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Reappraisal of AIDS - Is the Oxidation Induced by the Risk Factors the Primary Cause?

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Abstract - The emergence of AIDS as a recognisable disease, its epidemiology, the clinical and laboratory data and the way in which they have been interpreted to deduce the currently acceptable hypothesis of its aetiology and mechanism of transmission are critically examined. There is no compelling reason for preferring the viral hypothesis of AIDS to one based on the activity of oxidising agents. In fact, the latter is to be preferred, since unlike the viral hypothesis it leads to possible methods of prevention and treatment using currently available therapeutic substances.

Introduction

Acquired Immune Deficiency Syndrome (AIDS) was first recognised in 1981 and by late 1985 more than 14,000 people had been diagnosed with the disease in the United States alone. The patients belong almost exclusively to a number of high-risk groups. Homosexual or bisexual males constitute the largest group, followed by intravenous drug abusers, Haitians and haemophiliacs. The main clinical signs of the disease are lymphadenopathy, opportunistic infections and malignancies especially lymphomas and Kaposi's Sarcoma (KS). The patients also have a pronounced depression of cellular immunity. There is an absolute lymphopenia and reversal of the usual ratio of phenotypic Thelper (OKT4+) to Tsuppressor (OKT8+) cells whereby the latter come to dominate among circulating lymphocytes. The circulating lymphocytes have decreased capacity to form rosettes with red blood cells,respond poorly to mitogenic stimulation, have decreased natural killer cell activity and other functional abnormalities.

To account for the immunological abnormalities, especially the decrease in T4 cells believed to be unique to this disease, Francoise Barre-Sinuossi, Jean-Claude Chermann and Luc Montagnier at the Pasteur Institute in Paris and a group led by Robert Gallo at the National Cancer Institute in America proposed that AIDS may be caused by infection of the T4 cells with a virus from the family of human T-cell leukemia (lymphotropic) retroviruses (HTLV). These include two major subgroups of human retroviruses called human T-cell leukemia-lymphoma retroviruses HTLV-I and HTLV-II. The supposed AIDS virus is called LAV (Lymphadenopathy Associated Virus) by the Pasteur group and HTLV-III (Human T-cell Leukemia (lymphotropic) Virus type III) by the Americans.

Because the viral envelope, which is required for infectivity, is very fragile and tends to come off when the virus buds from the infected T-cells, a direct infected T4-cell-to-non infected T4-cell contact is assumed to be required for the spread of the retrovirus (l). The main immunological reason for postulating that a retrovirus of the HTLV family may be the aetiological agent of AIDS was the finding that these viruses are immunosuppressive in mitogenically stimulated cell cultures (see below). The epidemiology of AIDS was also interpreted as supporting the viral hypothesis. There is abundant evidence that immunological changes in the AIDS patients and the development of KS and opportunistic infections are related to the number of homosexual partners and frequent receptive anal intercourse. According to the American Group, "This finding suggests that HTLV-III is sexually transmitted and that the rectal mucosa may be unusually vulnerable to passage of this lymphocytotoxic agent" (2) . The Carribean area, especially Haiti and Africa, have been suggested as possible sources of the AIDS virus. The main reason for this suggestion is the supposed high incidence of sera reactive for HTLV in Africa and AIDS in Haitians emigrating to the United States.

There are a number of findings which suggest causes other than HTLV-III/LAV: (i) In diseases which are known to have causes other than HTLV infections, the immunological abnormalities are similar to those seen in AIDS. These include Evan's, Gardner's and Behcet's syndromes, macroglobulinemia, tuberculosis, malaria, diabetes, aplastic anaemia, and thalassaemia (3,4,5,6,7,8,9, 10,11). Immunological abnormalities including inversion of the T4/T8 ratio can be induced by other viral and non-viral agents such as Epstein-Barr virus, chemotherapeutic agents, prednisone and adrenalin (7,12.13.14,15). (ii) Areas with high seropositivity for HTLV infection appear to be free of AIDS. About 25% of the population in Southern Japan appears to have antibodies against the virus compared to about 5% in Haiti and 1% in the United States, yet so far only 14 AIDS cases have been reported from Japan (iii) The epidemiological finding that AIDS development in homosexual men is directly related to the number of homosexual partners and frequency of receptive anal intercourse can be equally well or even better accounted for if sperm is considered an etiological factor. (iv) The high incidence of immunological and clinical abnormalities

found in the AIDS risk-groups, is also found in at least two other groups: aged individuals and patients treated with immunosuppressive agents for organ transplantation.

The possibility arises that the immunosuppressive agents used in organ transplantation, some parameter(s) associated with ageing and the risk factors in AIDS share a common property by which they induce similar effects. Evidence will be presented that: All the above agents are oxidising agents and by their oxidative nature induce malignancies, immunosuppression and increased susceptibility to infection. In AIDS viral infection including HTLV-III/LAV, if it exists, is the result of the disease and not its aetiology, although once present can further aggravate the disease.

AIDS-like Symptoms in Other Subjects

The aged individual, like the homosexual male, has a significantly higher probability than a young heterosexual of developing opportunistic infection. Even the seropositivity for HTLV-III/LAV in apparently healthy individuals increase with age (17). It is widely known that with age there is a marked decline in immune function and a marked increase in all cancers including KS. The increase in oxidative stress with age and its relationship to cancer development is also well known (18). Less well known is the evidence that the decline in cellular immunity is mainly due to lymphopenia and the alteration in cell function as a result of oxidative stress (19). In vivo (animals) age-associated cancers, decline in immune function and even death can he postponed by treating the animals with antioxidants. Similarly in vitro, antioxidants enhance the immune response of both young and old cells, the effect being 10 times (21,22) greater in old cells.

A striking resemblance seems to exist between organ transplant patients who are treated with radiation, chemotherapy or a combination of the two and the AIDS patients in terms of their increased susceptibility to opportunistic infection and the development of KS and immunosuppression (23,39) . The in vivo and in vitro effects on the immune system of these agents is similar to that seen in AIDS (24). In the organ transplant patient there is a lack of helper cells and an inverted T4/T8 ratio which persists beyond one year post-transplantation independently of graft versus-host disease status. The lymphocyte is also abnormal for more than one. year after transplantation (25). All the agents with which organ transplant patients are treated are either (21) alkylating or oxidising agents. Their effects can be prevented by the use of reducing agents. Even KS has been observed to regress when immunosuppression therapy is reduced or stopped (23).

AIDS in Homosexuals

The diseases fitting the AIDS definition appeared in homosexuals before 1981 when their symptoms started to be reported in the medical literature under the inclusive term of AIDS (21). The dramatic increase of their incidence after 1981 is generally believed to be due to infection of these groups with HTLV-III/LAV and to its transmission by sexual contact. However, other factors often associated with homosexual practice such as anal deposition of sperm and nitrites could produce the clinical and immunological abnormalities seen in these patients.

According to Gallo et al, "The epidemiology of this syndrome - that is, the increasing incidence and clustering of cases, particularly in New York and California -suggest the involvement of a transmissible agent (28). However, around the time of the first AIDS report two important changes took place in homosexual's lifestyle in these areas: increase in promiscuity and exposure to drugs, especially nitrites (29,30). Although nitrites came into use in the United States in the late 1960's their use became widespread around 1975. It is of great interest that the latency for appearance of KS in patients treated with immunosuppressive agents for organ transplantation appears to be the same as that between homosexual exposure to nitrites and appearance of AIDS. Of interest also is the fact that these drugs were first manufactured in California and then transported to New York, the two areas with the highest incidence of AIDS (23). These drugs are immunosuppressive, mitogenic and carcinogenic (31,32). Nitrites are oxidising agents and by this property they play a significant role in many biological functions (33,34,35). For example anaerobic bacteria use nitrites in place of oxygen as the terminal electron acceptor for growth and respiration (36,37,38).

It has been shown in a number of studies and should be emphasised that, unlike all sexually transmitted diseases, where both partners are equally susceptible to the disease, in homosexual males immunosuppression appears in the anal sperm recipients but not in the exclusive sperm donors (39). The risk factors in AIDS development are the number of homosexual partners and frequency of receptive anal intercourse (2). Furthermore, many of the AIDS cases diagnosed in women may have resulted from the practice of anal intercourse by heterosexual couples (39, 40, 41). More importantly, carefully designed animal experiments leave no doubt that sperm is a strong immunosuppressive agent (41,42,43,44). Sperm is one of the best known mitotic agents and like all other mitogens is an oxidising agent, its electrophilicity being a prerequisite for fertilisation (45). During spermatogenesis two main processes take place in the testes; morphogenesis of the maturing gamete whose chromatin becomes progressively condensed and replacement of the somatic histones with protamines by the oxidation of the sulphydryl groups (SH) to disulphide (SS). Although maturation starts in the testes, spermatozoa released from the seminiferous epithelium

are not fully mature from a functional stand-point and must complete their maturation by the oxidation of the SH groups to SS during the passage through the epididymis. The amount of cysteine residues present as SH in the spermatozoa from the caput, corpus and cauda epididymis and vas deferens being 50, 15, 5, and 3% respectively (46,47,48,49). Of pivotal significance to the present discussion is the finding of Hurtenback that mature sperm is much more effective in producing immunosuppression than immature sperm (43). Since the significant difference between sperm derived from the seminiferous tubules and mature ejaculated sperm is its degree of oxidation, it is highly probable that this property determines its immunosuppressive effects. This is reinforced by the finding that sperm from older animals, whose tissues are known to be more oxidised, is more effective in inducing immunosuppression (43). For the same reason, the homosexual male's sperm may be even more immunosuppressive than that of healthy heterosexuals. The fact that sperm does not seem to produce immunosuppression during vaginal sexual intercourse can be accounted for by a critical structural difference between the epithelium of the rectum and vagina (39,50). The vagina is lined by thick stratified squamous epithelium which makes ulceration and penetration of the semen into the vascular lamina unlikely. In contrast the semen in the rectum is separated from blood vessels and lymphatics by a single layer of cells which is easily penetrated and ulcerated during anal intercourse. In addition to lymphoma and KS the homosexuals have two other malignancies, cancer of the tongue and rectum (51). The increased incidence of these two cancers like carcinoma of the cervix in women, may be related to periods of high local concentration of sperm.

Gonorrhoea, syphilis, hepatitis B, herpes and amoebiasis are much more common among homosexual males than among heterosexuals. They also have a number of bowel infections which cause persistent and recurrent diarrhoea (30,51). Many of the agents used for the treatment of these conditions are oxidising agents, mitogenic and immunosuppressive (52,53,54). Furthermore, viruses, like all other cells, require SH for division and growth (54) which they obtain from the host, thus oxidising its tissues. Because oxidation of the host's immune system leads to immunosuppression, the possibility that all viruses are immunosuppressive to a greater or lesser degree is very likely. Two viruses, cytomegalovirus and Epstein-Barr virus although present among homosexual men, seem to be universal in AIDS patients as a result of reactivation of latent viruses (23,51). Both viruses produce clinical and immunological abnormalities similar to those seen in AIDS patients. Fever, rash, lymphadenopathy and enhanced susceptibility to other infections are common manifestations of infection with these viruses (51). These viruses induce immunosuppression in vitro and in vivo, including abnormalities in the T4/T8 ratio both in humans and animals (15,30,51,55). Both viruses have been isolated from many sites, including KS, from almost all AIDS patients (30,51). Unlike the above viruses, HTLV-III/LAV has never been isolated in fresh AIDS tissues. Nor is there any evidence that it produces in humans the clinical and immunological abnormalities attributed to it. Yet HTLV-III/LAV and neither the above viruses nor any other factor(s) is considered as the etiological factor of AIDS.

HTLV-III/LAV Infection

Gallo and his group state "The cytopathic activity in vitro, the repeated isolation from patients with AIDS and people at risk, and results of the seroepidemiological studies are all consistent with HTLV-III being the aetiological agent of AIDS (56). It is proposed to examine the epidemiological and seroepidemiological evidence as well as the isolation of the virus in some detail.

Many researchers have predicted that AIDS, like other sexually transmitted diseases, will spread by any type of sexual intercourse and more and more cases will appear among heterosexuals. So far this has not happened. According to Harold Jaffe, head of epidemiological studies of AIDS at CDC, as quoted in a Science editorial, the epidemiological pattern of the disease has undergone "remarkable little changes". Unlike many other viral diseases, AIDS cannot be spread even by prolonged close exposure to AIDS patients. According to the Acting Assistant Secretary for Health James O. Mason, "This is a very difficult disease to catch" (57).

An antibody molecule like that of all other proteins is determined by the linear ordering of amino acids in the polypeptide chain and by its three dimensional structure. The prevailing opinion is that the linear chain is determined by gene transcription. However evidence exists that both DNA and gene structure and function are regulated by the state of condensation-decondensation (contraction- relaxation) of the chromatin, which in turn depends on the cellular redox and its oscillation (45,58). The bonds which play an essential role in the three-dimensional configuration of the molecule are the SS bonds. According to Karush "...the disulfide links of the antibody molecule play an essential role in the acquisition of immunological specificity and by virtue of their covalent nature, provide for the stabilization of the particular structure underlying the specific activity of the molecule" (59). Furthermore, the pattern of pairing of sulfhydryl groups to form disulfides is not an invariant property of the linear chain but depends on extrinsic factors including the redox (59,60). In other words protein synthesis and specificity in general and antibody synthesis and specificity in particular is redox dependant. If this is so, then any agents who will induce the same redox

changes as a virus, could induce the synthesis of viral antibodies and antigens in the absence of the virus.

Viruses including RNA tumor viruses share antigenic determinants with normal host cell components, a phenomenon known as molecular mimicry (61). The same phenomenon may exist in the case of the HTLV-III/LAV virus. The most prominent and persistently detected antigen in AIDS tests is a protein of a molecular weight of 41.000 (p41), which is approximately the molecular weight of polymerized actin, a protein found in all cells including bacteria (62). A protein of the same molecular weight, isolated from a number of viruses, has been shown to be actin and to a major constituent of many viruses including RNA tumour viruses (63). It is of interest to note that the polymerised form of actin increases with oxidation (64,65). Of interest is also the fact that mitogenic stimulation of normal cells with ConA leads to the expression of oncoviral antigens without virus particle synthesis (66).

The presence of "natural" antibodies in the sera of physiologically healthy animals, directed against a "variety of antigens has been well established and documented (67) . Antibodies against the oncoviral proteins are widespread in non-infected human sera and vary with age (68,69). Furthermore, substances as diverse as normal components of the serum, extracts of bacteria and nonprotein molecules such as glycogen are important factors in determining whether a given human serum registers positive for oncovirus infection. Snyder et al discussing their work on human oncoviral antibodies concludes: "The results are consistent with the idea that the antibodies in question are elicited as a result of exposure to many natural substances possessing widely cross-reacting antigens and are not a result of widespread infection of man with replication-competent oncoviruses" (68). Barbacid et al state: "This finding not only demonstrates that the antibodies were directed against cellular rather than the virus-coded antigenic determinants but also exclude the possibility that this immune response was elicited as a consequence of oncovirus exposure" (69).

There are two blood tests routinely used for AIDS detection, ELISA and Western blot neither of which detects the virus itself. Although the latter test is more accurate, both give persistent false positive results. "The false positive problem has led to harrowing decisions about what to tell patients whose samples appear positive, although manufacturers stress that the current tests are not intended for use in diagnosis" (70). It is significant that the false positive results increase with age and "stickyness" of the serum, and the "stickyness' (viscosity) is redox dependent and increases with oxidation (71,72). The outcome of the tests seems also to depend on who is performing them. Thus one group found 7/10 sera positive for viral antibodies whilst another group testing the same sera found none (73). Most importantly Biggar et al found that the probability of having a positive ELISA for HTLV-I, HTLV-II and HTLV-III/LAV increases with age, poverty, immune complexes concentration and especially with malaria and other parasitic diseases. They conclude, "If the human retrovirus reactivity observed in ELISA tests is frequently nonspecific among Africans the causes of the nonspecificity need to be clarified in order to determine how they might effect the seroepidemiology of retroviruses in areas other than Africa". The only sensible conclusion is therefore that seropositivity does not mean virus positivity. However Gallo and his collaborators are of a different opinion and state "...we should proceed with blood-bank antibody tests (56). They base their opinion on the fact that HTLV-III/LAV can be isolated from the peripheral blood of >80% of people with serum antibodies to the virus. Although this is true, it is important to note that all the isolations are done in vitro (see below), after some unusual and drastic manipulation of the lymphocytes obtained from the patients.

The initial reaction to the retrovirus hypothesis was one of scepticism. However after the publications of the 1984 papers (Science 4 May) the theory became almost universally accepted. In these papers, in vitro experimental evidence for the detection and isolation of HTLV-III/LAV is documented. But in a paper subsequently published in the same journal in the same year (Science 7 December) the Americans, by using the Southern blot hybridization technique which can detect as little as one copy of viral DNA per cell, obtained negative results on fresh peripheral lymphocytes, lymph nodes, KS, bone marrow and spleen from AIDS patients and AIDS related complex (ARC). They conclude:"Thus the lymph node enlargement commonly found in ARC and AIDS patients cannot be due directly to the proliferation of HTLV-III infected cells as occurs with HTLV-I in adult T-cell leukemia. Whether the lymphocyte proliferation in lymph nodes occurs in response to infection with HTLV-III or another agent, or both, is not known. Similarly, the absence of detectable HTLV-III sequences in Kaposi's sarcoma tissue of AIDS patients suggest that this tumor is not directly induced by infection of each tumor cell with HTLV-III. Furthermore, the observation that HTLV-III sequences are found rarely, if at all, in peripheral blood mononuclear cells, bone marrow and spleen provides the first direct evidence that these tissues are not heavily or widely infected with HTLV-III in either AIDS of ARC".

In an article published this year by the French group it is stated: "It is unlikely however, that AIDS is the result of a direct progressive destruction of T4 cells by the virus for at least two reasons...". Thus the originators of the viral theory of AIDS agree that there is no direct evidence to support

their theory. What then about the claims of repeated isolation of HTLV from AIDS patients? All the experiments for detection, characterization, continuous production and isolation of HTLV-III/LAV are done on in vitro cultures. Furthermore, the cultures are not solely with T-cells from AIDS patients but cocultures with highly selected neoplastic T-cell lines (75). It must be emphasised that unlike other viruses HTLV-III/LAV has never been isolated as an independent stable particle. By isolation of the virus, in fact, it is meant transient detection in the cell culture of: viral antigens, viral antibodies, the enzyme reverse transcriptase (RT) and of virus like particles budding from the cellular membrane into the extracellular space. In the vast majority of cases isolation is synonymous with RT detection. However, apart from RT these cultures have almost any other enzyme implicated in DNA synthesis and "It has not been excluded that viral reverse transcriptases are cellular enzymes..." (76). The viral specificity of RT is believed to be given by the template primer it uses (76). For HTLV-III/LAV isolation the French and the Americans use either (dT)12-18.(A)n or (dT)15. (A)n as template primer (75,77). But, in earlier papers Gallo and his collaborators present evidence that "DNA polymerase gamma prefers exactly the same template as the one used for HTLV-III/LAV isolation (78,79). It is also significant that the kind of template a polymerase uses and its activity depends on the culture conditions and probably on the state of cellular development i.e. the activity of the enzyme depends on the normality of abnormality of the cells (79,80).

In rare cases by isolation is meant finding of virus like particles either in T-cells in vitro or cells other than T cells in fresh AIDS tissue (81,82). These particles are not only hard to detect but at least in some cases may be normal organelles not HTLV-III/LAV viruses (83). Furthermore, particle aggregation and budding have been proposed to be determined by actin-myosin interaction (84,85). It is of interest to note that actin-myosin interaction, particle aggregation and budding can be all induced by oxidising agents (84,85,86). Most importantly in vitro cultures with normal cells, virus-free, "...can be induced to produce particles which resemble RNA tumor viruses in every physical and chemical respect" (76). Aaronson et al. discussing their particular experiments can find only two explanations for this apparently universal phenomena: "The first was a chronic, low-level virus infection in the original primary embryo culture which could not be detected by the methods available. Under this hypothesis the virus could have persisted in a carrier state because there always were a few infected cells in the population...The second explanation was that virus began spontaneously in previously virus-free cells during the course of establishment of the cell lines. These findings provide strong support for the second model" (87). Although the retroviruses can arise spontaneously in virus-free cell cultures, the rate of appearance can be increased a million fold by the use of radiation chemical mitogens or infection of the culture with other viruses (88). Weiss et al in a paper entitled 'Induction of Avian Tumor Viruses in Normal Cells by Physical and Chemical Carcinogens' conclude: "The mechanism of induction is unknown. It is attractive to imagine that the endogenous viral genome exists as an integral part of the host cell chromosome, but there is little evidence for this assumption...We call them RNA tumor viruses in a taxonomic rather than an etiological sense...One can plausibly argue that the derepression of natural endogenous viruses is the result, not the cause of neoplastic changes...(89). At present the French believe that the AIDS virus does not belong to the "Superfamily" of leukemia viruses but is in fact a member of the lentivirus family of retroviruses as exemplified by visna virus(90). As far as the present discussion is concerned, this makes no difference. Induction of the visna virus as well as other viruses also requires in vitro activation (91,92). Of pivotal significance to the present discussion is the fact that the isolation and cytopathic effect of HTLV-III/LAV can be obtained and observed only in cells activated with various mitogenic agents such as ConA, PHA and irradiation. Notwithstanding, heroic measures such as pooling of AIDS sera, manipulation of culture conditions and selection of cell lines are necessary to isolate a virus (75). After all these conditions are satisfied "...only a small proportion of these cells is infected by the virus...at the peak of virus replication only 5-10 per cent of the cells express viral antigen...Furthermore only 10-20 per cent of clones derived from the CEM T4 cell line are susceptible to LAV infection even though they all express the T4 molecule on their surface (74. Meanwhile, the non-stimulated AIDS cocultures behave like normal cell cultures in respect to HTLV-III/LAV infection, that is, there is no infection (93). On the other hand, HTLV-III/LAV has been isolated from mitogenically stimulated cocultures from cells lacking both HTLV-III/LAV DNA and RNA (94). In a paper published this year in which Gallo is a co-author, it is stated, "In the present study T4 cells from normal donors that were infected with HTLV-III in vitro, after stimulation with PHA followed the same pattern of secretion of 1L-2 (day 1), production of HTLV-III and cell death", that is the same pattern as PHA stimulated cells from AIDS donors (93). Whereas the same infected cells "...did not produce IL-2 or express virus without immunological activation" (PHA stimulation). Since this is the case, even assuming that HTLV-III/LAV exists in vivo and is transmitted from a sick individual to a normal one, the normal person would never become ill unless he is exposed to high concentrations of mitogenic agents. In other words HTLV-III/LAV by itself cannot produce ill effects while the mitogenic agents would produce the immunological and clinical abnormalities associated with AIDS irrespective of

HTLV-III/LAV infection. It is important to note that in the above mentioned paper evidence is present that PHA produces immunological abnormalities in normal non infected cell cultures, including T4 loss. ConA is also immunosuppressive both in vivo and in vitro (95).

Equally important is the fact that when normal T and B lymphocytes are stimulated either in vivo or in vitro with ConA they display viral antigens on their surfaces (66). The situation is as follows: There are two agents A (HTLV-III/LAV) and B (sperm, nitrites, opiates, factor VIII), however only B is pathogenic on its own. Yet A is considered as the primary causative agent. This becomes even less probable if one realises that the methods for the detection of A are non-specific. Because the AIDS patients are also exposed to mitogenic agents, activation of different viruses can be expected. Thus unlike the HTLV-III/LAV infected T4 cells hypothesis, these mitogenic agents could account for both the viral activation and the AIDS related malignancies. Furthermore the mitogenic agents, being oxidising agents, can also account for the cellular immunosuppression observed in these patients. The lymphocytes have a relatively high negative charge (96). Their functions, including response to mitogens, rosette formation, suppressor/helper activity and natural killer cell activity depend on this negative charge. Oxidation leads to suppression of the above activities (96,97,98,99). As has been pointed out earlier, the absolute lymphopenia, preferential decrease in T4-cell numbers and the inversion of the T4/T8 ratio is not specific to AIDS but is widespread and exists in many diseases without retrovirus infection. In AIDS these abnormalities in T-cell numbers could be real or apparent and result from: (i) The extremely high sensitivity of T cells to oxidative stress (ii) T4 cells having a lower negative charge than the T8 cells (99) could be the first to be destroyed by persistent oxidative stress. (iii) The T4 cells could be preferentially sequestrated in diseased peripheral tissues. (iv) The binding of antibodies to the cell surface depends on the environmental redox state and the relative charge between the cell (negative) and antibody (positive), surface antigen and binding of antibodies decreasing with cellular oxidation (100,101,102). Modification of the environmental conditions leads to changes in the T4/T8 ratio in a given population of lymphocytes (103,104).

AIDS in Non-Homosexuals

According to Gallo and his group "...epidemiological studies carried out chiefly by the Centers for Disease Control in Atlanta, Georgia, particularly those pertaining to transmission of the disease by filtered factor VIII in blood transfusion cases strongly implicated a viral agent as etiological factor of AIDS" (56). It seems logical and has been already stated by Gordon that, "This finding is, however, also compatible with the possibility that factor VIII induces immunosuppression without the intervention of an infectious agent (105). The evidence available in the literature supports this latter interpretation. Seventy percent of hemophiliacs have been reported as being seropositive for HTLV-III infection as compared to about 45% of a randomly selected homosexual group from an area of high AIDS incidence (57). But only 0.06% of hemophiliacs develop the disease (106). Like in all other AIDS patients, the virus in these groups has been isolated only in vitro (107) . Factor VIII has been found to be immunosuppressive both in vitro and in vivo, the T4/T8 ratio being inversely correlated with the quantity of factor VIII concentrate administered. The in vivo studies led the authors to conclude: "...It is difficult to explain all of the observed immunological differences between patients with severe hemophilia A and those with hemophilia B purely by the transmission of an infectious agent..." (108). Evidence exists that all clotting factors are oxidising agents, the strongest being factor VIII. Factor VIII is a high molecular weight glycoprotein complex, whose subunits are linked by a large number of SS bonds. The SS bonds are required for agglutination activity. Antioxidants induce a dose related activity decrease of all coagulation factors including factor VIII and IX (109,110). There are reports which claim that the virus and thus the disease is transmitted via blood/blood products other than clotting factor concentrates. The first and best known appear to be that of a prematurely born infant who died at 17 months from recurrent infection and the 18 cases reported to the CDC, by August 1983 (111,112). The authors of the first report, although concluding that the infant developed AIDS as a result of HTLV-III/LAV infection transmitted by multiple blood administration, do not exclude the possibility that he was born with a primary immunodeficiency disorder. More importantly, all blood was irradiated with 30Gy before administration. Radiation is known to produce both immunosuppression and activation of proviruses. The 18 cases reported to the CDC and classified as transfusion associated AIDS via HTLV-III/LAV were diagnosed during approximately a 12 month period when over 3 million Americans received transfusions. Two of the patients most probably had received radiation, chemotherapy or both. These 18 patients were older than other groups with AIDS (40% were over 60 years of age). Fifteen of these patients (83%) received transfusion in association with surgery. Surgery may be immunosuppressive (113) and is known to be associated with infections other than HTLV-III/LAV, the risk increasing with age. More importantly Grady et al (l14) have shown that an inverse relationship exists between the percentage of T4 cells and the number of units transfused. The above authors conclude: "Accordingly we suggest that studies which purport to show a relationship between the transfusion of blood/blood products and AIDS be viewed with caution". What is now reported as AIDS in a very small proportion of hemophiliacs receiving

coagulation therapy and recipients of transfused blood is only manifested as opportunistic infection. Cases appearing before 1981 would not have been identified as AIDS. Since tissues of AIDS patients in general are likely to be abnormally highly oxidised, clotting and blood factors from these patients can he expected to contain more SS bonds and there fore be even more immunosuppressive. Heating the agglutination factors to inactivate a supposed AIDS virus will, in fact, break at least part of the SS bonds and thus decrease both their immunosuppressive activity and therapeutic effectiveness.

Immunological and clinical abnormalities similar to those seen in AIDS have been reported in drug abusers as far back as 1973 (115,116,117). The immunological abnormalities include: absolute lymphopenia, decreased concentration of Igm and IgG antibodies and false-positive serological tests in as many as 40% of drug users. The clinical abnormalities include: lymphadenopathy ranging from benign hyperplasia to malignant lymphoma, other malignancies, fever, night sweats, chills, weight loss and increased susceptibility to infection. Opiates, like nitrites, are oxidising agents. They produce their effects by binding to the membrane SH. Their effects can be prevented and reversed by reducing agents. The effectiveness of the reducing agents is directly related to their negative redox potential, Eo.

According to Gallo the HTLV-III/LAV and thus AIDS originated in Africa (56). He bases his hypothesis on: (i) The isolation from the lymphocytes of the African Green Monkey of a retrovirus closely related to HTLV-III/LAV (119). (ii) The reported high seropositivity for HTLV infection in Africans (56). (iii) The finding of HTLV-III/LAV, antibodies in sera collected from Africans before the recognition of AIDS (71). (iv) The diagnosis of AIDS in Haitians via which the HTLV-III/LAV is supposed to have been transmitted from Africa to America. The virus was isolated in vitro cell cocultures and the monkeys were healthy and free of AIDS. Although some authors claim high seropositivity for HTLV infection in Africans, others find only negative results. Thus Weiss et al did not find antibodies to HTLV-I in 1225 sera from donors of different African countries nor did Karpas et al in sera from Israeli Falashas in which others have reported a 37% positivity (73,120). The prevalence of antibodies against the HTLV-III/LAV virus has been reported to vary from 6-50% in different African countries. Yet relatively few AIDS cases have been reported from this continent (117). It is important to note that the test for HTLV-III/LAV antibodies in Africans are non specific and that the reported AIDS cases from this continent seem to correspond geographically to these regions where anal intercourse is a common practice among heterosexual couples (17,121). Equally important is the fact that African sera tend to be "sticky", which means that antibody tests can give relatively high levels of false positives and some investigators contend that this problem increases with age of the serum (71). As far as the Haitian connection is concerned, "This speculation is based on no data..." (51). Furthermore, recent evidence became available which shows that "risk factors are present among most patients with AIDS in Haiti" (122).

Conclusion

There are good reasons to doubt that HTLV-III/LAV can be regarded as the exclusive single variable in the pathogenesis of AIDS. There is therefore a spectrum of possibilities. Either it plays no role at all, is of minor significance or it contributes significantly but not exclusively to the disease. Be that as it may the one major significant variable is the concurrent exposure of the patients to oxidising agents including sperm, nitrites, opiates and factor VIII. If this is true then prevention, and possibly even cure, may be achieved with the use of appropriate antioxidants.

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