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ACQUIRED IMMUNE DEFICIENCY SYNDROME—AN OVERVIEW

Articles, letters and comments on the Acquired Immune Deficiency Syndrome (AIDS) have rarely been absent from either the medical or popular press since the first clinical descriptions of the disease in June 1981 and this is a reflection of rapidly developing knowledge. These first reports recorded by the Centre for Disease Control (CDC) (1), detailed cases of five young homosexuals from Los Angeles who died of *Pneumocystis carinii* pneumonia (PC). This was soon followed by reports of the deaths of a further 26 homosexuals who had developed a rapidly progressive form of Kaposi's Sarcoma (KS) (2). It was soon apparent that these cases represented the first reports of a new epidemic, one which medicine had not seen before, and one which has had dramatic consequences scientifically, medically and socially.

Dysfunction of the patients' cell mediated immune system is the characteristic feature of the disease. As of October 1984 there have been approximately 7,000 reported cases of AIDS with a world wide mortality rate overall of around 40 per cent (3). However, this is an underestimate due to the long incubation period and it is clear that 80 per cent of the earliest diagnosed patients have now died. The growth of numbers of reported cases has been exponential in all countries especially the USA and if this pattern continues in Great Britain then by the end of 1985, the 88 recorded cases to date (1.12.84) will have risen to over 900 (4). Similarly in Europe the number of reported cases has risen by over 100 per cent in the last eight months. Originally it was thought to affect the following groups: homosexuals (5), haemophiliacs (6), Haitians (7) and intravenous drug addicts (8) but now there are also well documented reports of AIDS in blood transfusion recipients (9), sexual partners of AIDS victims (10) and even babies of affected mothers (11). Table I gives a breakdown of recorded cases in Britain.

Most of the victims die of either an aggressive form of KS, opportunistic pneumonia caused by PC or a combination of both. Persons who present with KS generally have a lesser immunodeficiency and a better prognosis than those with opportunistic infections. There have also been many reports (12) of other infections or disorders associated with AIDS as shown in Table II.

Immunology

So why do these patients succumb to opportunistic infections or KS? The main problem seems to be a deficient cell mediated immune response. This is characterised by a striking lymphopenia, with a reduction in absolute numbers of the helper cell subset of T lymphocytes (T_4). This along with usually normal T suppressor (T_8) numbers consequently gives rise to a reversal of the normal T_4/T_8 subset ratio (13). Although not in itself diagnostic of AIDS, the subset ratio is one of the first laboratory tests to become abnormal in AIDS. However, for asymptomatic 'at risk' members of the community, who may have a normal lymphocyte count, quoting reversed subset ratios can be misleading as it may conceal increased T8 cells due to infections which although unrelated or irrelevant to the cause of AIDS are found more often in the 'at risk' populations. Many clinicians have also failed to realise that the phenotypic descriptions given to lymphocytes by the presence of surface markers *i.e.* helper (T_4) and suppressor (T_8) do not always reflect the cell's function. Early in maturation T cells express both T_4 and T_8 markers and only once more mature do they express either marker alone. The surface markers may be more involved in cell to cell communication than in indicating the cell's function (14) as exceptions to the rule that T_4 = helper activity and T_8 = suppressor/cytotoxic activity exist (15). So how does an upset to the normal T_4/T_8 ratio affect the function of the immune response? To most clinicians a successful cell mediated response with the expulsion of foreign antigen results from T cells reacting with antigen and recruiting

Table I. Reported cases of AIDS in UK to December 1984.

No. of cases	88
Deaths	37
Homosexuals	77
Haemophiliacs	3
Africans (all women)	3
Others	5

Table II. Immunologic abnormalities associated with AIDS.

1. **Clinical Features**
   - (I) Lymphopenia—Due to Selective Deficiency in Absolute Numbers of T_4^+ Helper T-Lymphocytes
   - (II) Opportunistic Infections and/or Kaposi's Sarcoma.
   - (III) Reduced or absent DTH to recall antigens.
   - (IV) Hyperglobulinaemia—often elevation of one or more immunoglobulin class.
2. **Laboratory Findings**
   - (I) Decreased reponse of peripheral blood lymphocytes to:
     - (a) Mitogen
     - (b) Antigen
   - (II) Decreased NK Activity
   - (III) Altered Monocyte Function
   - (IV) Inversal of T_4/T_8 Ratio—due to decrease in absolute No T_4 cells.
3. **Other Findings**
   - (I) Elevation of B_2 Microglobulin and α_1Thymosin Serum Levels
   - (II) Decrease Production of Interleukin 2 and Immune-Gamma-Interferon.

killer cells by releasing various factors. Although essentially correct, this view of the immune response is rather simplistic. Mature immune T cells recognise foreign antigen only when it is presented in conjunction with molecules of the major histocompatability complex (MHC). This phenomenon was discovered by Zinkernagel and Docherty (16) when they found that a T cell once selected by a specific antigen in conjunction with one of the polymorphic variants of the MHC can only be activated by the same antigen-MHC molecule combination. This is 'MHC-Restriction' and is now one of the fundamental concepts of modern Immunology (17). T cells are restricted by either class I (HLA-A, B, C) or class II (HLA-D region) antigens. Regulatory T cells (helpers and suppressors) recognise antigen in association with class II antigens whereas the cytotoxic effector T cells respond to antigen in the context of class I MHC molecules. Helper T cells recognise antigen presented to them by macrophages or other Ia(Dr)positive antigen presenting cells. This stimulates them to proliferate and release factors such as Interleukin 2 which provides one of the signals required to activate the responder cells. The importance of the helper cell in a cell mediated response and the lack of such cells as in AIDS patients is self apparent.

In vitro studies on T cell function using peripheral blood lymphocytes from AIDS patients show decreased transformation responses to antigen or mitogen (such as PHA, PWM) (1, 5, 13). Remaining helper T cells from AIDS patients seem to respond abnormally whilst T_8 are unaffected. *In-vivo* skin test studies show that AIDS patients are anergic to challenge with recall antigens (1, 3). This seems to be due to a failure of the T_4 cells involved in triggering a delayed type hypersensitivity response rather than a failure of the final pathway of the inflammatory response which seems to be normal.

The low pokeweed mitogen response suggests that B cell function is also affected. AIDS patients are usually hyperglobulinaemic with approximately 90 per cent of them having elevated levels of at least one immunoglobulin isotype (18). This suggests polyclonal activation a suggestion which is backed up by *in vitro* studies (19). This finding is somewhat surprising as antibody production ususally requires T_4 cells (which are very low or absent in AIDS patients) to stimulate B cell differentiation. Also T_8 cells which seem normal in these patients would be expected to suppress antibody production. It has been suggested that the intrinsic B cell defect results from *in vivo* stimulation of the B cells which then cannot respond to mitogens *in vitro*. This accounts for the observed hyperglobulinaemia rather than hypogammaglobulinaemia which one would expect to be associated with a poor PWM proliferation response.

Natural killer cell (NK) activity as detected by the K562 cytotoxicity assay seems to be reduced by up to 50 per cent in AIDS patients (3, 20). This parallels the reduction

of cells found in the blood which react with HNK or Leu 7 *i.e.* monoclonal antibodies specific for NM cells. Monocytic function is also defective but tissue macrophage dysfunction may be a result of defective T cell-macrophage cooperation (21, 22).

Other abnormal findings in AIDS patients include decreased, levels of gamma interferon and interleukin 2, and elevated levels of B_2-microglobulin and α_1-thymosin (23-25). A summary of immunologic abnormalities is given in Table III.

Table III. Major disorders in AIDS patients.

Opportunistic Infections	Tumours
Parasitic	
Pneumocystis carinni pneumonia	Kaposi's Sarcoma
Cryptosporidiosis	Lymphocytic Leukaemia
Toxoplasmosis	CNS Lymphoma
Strongylodosis	Burkitt Like Lymphoma
Isospora Belli	Undifferentiated Non-Hodgkin's Lymphoma
	Angioblastic Lymphadenopathy
Fungal	
Candidiasis	
Aspergillosis	
Cyptococcosis	
Nocardiosis	
Zygomycosis	
Histoplasma	
Bacterial	
Mycobacterium tuberculosis	
Mycobacterium avium intracellulare	
Salmonella spp.	
Viral	
Cytomegalovirus	
Herpes Simplex	
Varicella Zoster	

Epidemiology

Questions have been asked regarding where the disease started and how it has spread. Retrospective studies have suggested that AIDS has been present in Zaire since 1976 about two years before the first recorded cases in USA or Haiti. It has been suggested that Haitians who over the years worked and lived in Zaire have taken the disease back to Haiti. Haiti is a favourite holiday island for American homosexuals and many of the European homosexual cases have admitted relationship with US homosexuals. They could therefore have brought the disease across the Atlantic into Europe where it has spread onto the other 'at risk' groups. It has been suggested that the early Portugese explorers may have taken HTLV to the affected islands of Japan because they took African slaves with them on their journeys.

Aetiology

It now seems certain that a specific transmissible agent is responsible for AIDS (27-30). There have, however, been other hypothesis put forward which may or may not contribute to the disease in certain circumstances. At an early stage in the epidemic it seemed that the disease was confined to the promiscuous homosexual community. This led to suggestions that the use of various 'relaxing drugs' especially amylnitrite could be an associated factor. Although some studies supported this idea, nitrites no longer seem to be a major causative factor. Secondly, the abnormal sexual practices of homosexuals also gave rise to the suggestion that sperm absorbed into the blood stream from the rectum may be involved (31). Animal experiments have shown that repeated injection of allogeneic sperm can be immunosuppressive and clinical studies have found anti-sperm antibodies in homosexuals (32). A further suggestion was that the introduction of allogeneic lymphocytes into the lymphatics or blood stream by anal intercourse could cause immunosuppression. Again animal experiments led to this idea when it was shown that injecting parental leukocytes into F_1 hybrid mice resulted in long lasting immunosuppression of both T (33) and some B cell (34) responses. These two experimental findings coupled to the effects of multiple infections from which homosexuals suffer led to the hypothesis that an antigen overload was causing AIDS. However, both of the these hypotheses on the cause of AIDS had the main weakness that they did not account for the cases of AIDS in non-homosexuals *e.g.* blood product recipients. All the evidence now suggests that the disease is caused by a transmissible agent.

Early thoughts on the identity of the virus which could cause such a disease included Hepatitis B virus or a mutated Cytomegalovirus (CMV). Although CMV is found in almost 100 per cent of homosexuals there seemed no difference between the strains isolated from either AIDS victims or the seemingly asymptomatic population (3). The search continued for another virus and in May 1983 human T cell leukaemia virus HTLV was first suggested (35). It had already been noted that a virus called Feline Leukaemia Virus, not dissimilar to HTLV,

produced AIDS-like symptoms in cats (36). Gallo's group at the National Cancer Institute reported the isolation of HTLV from an AIDS victim (35). Essex and others reported antibodies to HTLV in both AIDS patients and lymphadenopathy patients (37). At the same time Montagnier's group at the Pasteur Institute in Paris reported the isolation from lymphadenopathy patients of a virus distinct from HTLV I (38). They called it lymphadenopathy Associated Virus (LAV). This virus showed a tropism for T helper cells, caused giant cell formation after infection and displayed a cytopathic effect on T helper cells. The breakthrough came in May of this year when Gallo and coworkers published results of extensive work into the study of a new virus which was isolated from AIDS victims (27-30). This virus, distinct from HTLV types I and II, was called HTLV III. Studies now suggest that it is probably identical to that originally isolated by the Paris group.

HTLV III has been shown to be preferentially lymphotrophic for T4 cells. This would account for the low T4 numbers found in AIDS patients. On infection it involves formation of giant multinucleated cells which are often seen in infected patients. It is not known how HTLV III initially infects the cells but it is thought that the helper cells must be activated before they can become infected. This would put homosexuals at great danger as they often have activated cells due to the numerous unrelated infections they contract. Virus particles have now been shown to be released from infected cells by a budding process.

Tests have recently become available to test for antibody to HTLV III. Studies in London (39, 40) have shown that almost 100 per cent of AIDS patients and 89 per cent of patients with persistent generalised lymphadenopathy were seropositive. Perhaps of more interest is the relatively high seropositivity in either symptomatic or asymptomatic 'at risk' patients. Other studies have shown that a proportion of asymptomatic people who were seropositive have gone on to develop AIDS or AIDS related complex. However, one should not assume that all seropositive subjects will develop AIDS. A more worrying statistic is that around 34 per cent of the haemophiliacs in the London study who had received FVIII concentrate are seropositive. As yet it is not known whether these patients have been challenged with virus and have raised a successful immune response to it or whether the long incubation time of this disease will mean that these patients will eventually show symptoms of AIDS.

The virus itself has now been isolated from many AIDS cases. Recent publications (41-43) have isolated the virus from semen, saliva and blood of not only pre-AIDS or AIDS patients but also from seemingly healthy homosexuals. It is not known yet whether these virus positive homosexuals will succumb to AIDS but the findings of virus in these various body fluids must increase the fear that horizontal transmission of this disease will become an increasingly important problem.

Much work is now being done on the molecular cloning and characterisation of HTLV III (44). This has been made possible because of the discovery of a T-cell line (H9) which permits the growth of HTLV III without itself being destroyed by the virus. Results show that different isolates show substantial diversity in restriction enzyme cleavage patterns. The possibility of virus variability has important implications in trying to devise preventative measures against AIDS similar to the problem of trying to produce a successful anti-influenza vaccine.

Implications

So what are the implication for already diagnosed AIDS patients and for those who fall into 'at risk' groups? Obviously the goal is to find a cure but until then what must be done for sufferers and 'at risk' groups? The media coverage which AIDS has attracted must surely have alerted all who may be at risk (with the exception of babies). It is probable that like hepatitis B and nonA-nonB the virus may be transmitted in blood and blood products. Already there have been over 70 reported cases of AIDS in patients who did not belong to any at risk group but who had previous blood transfusions (9, 45). There have recently been press reports from Australia that three babies have died of AIDS and one is seriously ill after receiving

blood transfusions from a homosexual who has now been confirmed as suffering from AIDS. This has serious implications because now it is necessary to look at the safety procedures used in obtaining blood and blood products. The first approach must be containment. In America blood donors are now screened for the presence of antibody to HTLV III and if found to be positive will be excluded from donating. In Scotland if they belong to any 'at risk' group they will be excluded. More work is immediately needed into methods of sterilisation of blood products by heating or other physical methods. From January 1985 all Factor VIII for use in haemophilia in Scotland will be heat treated.

There have, as already mentioned, been cases of AIDS in haemophiliacs (6, 46) caused it is thought, by infusion of contaminated Factor VIII concentrates. However, for haemophiliacs in Scotland the picture may be different. Although Britain as a whole will not be self sufficient in FVIII until 1986 here in Scotland we now produce enough concentrate from locally collected blood to meet demands. In a recent study in our department (submitted for publication), of 77 patients there was antibody seropositivity to HTLV III in only 13 per cent of them. This is much less than that found in London (39) (34%). The one haemophiliac who has died of AIDS in Scotland received a large amount of commercial FVIII from the USA whilst being treated in England. The implications are that in Scotland the AIDS virus does not seem to have affected the donor pool as yet but a test for HTLV III virus antigen, which should be available soon, will be valuable in screening for virus contamination. Until then, however, there still is a possibility of a donor with a pre-clinical infection giving blood which might be processed into a large pool of FVIII concentrate and other blood products. In America there are now over fifty reported cases of AIDS in haemophiliacs (47). The commonest infection is PC and unlike AIDS in other 'at risk' populations KS has been absent except for one report in a patient who was factor V deficient. There are some other differences between AIDS in haemophilia compared to homosexuals. No patient was described before late 1981, the original cases were in areas not previously associated with AIDS *i.e.* Ohio and Georgia and the age distribution is much wider (10-70 years). There has been no common batch of FVIII associated with the cases of AIDS and in fact there are numerous other patients who received the same batches but have not presented with symptoms of the disease. An American study looking for antibody to HTLV III virus in haemophiliacs showed seropositivity of 74 per cent for FVIII recipients and 39 per cent for FIX recipients (42). Also 30 of the 52 cases in America have died and only three of the survivors were diagnosed more than a year ago (47). Another great problem is how to treat confirmed cases of AIDS. Gallo's recent findings (41, 43) that virus can be isolated from various body fluids means that barrier nursing and great care in handling samples is essential. At the moment the recommendation is that this should be similar in nature to the regulations for the handling of hepatitis B patients. It is thought that current laboratory procedures are adequate when handling samples from those who although belonging to 'at risk' groups show no clinical signs of disease.

It is important to emphasise that no health workers involved in the study of AIDS patients have themselves contracted the disease but the reported cases of both heterosexual spread to partners of AIDS victims (10) and to babies of infected mothers (11) does show that in certain circumstances horizontal transmission is possible.

The prognosis for already diagnosed patients seems at the moment to be poor, as to date, there have been no reports of successful treatment as indicated by the high mortality rate. There have been various attempts to find effective therapy. Direct attempts to tackle the opportunistic infections with drug therapy have had limited success. Cotrimoxazole is still the drug of first choice for PC and this may be given prophylactically. Cytotoxic therapy for KS has also been difficult because of the danger of further immunosuppression. More adventurous attempts at therapy have included white cell tranfusion (48), bone marrow and thymic transplantations, but those have met with little or no success. Attempts have been

made to augment any remaining immune response by injections of the missing lymphokines *e.g.* Interleukin 2 and gamma-interferon but although *in vitro* studies were promising, the clinical trials have not been encouraging. An immunopotentiating drug, Isoprinosine, has also been tested. As the name suggests this drug should potentiate the immune response. There have been some suggestions that this drug has had limited success in restoring the immune response by increasing NK activity, increasing lymphocyte count (especially helpers) and returning to normal the levels of Interleukin 1 and Interleukin 2; though much more work is required to fully evaluate its role in therapy.

In summary, there is obviously much work still to be done on AIDS. It is essential to find exactly what factors predispose certain people to the disease whilst others seem resistant to infection. It is also important to find a test which will predict the onset of the disorder and to establish the implications for people who are seropositive for antibodies to HTLV III.

Finally, the goal must be to develop botl rational therapy for AIDS sufferers and ai effective vaccine against the causative retrovirus.

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