American counterparts: about 50% of the 6,000 German hemophiliacs are HIV-positive (Koerper, 1989). Only 37 or $\sim 1\%$ of these developed AIDS-defining diseases during 1991 (Leonhard, 1992), and 186 or 1.5% annually during the four years from 1988 to 1991 (Schwartlaender *et al.*, 1992).

The 1.3% to 2% annual AIDS risk indicates that the average HIV-positive hemophiliac would have to wait for 25 to 35 years to develop AIDS diseases from HIV. Indeed latent periods of over 20 years have just been calculated for HIV-positive hemophiliacs based on the loss of T-cells over time (Phillips *et al.*, 1994b).

By contrast, the annual AIDS risk of the average, HIV-positive American is currently 6%, because there are now about 60,000 annual AIDS cases (Centers for Disease Control, 1993) per 1 million HIV-positive Americans (Curran *et al.*, 1985; Centers for Disease Control, 1992b; Duesberg, 1992a). This reflects the annual AIDS-risks of the major risk groups, the male homosexuals and intravenous drug users who make up about 93% of all American AIDS patients (Centers for Disease Control, 1993). The annual AIDS risks of intravenous drug users (Lemp *et al.*, 1990) and male homosexuals appear to be the same, as both were estimated at about 5–6% (Anderson & May, 1988; Lui *et al.*, 1988; Lemp *et al.*, 1990) (Table 1).

In view of the compromised health of hemophiliacs, it is surprising that the annual AIDS risk of HIV-infected hemophiliacs is only 1.3% to 2% and thus 3–5 times lower than that of the average HIV-infected, non-hemophiliac American or European (Table 1). Commenting on the relatively low annual AIDS risk of hemophiliacs compared to that of homosexuals, the hematologists Sullivan *et al.* noted that 'The reasons for this difference remain unclear' (Sullivan *et al.*, 1986). Hardy *et al.* from the CDC also noted the discrepancy in the latent periods of different risk groups. "The magnitude of some of the differences in rates is so great that even gross errors in denomination estimates can be overcome" (Hardy *et al.*, 1985). And Christine Lee, senior author of the study that had estimated latent periods of over 20 years from infection to hemophilia AIDS (Phillips *et al.*, 1994b), commented on the paradox "It may be that hemophiliacs have got that cofactor [of foreign blood contaminants], homosexuals have got another cofactor, drug users have got another cofactor, and they all have the same effect, so that at the end of the day you get [approximately] the same progression rate." (Jones, 1994).

Thus, the 3–5-fold difference between the annual AIDS risks of HIV-positive hemophiliacs and the other major risk groups is not compatible with the HIV hypothesis. However, it can be reconciled with the foreign-protein and drug-AIDS hypothesis (Duesberg, 1992a, 1994), because different causes, i.e. drugs and foreign proteins, generate AIDS diseases at different rates.

4.3 *The age bias of hemophilia-AIDS.* The HIV-AIDS hypothesis predicts that the annual AIDS risks of HIV-positive hemophiliacs is independent of their age, because virus replication is independent of the age of the host. Predictions would have to be adjusted, however, by the hypothetical lag period between infection and AIDS. If the average latent period from HIV to AIDS is 10 months, as was postulated in 1984 (Auerbach *et al.*, 1984), less than 10-month-old HIV-positive hemophiliacs would have a lower probability of having AIDS. If the average latent period from HIV to AIDS is 10 years (Institute of Medicine, 1988; Lui *et al.*, 1988; Lemp *et al.*, 1990; Weiss, 1993), HIV-positive hemophiliacs under 10 years of age would have a lower probability of having AIDS. In other words, if the time of infection is unknown, the annual AIDS risks of HIV-positive hemophiliacs over 10 months or 10 years, respectively, would be independent of the age of the HIV-positive hemophiliac.

By contrast, the foreign-protein hypothesis predicts that the annual AIDS risk of HIV-positive and negative hemophiliacs increases with age because immunosuppression is the result of the lifetime dose of proteins transfused (Pollack *et al.*, 1985; Brettler *et al.*, 1986;

*Table 1.* Annual AIDS risks of HIV-infected groups.

| American/European risk group | annual AIDS in % | References |
|---|---|---|
| Hemophiliacs | 1.3–2 | see text |
| Male homosexuals | 5–6 | (Lui *et al.*, 1988), (Anderson & May, 1988), (Lemp *et al.*, 1990) |
| Intravenous drug users | 5–6 | (Lui *et al.*, 1988), (Anderson & May, 1988), (Lemp *et al.*, 1990) |

Sullivan *et al.*, 1986; Koerper, 1989) (see above). The more years a hemophiliac has been treated with unpurified blood products, the more likely he is to develop immunodeficiency. Thus, the foreign-protein hypothesis predicts that the annual AIDS risk of a hemophiliac would increase with age.

Statistics show that the median age of hemophiliacs with AIDS in the U.S. (Evatt *et al.*, 1984; Koerper, 1989; Stehr-Green *et al.*, 1989) and other countries (Darby *et al.*, 1989; Biggar and the International Registry of Seroconverters, 1990; Blattner, 1991) is about 5–15 years higher than the average age of hemophiliacs. In the U.S., the average age of hemophiliacs was 20–27 years from 1980 to 1986, while that of hemophiliacs with AIDS was 32–35 years (Evatt *et al.*, 1984; Koerper, 1989; Stehr-Green *et al.*, 1989).

Likewise, the annual AIDS risk of HIV-positive hemophiliacs shows a strong age bias. An international study estimated the annual AIDS risk of children at 1% and that of adult hemophiliacs at 3% over a 5-year period of HIV-infection (Biggar and the International Registry of Seroconverters, 1990). In the U.S., Goedert *et al.* reported that the annual AIDS risk of 1- to 17- year-old hemophiliacs was 1.5%, that of 18- and 34-year-old hemohiliacs was 3%, and that of 64-year-old hemophiliacs was 5% (Goedert *et al.*, 1989). Goldsmith *et al.* reported that the annual T-cell loss of hemophiliacs under 25 years was 9.5% and for hemophiliacs over 25 years 17.5% (Goldsmith *et al.*, 1991).

Lee *et al.* reported that the annual AIDS risk of hemophiliacs 11 years after HIV seroconversion was 31% under 25 years and 56% over 25 years (Lee *et al.*, 1991). They estimated that the relative risk of AIDS increased 5-fold over 25 years. The same group confirmed in 1994 that the annual AIDS risk of HIV-positive hemophiliacs over 30 years is 2-times higher than in those under 15 years of age (Phillips *et al.*, 1994b). Stehr-Green *et al.* estimated that '... the risk of AIDS increased two fold for each 10 year increase in age after controlling for year of seroconversion'. (Stehr-Green *et al.*, 1989). Likewise, Fletcher *et al.* reported a 4-fold higher incidence of AIDS in hemophiliacs over 25 years of age than in those aged 5 to 13 years (Fletcher *et al.*, 1992). Thus, the annual AIDS risk of hemophiliacs increases about 2-fold for each 10-year increase in age.

This confirms the foreign-protein hypothesis, which holds that the cumulative dose of transfusions received is the cause of AIDS-defining diseases among hemophiliacs. According to the hematologist Koerper, 'this may reflect lifetime exposure to a greater number of units of concentrate ...', and to Evatt *et al.*, 'This age bias may be due to differences in duration of exposure to blood products ...' (Evatt *et al.*, 1984; Koerper, 1989). A recent study of HIV-free hemophiliacs is directly compatible with the foreign-protein hypothesis. The study showed that despite the absence of HIV 'with increasing age, numbers of $CD4^+CD45RA^+$ cells decreased and continued to do so throughout life' (Fletcher *et al.*, 1992).

By contrast, AIDS caused by an autonomous infectious pathogen would be independent of the age of the recipient because the replication cycle of viruses, including HIV, is independent of the age of the host. Thus the foreign-protein-AIDS hypothesis, rather than the HIV-AIDS hypothesis, correctly predicts the age bias of hemophilia-AIDS.

4.4 *Hemophilia-specific AIDS diseases.* The 30 AIDS diseases fall into two categories, the microbial immunodeficiency diseases and the non-immunodeficiency diseases, i.e. diseases that are neither caused by, nor consistently associated with, immunodeficiency (Duesberg, 1992a, 1994). Based on their annual incidence in America in 1992, 61% of the AIDS diseases were microbial immunodeficiency diseases, including pneumocystis pneumonia, candidiasis, tuberculosis,

etc., and 39% were non-immunodeficiency diseases, including Kaposi's sarcoma, lymphoma, dementia, and wasting disease (Table 2) (Centers for Disease Control, 1993).

The virus-AIDS hypothesis predicts that the probability of all HIV-infected persons to develop a given immunodeficiency or non-immunodeficiency AIDS disease is the same and independent of the AIDS risk group. By contrast, the hypothesis that AIDS is caused by drugs or by foreign proteins predicts specific diseases for specific causes (Duesberg, 1992a).

In America, 99% of the hemophiliacs with AIDS have immunodeficiency diseases, of which 70% are fungal and viral pneumonias (Evatt *et al.*, 1984; Koerper, 1989; Papadopulos-Eleopulos *et al.*, 1994). Only one study reports that 1% of hemophiliacs with AIDS had Kaposi's sarcoma (Selik, Starcher & Curran, 1987). The small percentage of Kaposi's sarcoma may be due to aphrodisiac nitrite inhalants used by male homosexual hemophiliacs as sexual stimulants (Haverkos & Dougherty, 1988; Duesberg, 1992a). There are no reports of wasting disease or dementia in American hemophiliacs. An English study also reported predominantly pneumonias and other immunodeficiency diseases among hemophiliacs, and also three cases of wasting syndrome (Lee *et al.*, 1991). It appears that the AIDS diseases of hemophiliacs are virtually all immunodeficiency diseases, whereas 39% of the AIDS diseases of intravenous drug users and male homosexuals are non-immunodeficiency diseases (Table 2). Since AIDS diseases in hemophiliacs and non-hemophiliacs are not the same, their causes can also not be the same.

The almost exclusive occurrence of immunodeficiency AIDS diseases among hemophiliacs is correctly predicted by the foreign-protein-AIDS hypothesis, but not by the HIV-AIDS hypothesis. The prediction of the HIV hypothesis, that the distribution of immunodeficiency and non-immunodeficiency diseases among hemophiliacs is the same as in the rest of the American AIDS population, is not confirmed.

4.5 *Is hemophilia-AIDS contagious?* The virus-AIDS hypothesis predicts that AIDS is contagious, because HIV is a parenterally and sexually transmitted virus. It predicts that hemophilia-AIDS is sexually transmissible. Indeed, AIDS researchers claim that the wives of hemophiliacs develop AIDS from sexual transmission of HIV (Booth, 1988; Lawrence *et al.*, 1990; Weiss & Jaffe, 1990; Centers for Disease Control, 1992a, 1993). Further, the HIV-AIDS hypothesis predicts that wives of hemophiliacs will develop the same AIDS diseases as other risk groups.

The foreign-protein hypothesis predicts that AIDS is not contagious and that the wives and sexual partners of hemophiliacs do not contract AIDS from their mates.

To test the hypothesis that immunodeficiency of hemophiliacs is sexually transmissible, the T4 to T8-cell ratios of 41 spouses and female sexual partners of immunodeficient hemophiliacs were analyzed (Kreiss *et al.*, 1984). Twenty-two of the females had relationships with hemophiliacs with T-cell ratios below 1, and 19 with hemophiliacs with ratios of 1 and greater. The mean duration of relationships was 10 years, the mean number of sexual contacts was 111 during the previous year, and only 12% had used condoms (Kreiss *et al.*, 1984). Since the T-cell ratios of all spouses were normal, averaging 1.68 — exactly like those of 57 normal controls — the authors concluded that 'there is no evidence to date for heterosexual or household-contact transmission of T-cell subset abnormalities from hemophiliacs to their spouses ...' (Kreiss *et al.*, 1984).

The CDC reports that between 1985 and 1992, 131 wives of American hemophiliacs were diagnosed with unnamed AIDS diseases (Centers for Disease Control, 1993). If one considers that there have been 15,000 HIV-positive hemophiliacs in the U.S. since 1984 and that one-third are married, then there are 5,000 wives of HIV-positive hemophiliacs. About 16 of these women have developed AIDS annually during the 8 years (131 : 8) from 1985 to 1992. But these 16 annual AIDS cases would have to be distinguished from the at least 80 wives of hemophiliacs that are expected to die per year based on natural mortality. Considering the human life span of about 80 years and that on average at least 1.6% of all those over 20 years of age die annually, about 80 out of 5,000 wives over 20 would die naturally per year. Thus, until controls show that among 5,000 HIV-positive wives of hemophiliacs 16 more than 80, i.e. 96, die annually, the claim that wives of hemophiliacs die from sexual or other transmision of HIV is unfounded speculation.

Moreover, it has been pointed out that all AIDS-defining diseases of the wives of hemophiliacs are typically age-related opportunistic infections, including 81% pneumonia (Lawrence *et al.*, 1990). Kaposi's sarcoma, dementia, lymphoma, and wasting syndrome are not observed in wives of hemophiliacs (Lawrence *et al.*, 1990).

*Table 2.* AIDS defining diseases in the U.S. in 1992[a].

| Immunodeficiencies | Non-immunodeficiencies |
|---|---|
| 42% pneumonia | 20% wasting disease |
| 17% candidiasis | 9% Kaposi's sarcoma |
| 12% mycobacterial, including 3% tuberculosis | 6% dementia |
| | 4% lymphoma |
| 8% cytomegalovirus | |
| 5% toxoplasmosis | |
| 5% herpesvirus | |
| Total = 61% (> 61% due to overlap) | Total = 39% |

[a] = (Centers for Disease Control, 1993)

Again, the foreign-protein, but not the HIV hypothesis, correctly predicts the non-contagiousness of hemophilia-AIDS. It also predicts the specific spectrum of AIDS diseases in wives of hemophiliacs. By contrast, the virus-AIDS hypothesis predicts the same spectrum of AIDS diseases among wives of hemophiliacs as among the major risk groups (see Table 2). It appears that the virus-AIDS hypothesis is claiming normal morbidity and mortality of the wives of hemophiliacs for HIV.

4.6 *Immunodeficiency in HIV-positive and -negative hemophiliacs.* The HIV hypothesis predicts that immunodeficiency is observed only in HIV-positive hemophiliacs. By contrast, the foreign-protein hypothesis predicts that immunodeficiency is a function of the lifetime dose of transfusions received, and not dependent on HIV or antibodies against HIV. The foreign-protein hypothesis also predicts that HIV-positive hemophiliacs are more likely to be immunosuppressed than HIV-negatives because HIV is a rare contaminant of blood transfusion and thus is a marker for the number of transfusions received (see Section 3, and below) (Tsoukas *et al.*, 1984; Ludlam *et al.*, 1985; Kreiss *et al.*, 1986; Sullivan *et al.*, 1986; Koerper, 1989; Fletcher *et al.*, 1992).

Twenty-one studies, summarized in Table 3, have observed 1,186 immunodeficient hemophiliacs, 416 of whom were HIV-free. Immunodeficiency in these studies was either defined by a T4 to T8-cell ratio of about 1 or less than 1, compared to a normal ratio of 2, or by other tests such as immunological anergy. Since immunodeficiency was observed in the absence of HIV, most of the studies listed in Table 3 have concluded that immunodeficiency in hemophiliacs was caused by

*Table 3.* Immunosuppression in HIV-negative and -positive hemophiliacs.

| Study | HIV-negative | HIV-positive |
|---|---|---|
| 1.) (Tsoukas *et al.*, 1984 | 6/14 | 9/15 |
| 2.) (Carr *et al.*, 1984) | 18/53 | |
| 3.) (Ludlam *et al.*, 1985) | 15 | |
| 4.) (Moffat and Bloom, 1985) | 23 | 23 |
| 5.) (AIDS-Hemophilia French Study Group, 1985) | 33 | 55 |
| 6.) (Hollan *et al.*, 1985) | 30/104 | |
| 7.) (Sullivan *et al.*, 1986) | 28 | 83 |
| 8.) (Madhok *et al.*, 1986) | 9 | 10 |
| 9.) (Kreiss *et al.*, 1986) | 6/17 | 22/24 |
| 10.) (Gill *et al.*, 1986) | 8/24 | 30/32 |
| 11.) (Brettler *et al.*, 1986) | 4 | 38 |
| 12.) (Sharp *et al.*, 1987) | 5/12 | |
| 13.) (Matheson *et al.*, 1987) | 5 | 3 |
| 14.) (Mahir *et al.*, 1988) | 6 | 5 |
| 15.) (Antonaci *et al.*, 1988) | 15 | 10 |
| 16.) (Aledort, 1988) | 57 | 167 |
| 17.) (Jin *et al.*, 1989) | 12 | 7 |
| 18.) (Lang *et al.*, 1989) | 24 | 172 |
| 19.) (Jason *et al.*, 1990) | 31 | |
| 20.) (Becherer *et al.*, 1990) | 74 | 136 |
| 21.) (Smith *et al.*, 1993) | 7 | |
| Totals | 416 | 770 |

If two numbers are listed per category, the first reports immunodeficient and the second healthy plus immunodeficient hemophiliacs per study group. In most studies immunodeficiency was expressed by the T4/T8 cell ratio, in others by anergy. In a normal immune system the T4/T8 cell ratio is about 2. In immunodeficient persons it is about 1 or below 1. Studies which list both HIV-positive and negative groups indicate that HIV-positives are more likely to be immunodeficient than negatives. This is because HIV is a marker for the number of transfusions received, and transfusion of foreign proteins causes immunodeficiency (see Sections 3 and 4.6).

transfusion of factor VIII and contaminating proteins. According to the first of Koch's postulates (Merriam-Webster, 1965), the absence of a microbe, i.e. HIV, from a disease excludes it as a possible cause of that disease. Thus, transfusion of foreign protein, not the presence of HIV, emerges as the common denominator of all hemophiliacs with immunodeficiency.

Nevertheless, several of the controlled studies listed in Table 3, which compare HIV-negative to HIV-positive hemophiliacs, have shown that immunodeficiency is more often associated with HIV-positives

than with negatives. Although some studies did not report immunodeficiency in HIV-positives, Table 3 lists 770 HIV-positives and 416 HIV-negatives per 1,186 immunodeficient hemophiliacs. In view of this, one could argue that HIV is one of several possible causes of immunodeficiency.

However, some of the investigators listed in Table 3 (Tsoukas *et al.*, 1984; Ludlam *et al.*, 1985; Kreiss *et al.*, 1986; Madhok *et al.*, 1986; Sullivan *et al.*, 1986) and others who have not performed controlled studies (Koerper, 1989) have proposed that HIV is just a marker for the number of transfusions received (Section 3). As a rare contaminant of factor VIII, HIV has in fact been a marker for the number of transfusions received before it was eliminated from the blood supply in 1984, just like hepatitis virus infection was a marker of the number of transfusions received until it was eliminated from the blood supply earlier (Anonymous, 1984; Koerper, 1989). According to Kreiss *et al.*, 'seropositive hemophiliac subjects, on average, had been exposed to twice as much concentrate ... as seronegative[s]' (Kreiss *et al.*, 1986). Sullivan *et al.* also reported that 'Seropositivity to LAV/HTLV-III (HIV) was 70% for the hemophiliac population and ... varied directly with the amount of factor VIII received' (see Section 3) (Sullivan *et al.*, 1986). More recently, Schulman reported that 'a high annual consumption' of factor VIII concentrate 'predisposed' to HIV-seroconversion (Schulman, 1991), and Fletcher *et al.* described a positive 'relationship between the amount of concentrate administered and anti-HIV prevalence rate . . .' (Fletcher *et al.*, 1992).

The chronology of studies investigating immunodeficiency in HIV-free hemophiliacs faithfully reflects the popularity of the HIV hypothesis: the more popular the HIV hypothesis became over time the fewer studies investigated immunodeficiency in HIV-free hemophiliacs. Indeed, most of the controlled studies investigating the role of HIV in immunodeficiency of HIV-positive and matched HIV-negative hemophiliacs were conducted before the virus hypothesis became totally dominant in 1988 (Institute of Medicine, 1988), namely between 1984 and 1988 (Table 3). The studies by Jin, Cleveland and Kaufman, and Lang *et al.*, both dated 1989, and the studies by Becherer *et al.* and by Jason *et al.*, both dated 1990, all described data collected before 1988 (Table 3). After 1988 the question whether HIV-free hemophiliacs developed immunodeficiency became increasingly unpopular. As a result, only a few studies have described immunodeficiency in HIV-free hemophiliacs.

For example, Schulman reported 'worrisome evidence of similar immunological disturbances has been observed, albeit to a lesser degree, in anti-HIV-negative hemophiliacs' and that immunodeficiency in hemophiliacs 'correlates more strongly with annual consumption of factor concentrates than with HIV status' (Schulman, 1991). Fletcher *et al.* published a median T4/T8-cell ratio of 1.4, with a low 10-percentile of 0.8, in a group of 154 HIV-free hemophiliacs, and also showed a steady decline of T-cell counts with treatment years (Fletcher *et al.*, 1992). Likewise, Hassett *et al.* reported that 'patients with hemophilia A without human immunodeficiency virus type 1 (HIV-1) infection have lower $CD4^+$ counts and $CD4^+/CD8^+$ ratios than controls' (Hassett *et al.*, 1993). The study observed an average T4/T8-cell ratio of 1.47 in a group of 307 HIV-free hemophiliacs, differing over 50 years in age, compared to an average of 1.85 in normal controls. Unlike others Hassett *et al.* attributed the lowered $CD4^+$ counts to a hemophilia-related disorder rather than to foreign proteins, but like others they attributed increased $CD8^+$ counts to treatment with commercial factor VIII. However, Fletcher *et al.*'s and Hassett *et al.*'s practice of averaging immunodeficiency markers of large numbers of people, differing over 50 years in age, obscures how far the immunity of the longest, and thus most treated cases had declined compared to cases which have received minimal treatments.

Since the authors of these studies did not report the life time dosage of factor VIII treatments of HIV-free hemophiliacs, a correlation between foreign-protein dosage and immunosuppression cannot be determined. On the contrary, averaging immunodeficiency parameters of newcomers and long-term treatment recipients obscures the relationship between the lifetime dosage of factor VIII and immunosuppression.

Moreover, the CDC reported 7 HIV-free hemophiliacs with AIDS (Smith *et al.*, 1993). This study was one of a package that proposed to set apart HIV-free AIDS from HIV-positive AIDS with the new term *idiopathic CD4 lymphocytopenia*. The goal of these studies was to save the virus-AIDS hypothesis, despite the presence of HIV-free AIDS (Duesberg, 1993b, 1994; Fauci, 1993). Nevertheless all of the 7 HIV-free hemophiliacs met one or more criteria of the CDC's clinical AIDS definition from 1993 (Centers for Disease Control and Prevention, 1992), e.g. they all had less than 300 T-cells per microliter (range from 88 to 296), and three also had AIDS defining diseases such as herpes and thrombocytopenia (Smith *et al.*, 1993).

The occurence of immunodeficiency in HIV-free hemophiliacs demonstrates most directly that long-term transfusion of foreign proteins contaminating factor VIII is sufficient to cause immunodeficiency in hemophiliacs. To prove the foreign-protein hypothesis it would be necessary to show that treatment of HIV-positive hemophiliacs with pure factor VIII does not cause immunodeficiency. It is shown below that this is actually the case.

4.7 *Stabilization, even regeneration of immunity of HIV-positive hemophiliacs by treatment with pure factor VIII.* Commercial preparations of factor VIII contain between 99% and 99.9% non-factor VIII proteins (Eyster & Nau, 1978; Brettler & Levine, 1989; Gjerset *et al.*, 1994; Mannucci *et al.*, 1992; Seremetis *et al.*, 1993). The foreign-protein-hemophilia-AIDS hypothesis predicts that long-term transfusion with commercial factor VIII would be immunosuppressive, because of the presence of contaminating proteins. Further, it predicts that pure factor VIII, containing 100- to 1,000-times less foreign protein per functional unit, may not be immunosuppressive.

Several studies have recently tested whether the impurities of factor VIII or factor VIII by itself are immunosupressive in HIV-positive hemophiliacs. De Biasi *et al.* showed that over a period of two years the average T-cell counts of ten HIV-positive hemophiliacs treated with non-purified, commercial factor VIII declined two-fold, while those of matched HIV-positive controls treated with pure factor VIII remained unchanged. Moreover, four out of six anergic HIV-positive patients treated with purified factor VIII recovered immunological activity (de Biasi *et al.*, 1991). Goldsmith *et al.* also found that the T-cell counts of 13 hemophiliacs treated with purified factor VIII remained stable for 1.5 years (Goldsmith *et al.*, 1991). Seremetis *et al.* have confirmed and extended de Biasi *et al.*'s conclusion by establishing that the T-cells of HIV-positive hemophiliacs were not depleted after treatment with pure factor VIII for three years (Seremetis *et al.*, 1993). Indeed, the T-cell counts of 14 out of 31 HIV-positive hemophiliacs increased up to 25% over the three-year period of treatment with purified factor VIII — despite infection by HIV. By contrast, in the group treated with unpurified factor VIII, the percentage of those with less than 200 T-cells per $\mu$l increased from 7% at the beginning of the study to 47% at the end.

Likewise Hilgartner *al.* reported individual increases of T-cell counts of up to 50% in a group of 36 HIV-positive hemophiliacs treated with purified factor VIII whose average T-cell count had declined 1% during 6 months (Hilgartner *et al.*, 1993). Goedert *et al.* have also reported that "T-cell counts fell less rapidly with high purity products" (Goedert *et al.*, 1994). Moreover, Schulman observed that four HIV-positive hemophiliacs recovered from thrombocytopenia upon treatment with pure factor VIII for 2–3 years, and others from CD8-related immunodeficiency upon treatment for 6 months (Schulman, 1991).

However, despite the evidence that purified factor VIII is beneficial in maintaining or even increasing T-cell counts, several studies testing purified factor VIII are ambiguous about its effectiveness in preventing or treating AIDS (Goldsmith *et al.*, 1991; Hilgartner *et al.*, 1993; Gjerset *et al.*, 1994; Goedert *et al.*, 1994; Phillips *et al.*, 1994a). Some of these studies have only tested partially purified, i.e. 2–10 units/mg, instead of highly purified, i.e. 2000–3000 units/mg, factor VIII (Gjerset *et al.*, 1994). But each of the studies that are ambiguous about the benefits have also treated their patients with toxic antiviral DNA chain terminators like AZT. Indeed the study by de Biasi *et al.* was the only one that has tested purified factor VIII in the absence of AZT. The study by Seremetis *et al.* initially called for no AZT, but later allowed it anyway. Thus in all but one study, the potential benefits of highly purified factor VIII have been obscured by the toxicity of AZT (see Section 5.4).

It is concluded that treatment of HIV-positive hemophiliacs with pure factor VIII provides lasting stabilization of immunity, and even allows regeneration of lost immunity. It follows that foreign proteins, rather than factor VIII or HIV, cause immunosuppression in HIV-positive hemophiliacs.

## 5. Conclusions and discussion

Four criteria of proof have been applied to distinguish between the virus and the foreign-protein hypothesis of hemophilia-AIDS: (i) correlation, (ii) function (Koch's third postulate), (iii) predictions, (iv) therapy and prevention. Each of these criteria proved the foreign-protein hypothesis valid and the HIV hypothesis invalid.

5.1 *Correlations between hemophilia-AIDS and the long-term administration of foreign proteins or HIV.* Although correlation is not sufficient, it is necessary to prove causation in terms of Koch's postulates

(Merriam-Webster, 1965). The first of Koch's postulates calls for the presence of the suspected cause in all cases of the disease, i.e. a perfect correlation; the second calls for the isolation of the cause; and the third for causation of the disease with the isolated causative agent.

All hemophiliacs with immunodeficiency described here have been subject to long-term treatment with foreign proteins contaminating factor VIII. This establishes a perfect correlation between foreign-protein transfusion and hemophilia-AIDS, and fulfills Koch's first postulate.

By contrast, a summary of 21 separate studies showed that 416 of 1,186 immunodeficient hemophiliacs were HIV-free (Table 3). Since HIV does not correlate well with hemophilia-AIDS, it fails Koch's first postulate and is thus not even a plausible cause of AIDS.

5.2 *Foreign-protein hypothesis, but not HIV hypothesis, meets Koch's third postulate as cause of immunodeficiency.* The fact that all hemophiliacs with immunodeficiency had been subject to long-term treatment with foreign proteins, and that factor VIII treatment in the absence of foreign proteins does not cause immune suppression, and may even revert it, provides functional proof for the foreign-protein hypothesis. Thus, the foreign-protein hypothesis meets Koch's third postulate of causation.

Regeneration of immunity of HIV-positives by treatment with pure factor VIII further indicates that HIV by itself or in combination with factor VIII is not sufficient for hemophilia-AIDS. Therefore, HIV fails Koch's third postulate as a cause of AIDS.

5.3 *Foreign-protein hypothesis correctly predicts hemophilia-AIDS and resolves paradoxa of HIV hypothesis.* The ability to make verifiable predictions is the hallmark of a correct scientific hypothesis. Application of the two competing hypotheses to hemophilia-AIDS proved that the foreign-protein hypothesis, but not the HIV hypothesis, correctly predicts seven characteristics of hemophilia-AIDS (see Sections 4.1–4.7):

1) The increased life span of American hemophiliacs, despite infection of 75% by HIV, due to factor VIII treatment, that extended their lives and disseminated harmless HIV;
2) the 3–5 times lower annual AIDS risk of hemophiliacs, compared to other AIDS risk groups;
3) the age bias of the annual AIDS risk of hemophiliacs, increasing 2-fold for each 10-year increase in age;
4) the restriction of hemophilia-AIDS to immunodeficiency-related AIDS diseases, setting it apart from the spectrum of AIDS diseases in other risk groups;
5) the non-contagiousness of hemophilia-AIDS, i.e. the absence of AIDS diseases above their normal background in sexual partners of hemophiliacs;
6) the occurrence of immunodeficiency in HIV-free, factor VIII-treated hemophiliacs;
7) the stabilization, even regeneration, of immunity of HIV-positive hemophiliacs upon long-term treatment with pure factor VIII.

It follows that the foreign-protein hypothesis, but not the HIV hypothesis, correctly predicts hemophilia-AIDS. In addition, the foreign-protein hypothesis resolves all remaining paradoxa of the HIV hypothesis (see Section 2):

1) The failure of HIV neutralizing antibody to protect against AIDS — because HIV is not the cause of AIDS.
2) The non-correlation between the loss of T cells and HIV activity — because foreign proteins rather than HIV are immunotoxic.
3) The failure of HIV to kill T cells — because T cell synthesis is suppressed by immunotoxic foreign proteins.
4) The latent periods of 10 to 35 years between HIV and hemophilia-AIDS — because the lifetime dosage of foreign proteins, not HIV, causes AIDS.

5.4 *Treatment and prevention of AIDS.* The prevention or cure of a disease, by eliminating or blocking the suspected cause, provides empirical proof of causation.

*(i) Drug-Treatment based on HIV hypothesis:* On the basis of the HIV hypothesis, AIDS has been treated since 1987 with anti-HIV drugs, such as the DNA chain terminators AZT, ddI, etc. (Duesberg, 1992a). The rationale of the AZT treatment is to prevent HIV DNA synthesis at the high cost of inhibiting cellular DNA synthesis, the original target of AZT cancer chemotherapy (see above). However, not a single AIDS patient has ever been cured with AZT. Since 1989, healthy HIV-positive hemophiliacs have also been treated with DNA chain terminators in efforts to prevent AIDS. But the alleged ability of AZT to prevent AIDS has recently been discredited by several large clinical trials (Oddone *et al.*, 1993; Tokars *et al.*,

1993; Goedert *et al.*, 1994; Lenderking *et al.*, 1994; Lundgren *et al.*, 1994; Seligmann *et al.*, 1994). Moreover, all studies of AZT treatments have confirmed the unavoidable cytotoxicity of DNA chain terminators (Duesberg, 1992; Oddone *et al.*, 1993; Tokars *et al.*, 1993; Lenderking *et al.*, 1994; Lundgren *et al.*, 1994; Seligmann *et al.*, 1994). One study observed a 25% increased mortality (Seligmann *et al.*, 1994), and another a 4.5-fold higher annual AIDS risk and a 2.4-fold higher annual death risk in AZT-treated HIV-positive hemophiliacs compared to untreated controls (Goedert *et al.*, 1994).

The failure of AZT therapy to cure or prevent AIDS indicates either that the drug is not sufficient to inhibit HIV or that HIV is not the cause of AIDS. The lower mortality and much lower incidence of AIDS defining diseases among hemophiliacs not treated with AZT compared to those treated indicates that AZT causes AIDS-defining diseases and mortality. Thus, there is currently no rational or empirical justification for AZT treatment of HIV-positives with or without AIDS.

The apparent ability of AZT to cause AIDS defining and other diseases in hemophiliacs is just one aspect of the many roles that drugs play in the origin of AIDS (see footnote).

*(ii) Treatment based on foreign-protein hypothesis:* In the light of the foreign-protein hypothesis, hemophiliacs have been treated with factor VIII freed of foreign proteins. This treatment has provided lasting stabilization of immunity in HIV-positive hemophiliacs. Moreover, the long-term treatment of immunodeficient, HIV-positive hemophiliacs with purified factor VIII has even regenerated lost immunity. Immunological anergy has disappeared and the T-cells in HIV-positive hemophiliacs have increased up to 25% in the presence of pure factor VIII (see Section 4.7) (de Biasi *et al.*, 1991; Seremetis *et al.*, 1993). Thus, therapeutic benefits including AIDS prevention and even recovery of lost immunity by omission of foreign proteins from factor VIII lend credence to the foreign-protein-AIDS hypothesis.

*(iii) Two treatment hypotheses – and one treatment dilemma:* The failure to distinguish between two alternative hypothetical AIDS causes, HIV and foreign proteins, has created a dilemma for contemporary hemophilia treatment. For example, Goedert *et al.* acknowledge that "CD4 count fell less rapidly with high purity products" (Goedert *et al.*, 1994). But since they are also treating their patients with toxic AZT (see Section 4.1), they observe that "F VIII related changes in CD4 concentration may have little relevance to clinical disease" (Goedert *et al.*, 1994). Indeed the group had published a rare comparison between the annual AIDS- and death risks of hemophiliacs treated and not treated with AZT which indicated that the AIDS risk of AZT-treated hemophiliacs is 4.5-times and the death risk 2.4-times higher than in untreated controls.

In order to reconcile the apparent benefits of purified factor VIII on T-cell counts with the apparent toxicity of simultaneous AZT treatment, they try to separate T-cell loss from AIDS diseases. However, despite non-immunodeficiency AIDS diseases (see Table 2, Section 4.4), AIDS is defined as a T-cell deficiency (Institute of Medicine and National Academy of Sciences, 1986; Institute of Medicine, 1988) and dozens of AIDS researchers have observed that 'AIDS tends to develop only after patients' CD4 lymphocyte counts have reached low levels . . .' (Phillips *et al.*, 1994b). Indeed, as of January 1993 the CDC defined less than 200 T-cells per $\mu$l as an AIDS disease (Centers for Disease Control and Prevention, 1992), and sequential T-cell counts of hemophiliacs are used as a basis to calculate their long-term survival (Phillips *et al.*, 1994b).

Because of their exclusive faith in the HIV-AIDS hypothesis, readers of the study by Seremetis *et al.* (Seremetis *et al.*, 1993), which had demonstrated that foreign proteins associated with factor VIII suppress T-cell counts, have even proposed to 'consider the

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The drug-AIDS hypothesis, which applies to most American and European AIDS cases other than hemophiliacs (see Section 1) (Duesberg, 1992a), also derives support either from the absence of AIDS, or from the stabilization of, or spontaneous recovery from AIDS conditions in HIV-positives who don't use drugs. For example, in August 1993 there was no mortality during 1.25 years in a group of 918 British HIV-positive homosexuals who had 'avoided the experimental medications on offer', and chose to 'abstain from or significantly reduce their use of recreational drugs, including alcohol' (Wells, 1993). Assuming a 10-year latent period from HIV to AIDS, the virus AIDS-hypothesis would have predicted at least 115 (918/10 × 1.25) AIDS cases among 918 HIV-positives over 1.25 years. Indeed, the absence of mortality in this group over 1.25 years corresponds to a minimal latent period from HIV to AIDS of over 1,148 (918 × 1.25) years. On July 1st 1994 there was still not a single AIDS case in this group of 918 HIV-positive homosexuals (J. Wells, London, pers. Comm.). Further, the T-cell counts of 197 (58% of 326) HIV-positive homosexuals remained constant over 3 years, despite the presence of HIV (Detels *et al.*, 1988). These were probably those in the cohort who did not use recreational drugs or AZT. Moreover, it has been observed that the T-cells of 29% of 1,020 HIV-positive male homosexuals and intravenous drug users even increased up to 22% per year over 2 years (Hughes *et al.*, 1994). These HIV-positives belonged to the placebo arm of an AZT trial for AIDS prevention and thus were not intoxicated by AZT. It is probable that the 29% whose T-cells increased despite HIV may have given up or reduced immuno suppressive recreational drug use in the hope that AZT would work.

use of high-purity factor VIII concentrates in non-hemophiliac-HIV-positive patients' as a treatment for other AIDS patients, i.e. intravenous drug users and homosexuals. Since hemophiliacs treated with pure factor VIII did either not develop immunodeficiency or even recovered lost immunity, they assumed, in view of the HIV-hypothesis, that pure factor VIII must inhibit HIV and thus would help all AIDS patients (Schwarz *et al.*, 1994).

The solution to the treatment dilemma can only come from treatments that are each based only on one hemophilia-AIDS hypothesis: To test the foreign-protein hypothesis, two groups of hemophiliacs must be compared that are matched for their life time dosage of factor VIII, for their percentage of HIV-positives (for their percentage and dosage of prior AZT treatment, if applicable), and for their age. All AIDS-defining diseases must be diagnosed in each group clinically for the duration of the test. No anti-HIV treatments must be performed. One group would be treated with purified factor VIII, the other with commercial factor VIII contaminated with foreign proteins.

To test the HIV-AIDS hypothesis, two groups of hemophiliacs must be compared that are matched for their life time dosage of factor VIII treatment and their age. The two groups must differ only in the presence of antibody against HIV. Both groups would be treated with the same factor VIII preparation. Only the HIV-positive group would receive AZT. All compensatory treatments of AZT recipients, e.g. blood transfusions to treat for AZT-induced anemia, neutropenia or pancytopenia (Richman *et al.*, 1987; Volberding *et al.*, 1990; Duesberg, 1992), would have to be recorded. During the duration of the test, all AIDS-defining diseases would each be recorded clinically in both groups.

The outcome of each treatment strategy, purified factor VIII or AZT, would be determined based on morbidity and mortality, including AZT morbidity and mortality, and corrected for treatments compensating for AZT toxicity. As yet, no controlled treatment studies based on a single AIDS hypothesis have been performed.

Nevertheless, the study by de Biasi *et al.* (de Biasi *et al.*, 1991) and with reservations that by Seremetis *et al.* (Seremetis *et al.*, 1993) come close to the stated criteria for a test of the foreign-protein hypothesis (Section 4.7). Seremetis *et al.* initially excluded, but later allowed AZT treatment. Both studies showed that purified factor VIII improved immunodeficiency (see ii). However, since all subjects in these studies were HIV-positive, one could indeed argue that the improvement of those treated with purified factor VIII was due to a cooperation between HIV and purified factor VIII.

The definitive treatment of immunodeficiency in hemophiliacs, or of hemophilia-AIDS, could be only as far away as the duration of one carefully controlled treatment test.

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