REVIEW

The acquired immune deficiency syndrome

A. J. PINCHING *Department of Immunology, St Mary's Hospital Medical School, London,
UK*

INTRODUCTION

The emergence of a new and epidemic form of acquired cellular immunodeficiency over the last 5 years has had wide ranging implications—clinical, scientific and social. Few medical conditions can have caught the imagination of both the public and the scientific community so rapidly and so extensively as the acquired immune deficiency syndrome (AIDS). The exponential spread of the disease is matched by the increasing literature on the subject and our swiftly changing perception of the disease. While much has been learnt about how the disease behaves, major uncertainties remain as to aetiology and pathogenesis. For these reasons any review of the disorder, even more than usual, reflects a highly personal view of the evidence available at the time of writing. Underlying the present eclectic account is a set of hypotheses that to my mind best fit the data, but I shall indicate where major alternatives exist.

There are those who feel that the term 'acquired immune deficiency syndrome' is less than ideal because it ignores other recognized acquired immune deficiencies. While this may be so, the term is not inappropriate and is clearly used to refer to the epidemic variety. Alternative terms that have been proposed suggest aetiological or pathogenetic mechanisms of doubtful validity or imply that there are distinct syndromes affecting the different epidemiological groups. Few medical terms can have so rapidly become part of lay parlance and any attempt to change the terminology now would seem as doomed to failure as it is unnecessary. The definition of AIDS used by the Centers for Disease Control (CDC) in Atlanta, Georgia, USA for epidemiological purposes is 'a reliably diagnosed disease that is at least moderately indicative of an underlying cellular immune deficiency' in a person with 'no known underlying cause of cellular immune deficiency, or other cause of reduced resistance reported to be associated with that disease'. It may be paraphrased as meaning 'previously normal people behaving as though they had been immunosuppressed'. While the formal definition necessarily excludes many disorders that may ultimately be shown to be related to AIDS, it is currently preferable to a more inclusive definition as it avoids introducing a heterogeneity of aetiologies that would confound the search for the cause of AIDS. Once the aetiology has been established we may be able to perceive a much broader spectrum.

THE CLINICAL SYNDROME

Table 1 outlines the major disorders that have been described in patients with AIDS. While *Pneumocystis carinii* pneumonia and Kaposi's sarcoma are among the most distinctive features and remain the commonest manifestations, it is the overall pattern of secondary diseases that best delineates the underlying basis for the syndrome. The list of infections (Gottlieb *et al.*, 1981, 1983; Masur *et al.*, 1981; Siegal *et al.*, 1981; Follansbee *et al.*, 1982; Mildvan *et al.*, 1982a; Greene *et al.*, 1982; Goldfarb *et al.*, 1982; Masur *et al.*, 1982; Miller *et al.*, 1982; Andreani *et al.*, 1983; De Jong *et al.*, 1983; Wormser *et al.*, 1983; Davis *et al.*, 1983; Poon *et al.*, 1983; Elliott *et al.*, 1983; Vieira *et al.*, 1983; Pitchenik *et al.*, 1983; Malebranche *et al.*, 1983; Pape *et al.*, 1983) immediately presents a

Correspondence: Dr Anthony J. Pinching, Department of Immunology, St Mary's Hospital Medical School, Norfolk Place, London W2 1PG, UK.

A. J. Pinching

Table 1. Major disorders in AIDS

Opportunistic infections	Tumours
Pneumocystis carinii	Kaposi's sarcoma
Cytomegalovirus (reactivation)	Burkitt like lymphoma
Herpes simplex (locally invasive)	Unidifferentiated non-Hodgkin's lymphoma
Candida (locally invasive/disseminated)	CNS lymphoma
Mycobacterium avium intracellulare	Angioblastic lymphadenopathy
Mycobacterium tuberculosis	Lymphoblastic preleukaemia
Cryptococcus neoformans	
Toxoplasma gondii	
Salmonella spp.	
Cryptosporidium	
Isopora belli	
Papovavirus	
Nocardia	
Histoplasma	

pattern familiar from immunodeficiency diseases and, almost without exception, implies cellular immune deficiency. The pattern has been established in congenital disorders such as severe combined immunodeficiency (SCID) and in iatrogenic immunocompromise following immunosuppressive therapy, such as that after organ transplantation. Similarly, Kaposi's sarcoma (apart from the classical form) (Hymes *et al.*, 1981; Friedman-Kien *et al.*, 1982; Drew *et al.*, 1982; Pitchenik *et al.*, 1983; Pape *et al.*, 1983; Gottlieb *et al.*, 1983) and other tumours in AIDS (Ziegler *et al.*, 1982; Snider *et al.*, 1982; Volberding, 1984) are similar to those seen in patients on long term immunosuppressive therapy following organ transplantation or treatment for systemic lupus erythematosus (SLE). Many of these tumours have been associated with certain viral agents (cytomegalovirus [CMV] and Epstein–Barr [EB] virus) and may be regarded as examples of viral oncogenesis. It may be useful to consider such tumours a consequence of opportunist infection with oncogenic viruses. For convenience I shall refer to them as opportunist tumours. The novel occurrence of these opportunist infections and tumours in the same epidemiological groups (see below) leads to the hypothesis that AIDS comprises a central underlying immunodeficiency that may manifest itself by a wide variety of secondary diseases. These multiple final paths may vary in pattern according to genetic factors (e.g. ethnic background and HLA DR5 in Kaposi's sarcoma, Friedman-Kien *et al.*, 1982; Pollack *et al.*, 1983), exposure to environmental opportunist pathogens (differences between geographical areas) and previous exposure to microbial agents that can remain latent in host cells (e.g. CMV and Herpes simplex in homosexuals, toxoplasma and *Mycobacterium tuberculosis* in Haitians). The primary cause of the immunodeficiency need not be one of the causes of the opportunist infections or tumours.

A detailed description of the clinical presentations of individual manifestations of AIDS is beyond the scope of this article and readers are referred to the review by Gottlieb *et al.* (1983) as well as to individual reports (see previous references). A number of points should however be highlighted because they have direct implications for the immunological appraisal of AIDS. In general opportunist disease in AIDS is more severe than that seen in iatrogenically immunosuppressed patients although it may not be so broad. In AIDS this certainly leads to more widespread or more invasive disease with a higher yield of organisms (e.g. Pneumocystis) and minimal or no evidence of host response, either systemically or in tissue (e.g. granulomata in Mycobacterial infection, Greene *et al.*, 1982). The rate of progression of tumours similarly tends to be greater than in other comparable settings. Some of the organisms are of a type rarely seen even in other immunosuppressed hosts (e.g. *Mycobacterium avium intracellulare*), another indication of the depth of immunosuppression. Further evidence of this comes from the lesser efficacy of anti-microbial therapy for given infections in AIDS as compared with other immunosuppressed states (e.g. failure to respond to cotrimoxazole and/or pentamidine in Pneumocystis infection). The high mortality

rate of AIDS (over 80% 2 year mortality) reflects the irreversible immunodeficiency and the ultimate development of untreatable opportunist infections or of extensive tumour dissemination. It is notable that for patients with opportunist infections (with or without tumours) the 2 year mortality is over 95% while it is much less for those with opportunist tumours (Kaposi's sarcoma alone, ≃50% 2 year mortality). The better prognosis appears to apply where evidence of immunosuppression is least. Other evidence of disordered immune regulation is indicated by the occurrence of autoimmune disorders—notably idiopathic thrombocytopenic purpura (Morris *et al.*, 1982) and haemolytic anaemia—in the same 'at risk' groups. Although initially ascribed to autoantibodies, these may be immune complex-mediated (Karpatkin, Walsh & Morris, 1984). The occurrence of a similar syndrome in infants (O'Reilly *et al.*, 1982; Oleske *et al.*, 1983; Rubinstein *et al.*, 1983), usually born to mothers with or who subsequently developed AIDS, poses a problem in distinguishing such cases from previously recognized forms of cellular immunodeficiency (SCID, Nezelof's syndrome). The balance of evidence favours the view that there is a form of AIDS occurring in children.

EPIDEMIOLOGY

Existing surveillance methods for Kaposi's sarcoma and especially for *Pneumocystis carinii* pneumonia in the USA were able to detect the emergence of these two diseases in homosexuals and other new at risk groups. These surveillance records make it certain that AIDS was indeed new to the USA in 1978/79 (Auerbach *et al.*, 1982); all previous cases were in individuals known to be immunosuppressed or at risk from Kaposi's. Similarly it is now clear from records in Haiti that the disease first appeared there at about the same time (Malebranche *et al.*, 1983; Pape *et al.*, 1983; Leonidas & Hyppolite, 1983). On the other hand, cases related to Central Africa date back to 1976 (Bygbjerg, 1983; Brunet *et al.*, 1983) and possibly much further (see later). Within the USA, an exponential rise in cases has ensued with New York apparently about a year ahead of the West Coast. Over 2,500 cases were reported to the end of October 1983 for the USA, with a 6 month doubling time. Although sporadic cases have been seen in Europe since the late 1970s, in most countries the major rise in cases has occurred in 1982 (e.g. France) or 1983 (e.g. UK), some 3 years behind the American epidemic. Figures for the whole of Europe exceed 250 and current UK figures are 26.

While AIDS was first recognized in homosexual males, it is now seen to affect a number of distinct subpopulations (CDC, 1983): homosexuals/bisexuals (71%), intravenous drug abusers (17%), haemophiliacs and others receiving large amounts of blood or blood products (1%), female sexual partners of AIDS patients and infants of females with AIDS. Haitians (5%) and residents of Central Africa, both at home and following recent emigration, also appear to be affected by AIDS, as may a small number of persons visiting these areas. The first groups form a pattern strongly reminiscent of hepatitis B infection and imply an infectious aetiology with an organism that is transmitted by sexual (especially homosexual) contact or blood inoculation. Other lines of evidence support an infectious aetiology, the epidemic rise in cases and in particular the occurrence of sexually associated case clusters, including a notable group of 48 (Auerbach *et al.*, 1984). The early epidemiological association of AIDS with 'fast lane' homosexual life styles involving large numbers of sexual partners, especially with those participating in multiple anonymous bathhouse contacts, could be most readily accounted for by the increased chance of exposure of such individuals to any new agent appearing in the homosexual community. Currently individuals with lower numbers of partners are increasingly being affected, probably indicating a greater prevalence of the agent in the communities. For individual patients, the number of sexual partners may be quite small (but presumably including an infected partner). The predilection for certain areas of New York, San Francisco and Los Angeles could be explained on the basis of the congregation of homosexuals with the most 'active' life styles.

The geographical dissociation of the haemophiliac cases (Davis *et al.*, 1983; Poon *et al.*, 1983; Elliott *et al.*, 1983) but their temporal association with the AIDS epidemic suggest that this is indeed the same disorder but transmitted differently: by blood products, probably Factor VIII concentrate, which is pooled from large donor numbers (at least 2,000) and transported to disparate

A. J. Pinching

geographical locations. The rare blood transfusion associated cases suggest such a link too, as most of such cases affect subjects having blood from many donors; for example, one of 19 blood donors for a child with rhesus disease who developed an AIDS like illness, himself later developed AIDS (Ammann *et al.*, 1983a). In intravenous drug abuse shared, blood contaminated, needles are the likely mode of spread and there are, perhaps for this reason, concentrations of such cases in particular areas (e.g. the Bronx in New York). Most mothers of affected children (O'Reilly *et al.*, 1982) with AIDS have been drug abusers (or Haitians), but transmission here is probably at or around the time of delivery, as with hepatitis B. Affected heterosexual partners of AIDS patients (Masur *et al.*, 1982; Harris *et al.*, 1983) have also included a preponderance of drug abusers as the possible source, so that accidental blood inoculation could be the vector. However heterosexual contact alone could have been responsible; some female prostitutes have been affected (Wallace *et al.*, 1983).

Contrary to earlier ideas, Haiti may well have acquired AIDS from the USA as it emerged at a similar time (Malebranche *et al.*, 1983; Pape *et al.*, 1983; Leonidas & Hyppolite, 1983). Haiti is a common holiday spot for American homosexuals. It is probable that sexual contact between American homosexuals and effectively bisexual or homosexual Haitians may have led to its appearance in Haiti (where the male to female ratio of AIDS cases is high); spread to heterosexual partners could then account for female Haitian cases. Taboos about homosexuality and differing perception of the term may prevent realistic data being acquired on this point although recent studies have been more explicit. Cases linked with Central Africa go back further (1976). However, the well recognized endemic Kaposi's sarcoma in Africa could be part of the same disease spectrum and may have similar transmission characteristics, as judged by the epidemiological features together with anthropological data (Weber, 1984). The opportunist infection end of the spectrum could easily have been missed in this setting. There is some suggestion that, within African countries too, the recent spread is of epidemic proportions.

Evidence collated from several sources, particularly imprisoned intravenous drug abusers (Wormser *et al.*, 1983) and transfusion associated cases (Andreani *et al.*, 1983), indicate that the latent period from the time of putative infection to declared immunodeficiency is between 4 months and 4 years. Discrete episodes of homosexual activity in high risk areas imply a similar figure for sexually acquired disease. However, the size of the inoculum, the number of exposures, the route of exposure and host factors may all play a part.

It is important to recognise that cofactors could play a role both in the development of disease and in its manifestations. Recreational drugs (especially nitrites) in homosexuals, other contamination of needles in drug addicts, malnutrition in Haitians, malaria or other insect borne factors in the tropics, immunological immaturity in neonates have all been proposed but more evidence is needed to establish their role. Genetic predisposition plays a part in determining which secondary disease emerges (HLA DR5 in Kaposi's sarcoma), as may the rate of onset or depth of immunosuppressive effect. This may explain the higher rates for Kaposi's in homosexuals as compared with drug addicts for example. Haemophiliacs may not develop Kaposi's because of their genetic background.

IMMUNOLOGICAL FEATURES

The central evidence of cellular immunodeficiency in AIDS is the pattern of opportunist disease in patients. In those with opportunist infection the depth of immunodeficiency judged clinically is considerable, with negligible evidence of host response; in patients with opportunist tumours, it appears less pronounced and prognosis is correspondingly better. The laboratory evidence on defective cellular immunity in large part supports that derived from the clinical picture: patients with opportunist infections show more severely disordered immune function *in vitro* than those with tumours.

Most studies have included data on T lymphocyte subsets and many have included data on proliferative responses to lectin, antigen and/or alloantigen (Gottlieb *et al.*, 1981, 1983; Masur *et al.*, 1981; Siegal *et al.*, 1981; Mildvan *et al.*, 1982a; Friedman-Kien *et al.*, 1982; Wormser *et al.*, 1983; Poon *et al.*, 1983; Elliott *et al.*, 1983; Vieira *et al.*, 1983; Pitchenik *et al.*, 1983; Malebranche *et al.*, 1983; Schroff *et al.*, 1983b; Ammann *et al.*, 1983, Rogers *et al.*, 1983). Lymphopenia (T

lymphopenia) is universal in AIDS with infection, and relative or absolute lymphopenia is seen with Kaposi's sarcoma. Characteristically it is cells of the T 'helper' phenotype (Th: OKT4, Leu 3a) that are specifically depleted. Cells of the T 'suppressor/cytotoxic' phenotype (Ts: OKT8, Leu 2a) are little changed. Unfortunately much data has been presented as decreased T helper/T suppressor (Th/Ts) ratios. In the context of lymphopenia (as in AIDS cases) a decreased Th/Ts ratio indicates Th depletion and Th depletion appears to be a good marker for AIDS. When translated to the setting of individuals who may have a normal lymphocyte count, especially in asymptomatic members of 'at risk' groups or in putative precursor syndromes, the Th/Ts ratio becomes a meaningless, and indeed misleading, formulation, as it may conceal two quite different patterns of abnormality: Th depletion or Ts increase. The latter may be seen following a number of infections that are probably irrelevant to the causation of AIDS but which are common in the at risk groups. There is no biological reason to link these two patterns together in a ratio. Many non-immunologists involved in AIDS work, for whom the ratio may have been an attractive simplification, have also failed to appreciate that the phenotypic descriptions 'helper' and 'suppressor' cannot be translated directly into functional terms. Indeed it is increasingly evident that the surface markers tell us more about the 'languages' that lymphocytes speak than about the work they do (Reinherz, Meuer & Schlossman, 1983). Finally one should exercise caution in ascribing functional implications to tests on peripheral blood without taking account of the behaviour and distribution of cells in lymphoid and other tissues. In AIDS the pattern in tissues however appears to resemble that seen in peripheral blood (Cochran *et al.*, 1983; Venet *et al.*, 1983).

Assays of T cell function *in vitro* using mixed cell populations derived from patients show decreased transformation responses to antigen, alloantigen and to lectins. These broadly match the altered representation of lymphocyte subpopulations. Among lectins, phytohaemagglutinin responses are reduced but pokeweed mitogen (PWM) responses are more affected (Lane *et al.*, 1983). Using phenotypically defined subpopulations with reconstitution *in vitro*, evidence has been produced that the remaining Th cells are functionally abnormal, while Ts cells are unaffected (Lane *et al.*, 1983). Selection of Th functional subsets or intrinsic defects in the remaining cells are possible causes.

Although humoral immunity was initially considered to be intact, immunoglobulins show a polyclonal increase in AIDS patients. The PWM defect suggests that B cells may also be affected and this has been confirmed by studies with a pure B cell mitogen (*Staphylococcus aureus* Cowan strain 1). Spontaneous immunoglobulin production by AIDS lymphocytes has been found to be substantially increased, confirming the polyclonal B cell activation. However capacity to produce immunoglobulin with PWM is reduced, indicating a decreased pool of partially activated cells. In co-culture experiments, B cells from AIDS patients produced little immunoglobulin with normal T cells, emphasizing an intrinsic B cell defect. *In vivo* and *in vitro* responses to neoantigen are negligible. Thus in AIDS polyclonal B cell activation and failure of response to neoantigens has been demonstrated (Lane *et al.*, 1983). This data, apart from its scientific value, has major implications for the interpretation of serological tests in such patients.

Delayed type cutaneous hypersensitivity responses to recall antigens are defective in AIDS and are an almost universal finding (Gottlieb *et al.*, 1981, 1983; Siegal *et al.*, 1981; Friedman-Kien *et al.*, 1982; Wormser *et al.*, 1983; Poon *et al.*, 1983; Elliott *et al.*, 1983; Pitchenik *et al.*, 1983; Malebranche *et al.*, 1983; Pape *et al.*, 1983). The anergy parallels the failure of *in vitro* lymphocyte responses. Most probably it reflects a failure of T cells involved in delayed type hypersensitivity responses, in T memory cells, or in co-operation with macrophages. It is unlikely to be a failure of the final common pathway of inflammatory response, which all the evidence suggests is intact.

Natural killer (NK) cell function is defective in AIDS patients as judged by conventional cytotoxic assays using targets such as K-562 cells (Siegal *et al.*, 1981; Poon *et al.*, 1983). It is apparently matched by a decrease in cells bearing the proposed NK cell marker (HNK1, Leu 7), even though this may only partially characterize the functional subpopulation. There are some grounds for thinking that the NK defect is the background to the development of opportunist tumours. Immune surveillance may operate for such tumours through these interferon (IFN)-dependent cells. The therapeutic response to IFN in some Kaposi's sarcoma patients (Krown *et al.*, 1983a, 1983b) (in those with the best preserved lymphocyte numbers) implies that IFN may be

boosting the numbers and/or function of the remaining cells of this proposed surveillance system.

Monocyte function is defective in AIDS, both in random locomotion and chemotaxis and in phagocytosis (Fc-dependent) (Maurice, Smith & Pinching, 1982, Pinching *et al.*, 1983). It is probable that the function of the tissue macrophages that derive from them is also abnormal. This may be an intrinsic defect or a result of failure of T cell–macrophage co-operation. Such defects are implied by the occurrence of infections with intracellular pathogens such as Toxoplasma, mycobacteria and *Salmonella* spp. By contrast neutrophil function is normal and there appears to be no defect in complement or in the mediators of the inflammatory or acute phase response. Circulating immune complexes may be detected.

Among soluble factors involved in cellular immune responses, abnormalities have been described in molecules involved in the maturation of T cells (thymic hormones) or in the regulation of immune responses (interleukins, lymphokines etc.). Much of this work is more tentative than the foregoing and its significance (cause or effect) remains to be established. Of the thymic factors thought to be relevant to the maturation of T cells, thymulin is apparently decreased (Dardenne, Bach & Safai, 1983), while α_1-thymosin is increased in serum (Hersh *et al.*, 1983). An alteration in end organ responsiveness has been proposed to account for the latter. Thymic dysplasia with loss of Hassall's corpuscles (Elie *et al.*, 1983) provides collateral evidence for thymic defects in AIDS.

α-IFN levels appear to be generally decreased in AIDS but, perhaps more characteristically, there are raised levels of an acid labile α-IFN similar to that found in SLE (DeStephano *et al.*, 1982). Alterations in interleukin production or responsiveness have been found. In particular, the production of interleukin-2 (IL-2), normally elaborated by Th cells, appears to be reduced; evidence of decreased cell responsiveness to exogenous IL-2 has also been provided. Among other serum tests, elevated levels of β_2-microglobulin have been noted (Francioli & Clement, 1982; Zolla-Pazner *et al.*, 1984).

An HLA association between DR5 and Kaposi's sarcoma, but not apparently with opportunist infection, has been described (Friedman-Kien *et al.*, 1982; Pollack *et al.*, 1983). This same association is reported to affect all other epidemiological groups previously known to be at risk from Kaposi's and indeed it may account for its high prevalence among subjects of Mediterranean or Ashkenazy Jewish extraction, in whom DR5 is more frequently represented. It now appears that the association between Kaposi's and DR5 is lost if Italian and Ashkenazy Jewish patients are excluded.

AETIOLOGY AND PATHOGENESIS

While in the early approaches to this problem the focus tended to be on aspects of male homosexual life style, the subsequent evidence that the same disorder has appeared over a similar time scale in a number of other distinct groups has led to rather different hypotheses. Any hypothesis must answer why AIDS has arisen now, must provide an explanation for its exponential increase and should account for its appearance in several disparate subgroups. Occam's razor must be applied.

A new disease with an exponential rise (not accounted for by ascertainment) strongly suggests an infectious disease and the evidence for this has been considered under epidemiology above. A hypothesis can be constructed which fits the above criteria by postulating a single causative agent for the underlying immune deficiency, an agent that may be transmitted (like hepatitis B) by homosexual contact and by blood products. The homosexual predominance may be because anorectal intercourse allows an agent present in seminal fluid either to enter through intact mucosa or through small mucosal tears direct into the blood. The fewer female and male heterosexual cases could be due to non-sexual spread, or could result from anal intercourse in the female. However, numbers of sexual contacts are smaller among heterosexuals than homosexuals and exposure to the AIDS agent in this group to date may have been substantially less, so it is possible that AIDS can be transmitted by normal heterosexual intercourse.

Does this hypothesis, which is now the most widely accepted, stand up to analysis in the light of other aspects of the epidemic? The probable increasing prevalence in the at risk communities of the agent could explain the tendency for a decrease in the number of sexual contacts (epidemiologically) of current AIDS patients. The epidemiological association with recreational drug (nitrites, etc)

usage (Marmor *et al.*, 1982) and with certain 'fast lane' styles of sexual activity ('fisting', 'rimming') (Jaffe *et al.*, 1983), may prove to be solely a link with increased likelihood of exposure to infected individuals, although some of these factors could enhance transmissibility or act as cofactors. Excluding for the moment cases from Haiti or Central Africa, the number of cases not fitting into the above at risk groups is very small; when cases without adequate information and those inadvertently included in the epidemiological definition are excluded from the current figures, only about 40 of 2,700 cases are unaccounted for (Curran, 1984). This strongly suggests that other routes of transmission are not important, unless a very much longer incubation period applies to those infected by other routes. The major group that has not been affected, and which that might be expected from hepatitis B analogy, is health care workers, especially nurses, doctors and laboratory staff. No direct spread can be seen to this group, either because of improved standards in the wake of hepatitis B, or because a large or repeated inoculum is required. None of the many persons suffering inoculation injury have developed disease.

According to the single infective agent hypothesis, the causative agent must be new, at least to Western countries. Either it is a truely novel agent, perhaps acquired from another human reservoir or as a zoonosis; alternatively it could be a familiar agent which has changed its properties, either by mutation or by some cofactor. In seeking the agent in AIDS patients there are many problems and pitfalls. If found, is it the AIDS agent or an opportunist? Is it an agent transmitted in a similar way and thus a marker for exposure to similarly transmitted agents? Serological evidence may be obscured by polyclonal B cell activation with increased titres of antibodies to previously encountered antigens, and no response to neoantigens (perhaps including the agent itself) (Lane *et al.*, 1983). Cell associated agents may be hard to find in late stage disease when the infected cells may have been largely eliminated. Ideally a particular agent should be present in all patients and all groups (among whom potentially confounding factors may not be shared). However it is likely that an agent would be more readily discovered early in the disorder before secondary disease develops. Unfortunately however, we are not yet able to define reliably subjects in a precursor or latent phase of the disease. If such an agent exists, then is AIDS the only manifestation? Are some individuals being exposed to the agent and eliminating it or developing mild or subclinical disease? It is certainly possible that AIDS is only the most severe form of the disease caused by the agent, either requiring cofactors or massive/repeated exposure.

Among the agents that are known that have been proposed as the aetiological agent of AIDS and for which some evidence has been adduced, are CMV (Gottlieb *et al.*, 1981), hepatitis B (McDonald, Hamilton & Durak, 1983; Ravenholt, 1983), EB virus and human T cell leukaemia virus (Essex *et al.*, 1983; Gelmann *et al.*, 1983; Gallo *et al.*, 1983) fall are apparently prevalent among AIDS patients to varying degrees. CMV is a strong candidate because it is so frequently found in reactivated form in AIDS patients and is known to be (mildly) immunosuppressive; a new strain is a possibility. Hepatitis B is also prevalent among the affected persons but is certainly not universal on the basis of antibody and antigen tests; it has been suggested that its pathogenicity could have been altered by a delta like agent (McDonald *et al.*, 1983). Human T cell leukaemia virus (HTLV) is especially attractive as an agent as it is a retrovirus with known tropism for T helper phenotype cells. In AIDS it could be causing cell destruction rather than malignant proliferation, an idea not without precedent. The evidence for this agent in AIDS patients is not entirely satisfactory and while viral genetic material has been found in cells from a few AIDS patients (Gellmann *et al.*, 1983; Gallo *et al.*, 1983), the only evidence of high prevalence of the virus in affected subjects is based on an assay of uncertain specificity applied at the limits of its sensitivity (Essex *et al.*, 1983). Another retrovirus has been identified in France (Barré Sinoussi *et al.*, 1983) but its broader relevance remains uncertain. A significant number of AIDS patients lack evidence for each of these agents, suggesting on balance that none is a common factor; they are all similarly transmitted and are thus likely to be passenger agents. No evidence has been found for the fanciful suggestion that African swine fever virus is responsible. If AIDS is indeed due to a viral agent, then it has probably not yet been identified. A number of alternative hypotheses have been put forward which merit consideration. The idea that recreational drugs, especially nitrites, might be immunosuppressive has now been largely abandoned for lack of evidence; the correlation epidemiologically appears to be with life style. The idea that multiple (sexually transmitted) infections somehow wear down the

immune system never seem very attractive on basic principles. An alternative is the idea that repeated infection over long periods with viral agents able to replicate in the host could lead to a summation of immunosuppressive effects. Increasing numbers of patients lack evidence of such a process prior to developing AIDS. Another interesting possibility is that soluble factors derived from colonizing gut organisms (e.g. amoebae, fungi) could be immunosuppressive (Pearce, 1983; Sell *et al.*, 1983). Tentative evidence has been adduced for the release of a cyclosporin like material from a colonizing or infecting fungus (Sell *et al.*, 1983); the basis for this colonization or infection would need to be established. Another line of reasoning has emphasized the immunosuppressive properties of seminal fluid, possibly related to the allogenicity of Ia bearing cells in seminal fluid (Shearer, 1983). The theory rests on a means of access of such cells via rectal mucosa and evidence from animals injected with seminal fluid intravenously. The hypothesis fails to provide convincing explanation of the newness of the syndrome, its epidemic behaviour and its simultaneous appearance in other and diverse groups.

By the time that AIDS develops clinically, the immunodeficiency is fully evolved and may have some immunological features that are secondary to deficiency or its consequent diseases. It is hard therefore to deduce pathogenetic mechanisms without stronger evidence concerning early events; these may become apparent when precursor syndromes are better defined and their relevance to AIDS better established. The depletion of T helper phenotype cells is a notable common feature in AIDS and shows appropriate variation in degree with the clinical severity of immunosuppression; the T helper cells that remain appear functionally defective. This evidence favours a mechanism operating through this cell type. Although decreased natural killer cell activity is another major feature it lacks specificity and is unlikely to be primary. Polyclonal B cell activation appears to be an early event, but again may denote a non-specific response to viral or other infection. Defects in monocyte and macrophage function are apparent *in vitro* and are implicit in the development of infection with intracellular pathogens; it is not clear whether these are primary defects or simply reflect failure of T cell–macrophage co-operation through the T helper cell lack. Alterations in thymic structure and hormones, in interferons and interleukins are hard to evaluate as primary or secondary events. The definition of the causative agent and the reliable delineation or precursor syndromes will greatly facilitate the search for pathogenetic mechanisms.

THERAPY IN AIDS

Therapy in AIDS must be divided into therapy for the underlying immunodeficiency and that directed at secondary diseases. The treatment of opportunist infections has largely been established in other immunosuppressed states and a number of these infectious agents are potentially treatable in the compromized host (e.g. pneumocystis, Candida, Toxoplasma, Cryptococcus, Salmonella, Herpes simplex virus). Treatment regimes established in other settings may also be effective in AIDS but treatment failures are more frequent. In some cases, apparently effective antibiotics (*in vitro*) are quite ineffective *in vivo* due to failure of host response.

Cytotoxic therapy for tumours cannot be readily transferred from other settings. Patients with Kaposi's Sarcoma have the best prognosis in AIDS and even a modest myelo or immunosuppressive effect of chemotherapy could tip them into being susceptible to opportunist infections with a correspondingly worse prognosis. In Kaposi's, the use of cloned α-IFN in high dosage is both logical and effective (Krown *et al.*, 1983a, 1983b). Its use stems in part from the idea that NK cells, which are IFN-dependent, are involved in immune surveillance against opportunist tumours like Kaposi's. Cessation of therapeutic immunosuppression in renal transplant patients following the development of Kaposi's sarcoma is frequently followed by tumour regression. It may be that the 40% response rate of Kaposi's in AIDS (complete or partial remissions) reflects a comparable immunorestoration. The benefit appears to be largely restricted to those subjects in whom immunity is best preserved (higher lymphocyte counts etc.) and is thus probably stimulating what remains. Interferon does not appear to be effective in treatment of opportunist infection in AIDS.

Many other approaches have been attempted in the course of seeking effective therapy for the underlying immunodeficiency. Transfer factor, thymic factors, thymic transplantation, white cell

transfusions, bone marrow transplantation, all of which might have seemed logical, have been disappointing in achieving clinical benefit in full blown AIDS. The failure of bone marrow grafting (the treatment of choice in SCID in children) is especially pertinent; failure despite successful engraftment may reflect infection of the new cells with the AIDS agent (Hassett *et al.*, 1983). Clinical trials of IL-2, which has shown encouraging improvements when used *in vitro* in terms of NK cell and CMV specific cytotoxicity (Rook *et al.*, 1983), are not yet fully evaluable, but are not encouraging.

The lack of progress with such therapy may be a genuine failure to correct the basic defect or to avert reinfection of immunocompetent cells within the host. Alternatively it may be that the measures have been introduced too late. Again, if precursor syndromes can be reliably identified, it seems likely that appropriate measures could prevent the progressive attrition of immunocompetence.

POSSIBLE PRECURSOR STATES AND SCREENING

The importance of defining immunodeficient individuals or those infected with the AIDS agent before they reach a stage of clinically apparant immunodeficiency has already been stressed. The first proposed precursor syndrome was that of persistent unexplained lymphadenopathy (Mildvan *et al.*, 1982b; Enlow *et al.*, 1983; Metroka *et al.*, 1983; Ragni *et al.*, 1983). The apparent increase in this clinical presentation at the same time as AIDS and in many of the same at risk groups suggested a link. Some patients with AIDS, especially those with Kaposi's, have prior lymphadenopathy. Some patients with unexplained lymphadenopathy have subsequently developed AIDS. However, as currently defined (generalized lymphadenopathy, lasting for more than 3 months, with biopsy showing reactive hyperplasia and not shown to be due to another cause) it is clear that it is potentially very heterogeneous. Individuals in high risk groups for AIDS have a high incidence of unrelated disorders that may cause lymphadenopathy. In studies in New York 19% have progressed to AIDS in 30 months of follow-up (Mildvan & Mathur, 1984), while a West Coast group has reported a 1% progression in 2 years (Abrams, Lewis & Volberding, 1984). These discrepancies may reflect different definitions and exclusions, or differing stages of the epidemic. They indicate the heterogeneity and hence lack of reliability of this loose definition as a precursor state. In New York, lymphadenopathy patients have the same HLA DR5 association as with Kaposi's (Enlow *et al.*, 1983). The group as a whole tends to show similar immune abnormalities as AIDS qualitatively but they are less severe (Mildvan *et al.*, 1982b; Stahl *et al.*, 1982; Wallace *et al.*, 1982). However, some of this rests on the use of Th/Ts ratios and may include some cases with the apparently unrelated Ts increase. Even if related to AIDS, some cases may be formes frustes that need not progress. Lymph node histology (Fernandez *et al.*, 1983; Metroka *et al.*, 1983) and immunohistology indicate some heterogeneity but longitudinal studies are needed. Other prodromal symptoms have been noted including unexplained weight loss, malaise, fatigue, diarrhoea and oral candidiasis (Mildvan & Mathur, 1984). While some may be due to undiagnosed opportunist infection, others may represent a definite precursor syndrome. Some groups are now using a term 'AIDS related complex' to describe a combination of some of a number of such clinical and AIDS like laboratory features, which may be more clearly predictive of the development of AIDS over a rather shorter time span (77% progression written 4 months according to one group; Mildvan & Mathur, 1984).

An alternative approach is to seek laboratory evidence of AIDS like immune defects in asymptomatic members of at risk groups (Goedert *et al.*, 1982; Stahl *et al.*, 1982; Kornfeld *et al.*, 1982; Wallace *et al.*, 1982; Detels *et al.*, 1982; Fahey, Detels & Gottlieb, 1983; Pinching *et al.*, 1983, 1984; Lederman *et al.*, 1983; Menitove *et al.*, 1983; Goldsmith *et al.*, 1983; Luban, Kelleber & Reaman, 1983). However this involves applying non-specific tests that are insufficiently validated outside defined clinical settings. Among other things, the high background of other (non-AIDS related) intercurrent illnesses which may affect such tests that are seen in at risk subjects make interpretation of these studies extremely difficult. Furthermore there is no *a priori* reason why the pattern seen in full blown AIDS will necessarily be preceded by the same pattern in its evolution. The predictive value of lymphopenia, Th depletion, Ts increase, Th/Ts ratio decrease, decreased

α-IFN (Lopez, Fitzgerald & Siegal, 1984), increased acid labile α-IFN (Eyster *et al.*, 1983) increased β_2-microglobulin (Zolla Pazner *et al.*, 1983), increased α_1-thymosin (Goldstein & Naylor, 1984), etc, all await validation in longitudinal studies in terms of the development of the disease. All show some promise on the basis of incidence in at risk groups. Preliminary results of such longitudinal studies of lymphocyte subpopulations have shown that not only does Ts increase (associated with prior viral infections) frequently revert to normal, but some instances of Th decrease may also improve spontaneously (Marmor *et al.*, 1984; Pinching *et al.*, 1984). A heterogeneity of causes for such patterns is thus likely and interpretation should be guarded at this stage. Careful prospective studies will however provide valuable information on others may clarify the background events occurring in these subpopulations. Only by such studies may the early phases of AIDS be recognized, enabling us to evaluate aetiological or pathogenetic hypotheses and therapeutic approaches. Intervention to stem the epidemic of AIDS is most likely to arise from knowledge obtained in this way.

CONCLUSIONS

A novel epidemic form of acquired immunodeficiency has arisen in distinct subsections of the community. In 5 years it has justifiably provoked unprecedented scientific activity as well as intense concern amongst the public. It is likely that our comprehension of basic mechanisms of immune regulation will be greatly advanced by the questions posed by this clinical problem. It is to be hoped that the social and political consequences of AIDS will be as positive.

REFERENCES

ABRAMS, D.I., LEWIS, B.J. & VOLBERDING, P.A. (1984) Lymphadenopathy: endpoint or prodrome—update of a 24 month prospective study. *Ann. N.Y. Acad. Sci.* (in press.)

AMMANN, A.J., COWAN, W.J., WARA, D.W., WEINTRUB, D., DRITZ, S., GOLDMAN, H. & PERKINS, H.A. (1983a) Acquired immunodeficiency in an infant: possible transmission by means of blood products. *Lancet*, i, 956.

AMMANN, A.J., ABRAMS, D., CONANT, M., CHUDWIN, D., COWAN, M., VOLBERDING, P., LEWIS, B. & CASAVANT, C. (1983b) Acquired immune dysfunction in homosexual men: immunologic profiles. *Clin. Immunol. Immunopath.* 27, 315.

ANDREANI, T., MODIGLIANI, R., LE CHARPENTIER, Y., GALIAN, A., BROUET, J.-C., LIANCE, M., LACHANCE, J.R., MESSING, B. & VERNISSE, B. (1983) Acquired immunodeficiency with intestinal cryptospoidiosis: possible transmission by Haitian whole blood. *Lancet*, i, 1187.

AUERBACH, D.M., BENNETT, J.V., BRACHMAN, P.J. *et al.* (1982) Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. *N. J. Engl. Med.* 306, 248.

AUERBACH, D., DARROW, W., JAFFE, H. & CURRAN, J. (1984) A cluster of the acquired immune deficiency syndrome: patients linked by sexual contact. *Am. J. Med.* (in press.)

BARRÉ-SINOUSSI, F., CHERMANN, J.C., REY, F., NUGEYRE, M.T., CHAMARET, S., GRUEST, J., DAUGUET, C., AXLER-BLIN, C., VÉZINET-BRUN, F., ROUZIOUX, C., ROZENBAUM, W. & MONTAGNIER, L.

(1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*, 220, 868.

BRUNET, J.B., BOUVET, E., CHAPERON, J., GLUCKMAN, J.C., KERNBAUM, S., KLATZMANN, D., LACHIVER, D., LEIBOWITCH, J., MAYAUD, C., PICARD, O., REVUZ, J., ROZENBAUM, W., VILLALONGA, J. & WESSELBERG, J. (1983) Acquired immunodeficiency syndrome in France. *Lancet*, i, 700.

BYGBJERG, I.C. (1983) AIDS in a Danish surgeon (Zaire 1976) *Lancet*, i, 925.

CENTERS FOR DISEASE CONTROL (1983) *Update on AIDS. MMWR*, 32, 309.

COCHRAN, A.J., NESTOR, M.S., GROOPMAN, J.E. & AHMED, A.R. (1983) Tumour infiltrates in acquired immunodeficiency symdrome patients with Kaposi's sarcoma. *Lancet*, i, 416.

CURRAN, J.W. (1984) The widening clinical spectrum of AIDS. *Ann. N.Y. Acad. Sci.* (in press.)

DARDENNE, M., BACH, J.-F. & SAFAI, B. (1983) Low serum thymic hormone levels in patients with acquired immunodeficiency syndrome. *N. Engl. J. Med.* 309, 48.

DAVIS, K.C., HORSBURGH, C.R., HASIBA, U., SCHOCKET, A.L. & KIRKPATRICK, C.H. (1983) Acquired immunodeficiency syndrome in a patient with hemophilia. *Ann. Int. Med.* 98, 284.

DE JONG, P.J., VALDERRAMA, G., SPIGLAND, J. & HORWITZ, M.S. (1983) Adenovirus isolates from urine of patients with acquired immunodeficiency syndrome. *Lancet*, i, 1293.

DESTEFANO, E., FRIEDMAN, R.M., FRIEDMAN-KIEN,

A.E. *et al.* (1982) Acid-labile human leucocyte interferon in homosexual men with Kaposi's sarcoma and lymphadenopathy. *J. Infect. Dis.* **146**, 451.

DETELS, R., FAHEY, J.L., SCHWARTZ, K., GREENE, R.S., VISSCHER, B.R. & GOTTLIEB, M.S. (1983) Relation between sexual practices and T-cell subsets in homosexually active men. *Lancet*, i, 609.

DREW, W.L., CONANT, M.A., MINER, R.C., HUANG, E.-S., ZIEGLER, J.L., GROUNDWATER, J.R., GULLETT, J.H., VOLBERDING, P., ABRAMS, D.I. & MINTZ, L. (1982) Cytomegalovirus and Kaposi's sarcoma in young homosexual men. *Lancet*, ii, 125.

ELIE, R., LAROCHE, A.C., ARNOUX, E., GUÉRIN, J.-M., PIERRE, G., MALEBRANCHE, R., SEEMAYER, T.A., DUPUY, J.-M., RUSSO, P. & LAPP, W.S. (1983) Thymic dysplasia in acquired immunodeficiency syndrome. *N. Engl. J. Med.* **308**, 841.

ELLIOTT, J.L., HOPPES, W.L., PLATT, M.S., THOMAS, J.G., PATEL, I.P. & GANSAR, A. (1983) The acquired immunodeficiency syndrome and *Mycobacterium avium*-intracellular bacteremia in a patient with hemophilia. *Ann. Int. med.* **98**, 290.

ENLOW, R.W., ROLDAN, A.N., LOGALBO, P., MILDVAN, D., MATHUR, U. & WINCHESTER, R.J. (1983) Increased frequency of HLA-DR5 in lymphadenopathy stage of AIDS. *Lancet*, ii, 51.

ESSEX, M., MCLANE, M.F., LEE, T.H., FALK, L., HOWE, C.W.S., MULLINS, J.I., CABRAOILLA, C. & FRANCIS, D.P. (1983) Antibodies to cell membrane antigens associated with human T-cell leukaemia virus in patients with AIDS. *Science*, **220**, 859.

EYSTER, M.E., GOEDERT, J.J., POON, M.-C. & PREBLE, O.T. (1983) Acid-labile alpha interferon: a possible preclinical marker for the AIDS in hemophilia. *N. Engl. J. Med.* **309**, 583.

FAHEY, J.L., DETELS, R. & GOTTLIEB, M. (1983) Immune-cell augmentation (with altered T-subset ratio) is common in healthy homosexual men. *N. Engl. J. Med.* **308**, 842.

FERNANDEZ, R., MOURADIAN, J., METROKA, C. & DAVIS, J. (1983) The prognostic value of histopathology in persistent generalised lymphadenopathy in homosexual men. *N. Engl. J. Med.* **309**, 185.

FOLLANSBEE, S.E., BUSCH, D.F., WOFSY, C.B., COLEMAN, D.L., GULLET, J., AURIGEMMA, G.P., ROSS, T., HADLEY, W.K. & DREW, W.L. (1982) An outbreak of *Pneumocystis carinii* pneumonia in homosexual men. *Ann. Int. Med.* **96**, 705.

FRANCIOLI, P. & CLÉMENT, F. (1982) Beta$_2$-microglobulin and immunodeficiency in a homosexual man. *N. Engl. J. Med.* **307**, 1402.

FRIEDMAN-KIEN, A.E., LAUBENSTEIN, L.J. RUBINSTEIN, P., BUIMOVICI-KLEIN, E., MARMOR, M., STAHL, R., SPIGLAND, I., KIM, K.S. & ZOLLA-PAZNER, J. (1982) Disseminated Kaposi's sarcoma in homosexual men. *Ann. Int. Med.* **96**, 693.

GALLO, R.C., SARIN, P.S., GELMANN, E.P., ROBERT-GUROFF, M., RICHARDSON, E., KALYANARAMAN, V.S., MANN, D., SIDHU, G.D., STAHL, R.E., ZOLLA-PAZNER, S., LEIBOWITCH, J. & POPOVIC, M. (1983) Isolation of human T-cell leukaemia virus in acquired immunodeficiency syndrome (AIDS). *Science*, **220**, 865.

GELMANN, E.P., BLAYNEY, D., MASUR, H., SIDHU, G., STAHL, R. & GALLO, R.C. (1983) Proviral DNA of a retrovirus, human T-cell leukaemia virus, in two patients with AIDS. *Science*, **220**, 862.

GOEDERT, J.J., NEULAND, C.Y., WALLEN, W.C., GREENE, M.H., MANN, D.L., MURRAY, C., STRONG, D.M., FRAUMENS, J.F. & BLATTNER, W.A. (1982) Amyl nitrite may alter T lymphocytes in homosexual men. *Lancet*, i, 412.

GOLDFARB, J., TANOWITZ, H., GROSSMAN, R. *et al.* (1982) Cryptospoidiosis: assessment of chemotherapy of males with AIDS. *M.M.W.R.* **32**, 589.

GOLDSMITH, J.C., MOSELEY, P.L., MONICK, M., BRADY, M. & HUNNINGHAKE, G.W. (1983) T-lymphocyte subpopulation abnormalities in apparently healthy patients with hemophilia. *Ann. Int. Med.* **98**, 294.

GOLDSTEIN, A.L. & NAYLOR, P.H. (1984) Thymosin α-1 as an early assay for identifying individuals at high risk of developing AIDS. *Ann. N.Y. Acad. Sci.* (In press.)

GOTTLIEB, M.S., GROOPMAN, J.E., WEINSTEIN, W.M., FAHEY, J.L. & DETELS, R. (1983) The acquired immunodeficiency syndrome. *Ann. Int. Med.* **99**, 208.

GOTTLIEB, M.S., SCHROFF, R., SCHANKER, H.M., WEISMAN, J.D., FAN, D.T., WOLF, R.A. & SAXON, A. (1981) *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N. Engl. J. Med.* **305**, 1425.

GREENE, J.B., SIDHU, G.S., LEWIN, S., LEVINE, J.F., MASUR, H., SIMBERKOFF, M.S., NICHOLAS, P., GOOD, R.C., ZOLLA-PAZNER, S.B., POLLACK, A.A., TRAPPER, M.L. & HOLZMAN, R.S. (1982) *Mycobacterium avium-intracellulare:* a cause of disseminated life-threatening infection in homosexuals/and drug abusers. *Ann. Int. Med.* **97**, 539.

HARRIS, C., SMALL, C.B., KLEIN, R.S., FRIEDLAND, G.H., MOLL, B., EMESON, E.E., SPIGLAND, I. & STEIGBIGEL, N.H. (1983) Immunodeficiency in female sexual partners of men with the acquired immunodeficiency syndrome. *N. Engl. J. Med.* **308**, 1181.

HASSETT, J.M., ZAROULIS, C.G., GREENBERG, M.L. & SIEGAL, F.P. (1983) Bone marrow transplantation in AIDS. *N. Engl. J. Med.* **309**, 665.

HERSH, E.M., REUBEN, J.M., RIOS, A., MANSELL, P.W.A., NEWELL, G.R., McCLURE, J.E. & GOLDSTEIN, A.L. (1983) Elevated serum thymosin α$_1$ levels associated with evidence of immune dysregulation in male homosexuals with a history of infectious diseases or Kaposi's sarcoma. *N. Engl. J. Med.* **308**, 45.

HYMES, K.B., CHEUNG, T., GREENE, J.B., PROSE, N.S., MARCUS, A., BALLARD, H., WILLIAM, D.C. & LAUBENSTEIN, L.J. (1981) Kaposi's sarcoma in homosexual men—a report of eight cases. *Lancet*, ii, 598.

JAFFE, H.W., CHOI, K., THOMAS, P.A., HAVERKOS, H.W., AUERBACH, D.M., GUINAN, M.E., ROGERS, M.F., SPIRA, T.J., DARROW, W.W., KRAMER, M.A., FRIEDMAN, S.M., MONROE, J.M. FRIEDMAN-KIEN, A.E., LAUBENSTEIN, L.J., MARMOR, M., SAFAI, B., DRITZ, S.K., CRISPI, S.J., FANNIN, S.L., ORKWIS, J.P., KELTER, A., RUSHING, W.R., THACKER, S.B. & CURRAN, J.W. (1983) National case-control study of Kaposi's sarcoma and *Pneumocystis carinii*

pneumonia in homosexual men. I. Epidemiological Results. *Ann. Int. Med.* **99**, 145.

KORNFELD, H., VANDE STOUWE, R.A., LANGE, M., REDDY, M.M. & GRIECO, M.H. (1982) T-lymphocyte subpopulations in homosexual men. *N. Engl. J. Med.* **307**, 729.

KROWN, S.E., REAL, F.X., CUNNINGHAM-RUNDLES, S., MYSKOWSKI, P.L., KOZINER, B., FEIN, S., MITTELMAN, A., OETTGEN, H.F. & SAFAI, B. (1983a) Preliminary observations on the effect of recombinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. *N. Engl. J. Med.* **308**, 1071.

KROWN, S.E., REAL, F.X., CUNNINGHAM-RUNDLES, S., MYSKOWSKI, P.L., KOZINER, B., MITTELMAN, A., OETTGEN, H.F. & SAFAI, B. (1983b) Interferon in the treatment of Kaposi's sarcoma. *N. Engl. J. Med.* **309**, 923.

LANE, H.C., MASUR, H., EDGAR, L.C., WHALEN, G., ROOK, A.H. & FAUCI, A.S. (1983) Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N. Engl. J. Med.* **309**, 453.

LEDERMAN, M.M., RATTNOFF, O.D., SCILLIAN, J.J., JONES, P.K. & SCHACTER, B. (1983) Impaired cell-mediated immunity in patients with classic hemophilia. *N. Engl. J. Med.* **308**, 79.

LEONIDAS, J.-R. & HYPPOLITE, N. (1983) Haiti and the acquired immunodeficiency syndrome. *Ann. Int. Med.* **98**, 1020.

LOPEZ, C., FITZGERALD, P.A. & SIEGAL, F.P. (1984) Deficiency of interferon and generation *in vitro* associated with opportunistic infections in AIDS patients. *Ann. N.Y. Acad. Sci.* (In press.)

LUBAN, N.L.C., KELLEHER, J.F. & REAMAN, G.H. (1983) Altered distribution of T-lymphocyte subpopulations in children and adolescents with haemophilia. *Lancet,* **i**, 503.

McDONALD, M.I., HAMILTON, J.D. & DURACK, D.T. (1983) Hepatitis B surface antigen could harbor the infective agent of AIDS. *Lancet,* **ii**, 882.

MALEBRANCHE, R., ARNOUX, E., GUÉRIN, J.M., PIERRE, G.D., LAROCHE, A.C., PÉAN-GUICHARD, C., MORISSET, P.H., SPIRA, T., MANDEVILLE, R., DROTMAN, P., SEEMAYER, T. & DUPUY, J.-M. (1983) Acquired immunodeficiency syndrome with severe gastrointestinal manifestations in Haiti. *Lancet,* **ii**, 873.

MARMOR, M., FRIEDMAN-KIEN, A.E., LAUBENSTEIN, L., BYRUM, R.D., WILLIAM, D.C., DONOFRIO, S. & DUBIN, N. (1982) Risk factors for Kaposi's sarcoma in homosexual men. *Lancet,* **i**, 1083.

MARMOR, M., EL-SADR, W., ZOLLA-PAZNER, S., LAZARO, C. & WILLIAM, D. (1984) Immunologic abnormalities among male homosexuals in New York City. *Ann. N.Y. Acad. Sci.* (In press.)

MASUR, H., MICHELIS, M.A., GREENE, J.B., ONORATO, I., VANDE STOUWE, R.A., HOLZMAN, R.S., WORMSER, G., BRETTMAN, L., LANGE, M., MURRAY, H.W. & CUNNINGHAM-RUNDLES, S. (1981) An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N. Engl. J. Med.* **305**, 1431.

MASUR, H., MICHELIS, M.A., WORMSER, G.P., LEWIN, S., GOLD, J., TAPPER, M.L., GIRON, J., LERNER, C.W., ARMSTRONG, D., SETIA, U., SENDER, J.A., SIBEKEN, R.S., NICHOLAS, P., ARLEN, Z., MAAYAN,

S., ERNST, J.A., SIEGAL, F.P. & CUNNINGHAM-RUNDLES, S. (1982) Opportunistic infection in previously healthy women: initial manifestations of a community acquired cellular immunodeficiency. *Ann. Int. Med.* **97**, 533.

MAURICE, P.D.L., SMITH, N.P. & PINCHING, A.J. (1982) Kaposi's sarcoma with benign course in a homosexual. *Lancet,* **i**, 571.

MENITOVE, J.E., ASTER, R.H., CASPER, J.T., LAUER, S.J., GOTTSCHALL, J.L., WILLIAMS, J.E., GILL, J.C., WHEELER, D.V., PIASKOWSKI, V., KIRSCHNER, P. & MONTGOMERY, R.R. (1983) T-lymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. *N. Engl. J. Med.* **308**, 83.

METROKA, C.E., CUNNINGHAM-RUNDLES, S., POLLACK, M.S., SONNABEND, J.A., DAVIS, J.M., GORDON, B., FERNANDEZ, R.O. & MOURAIDIAN, J. (1983) Generalized lymphadenopathy in homosexual men. *Ann. Int. Med.* **99**, 585.

MILDVAN, D. & MATHUR, U. (1984) Prodomal syndromes in AIDS. *Ann. N.Y. Acad. Sci.* (in press.)

MILDVAN, D., MATHUR, U., ENLOW, R.W., ROMAIN, P.L., WINCHESTER, R.J., COLP, C., SINGMAN, H., ADELSBERG, B.R. & SPIGLAND, I. (1982a) Opportunistic infections and immune deficiency in homosexual men. *Ann. Int. Med.* **96**, 700.

MILDVAN, D., MATHUR, U., ENLOW, R.E. *et al.* (1982b) Persistent, generalised lymphadenopathy among homosexual males. *M.M.W.R.* **31**, 249.

MILLER, J.R., BARRETT, R.E., BRITTON, C.B., TAPPER, M.L., BAHR, G.S., BRUNO, P.J., MARQUARDT, M.D., HAYS, A.P., McMURTRY, J.G., WEISSMAN, J.B. & BRUNO, M.S. (1982) Progressive multifocal leukoencephalopathy in a male homosexual with T-cell immune deficiency. *N. Engl. J. Med.* **307**, 1436.

MORRIS, L., DISTENFELD, A., AMOROSI, E. & KARPATKIN, S. (1982) Autoimmune thrombocytopenic purpura in homosexual men. *Ann. Int. Med.* **96**, 714.

OLESKE, J., MINNEFOR, A., COOPER, R., THOMAS, K., DELACRUZ, A., AHDIEH, H., GUERRERO, I., JOSHI, V.V. & DESPOSITO, F. (1983). Immune deficiency syndrome in children. *J.A.M.A.* **249**, 2345.

O'RIELLY, R., KIRKPATRICK, D., SMALL, C.B. *et al.* (1982) Unexplained immunodeficiency and opportunistic infections in infants. *M.M.W.R.* **31**, 665.

PAPE, J.W., LIAUTAUD, B., THOMAS, F., MATHURIN, J-R., ST AMAND, M.-M.A., BONCY, M., PEAN, V., PAMPHILE, M., LAROCHE, A.C. & JOHNSON, W.D.J. (1983) Characteristics of the acquired immunodeficiency syndrome (AIDS) in Haiti. *N. Engl. J. Med.* **309**, 945.

PEARCE, R.B. (1983) Intestinal protozoal infections and AIDS. *Lancet,* **ii**, 51.

PINCHING, A.J., McMANUS, T.J., JEFFRIES, D.J., MOSHTAEL, O., DONAGHY, M., PARKIN, J.M., MUNDAY, P.E. & HARRIS, J.R.W. (1983) Studies of cellular immunity in male homosexuals in London. *Lancet,* **ii**, 126.

PINCHING, A.J., WEBER, J., ROGERS, L.A., JEFFRIES, D.J. & HARRIS, J.R.W. (1984) A longitudinal study of cellular immunity in male homosexuals in London. *Ann. N.Y. Acad. Sci.* (in press.)

PITCHENIK, A.E., FISCHL, M.A., DICKINSON, G.M., BECKER, D.M., FOURNIER, A.M., O'CONNELL,

M.T., COLTON, R.M. & SPIRA, T.J. (1983) Opportunistic infections and Kaposi's sarcoma among Haitians: evidence of a new acquired immunodeficiency state. *Ann. Int. Med.* **98**, 277.

POLLACK, M.S., SAFAI, B., MYSKOWSKI, P.L., GOLD, J.W.M., PANDEY, J. & DUPON, B. (1983) Frequencies of HLA and Gm immunogenetic markers in Kaposi's sarcoma. *Tissue Antigens*, **21**, 1.

POON, M.-C., LANDAY, A., PRASTHOFER, E.F. & STAGNO, S. (1983) Acquired immunodeficiency syndrome with *Pneumocystis carinii* pneumonia and *Mycobacterium avium*-intracellulare infection in a previously healthy patient with classic hemophilia. *Ann. Int. Med.* **98**, 287.

RAGNI, M.V., LEWIS, J.H., SPERO, J.A. & BONTEMPO, F.A. (1983) Acquired-immunodeficiency-like syndrome in two haemophiliacs. *Lancet*, **i**, 213.

RAVENHOLT, R.T. (1983) Role of hepatitis B virus in acquired immunodeficiency syndrome. *Lancet*, **ii**, 885.

REINHERZ, E.L., MEUER, S.C. & SCHLOSSMAN, S.C. (1983) The delineation of antigen receptors on human T lymphocytes. *Immunol. Tod.* **4**, 5.

ROGERS, M.F., MORENS, D.M., STEWART, J.A., KAMINSKI, R.M., SPIRA, T.J., FEORINO, P.M., LARSEN, S.A., FRANCIS, D.P., WILSON, M., KAUFMAN, L. AND THE TASK FORCE ON AIDS. (1983) National case-control study of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia in homosexual men: Part 2 laboratory results. *Ann. Int. Med.* **99**, 151.

ROOK, A.H., MASUR, H., LANE, H.C., FREDERICK, W., KASAHARA, T., MACHER, A.M., DJEU, J.Y., MANISCHEWITZ, J.F., JACKSON, L., FAUCI, A.S. & QUINNAN, G.V. (1983) Interleukin-2 enhances the depressed natural killer and cytomegalovirus-specific cytotoxic activities of lymphocytes from patients with the acquired immune deficiency syndrome. *J. clin. Invest.* **72**, 398.

RUBINSTEIN, A., SICKLICK, M., GUPTA, A., BERNSTEIN, L., KLEIN, N., RUBINSTEIN, E., SPIGLAND, I., FRUCHTER, L., LITMAN, N., LEE, H. & HOLLANDER, M. (1983) Acquired immunodeficiency with reversed T4/T8 ratios in infant born to promiscuous and drug-addicted mothers. *J.A.M.A.* **249**, 2350.

SCHROFF, R.W., GOTTLIEB, M.S., PRINCE, H.E., CHAI, L.L. & FAHEY, J.L. (1983) Immunological studies of homosexual men with immunodeficiency and Kaposi's sarcoma. *Clin. Immunol. Immunopathol.* **27**, 300.

SELL, K.W., FOLKS, T., KWON-CHUNG, K.J., COLIGAN,, J. & MALOY, W.L. (1983) Cyclosporin immunosuppression as the possible cause of AIDS. *N. Engl. J. Med.* **309**, 1065.

SHEARER, G. (1983) AIDS: a consequence of allogeneic Ia-antigen recognition. *Immunol. Tod.* **4**, 181.

SIEGAL, F.P., LOPEZ, C., HAMMER, G.S., BROWN, A.E., KORNFELD, S., GOLD, J., HASSETT, J., HIRSCHMAN, S.Z., CUNNINGHAM-RUNDLES, C., ADELSBERG, B.R., PARHAM, D.M., SIEGAL, M., CUNNINGHAM-RUNDLES, S. & ARMSTRONG, D. (1981) Severe acquired immunodeficiency in male homosexuals manifested by chronic perianal ulcerative Herpes simplex lesions. *N. Engl. J. Med.* **305**, 1439.

SNIDER, W.D., SIMPSON, D.M., ARONYK, K.E. & NIELSEN, S.L. (1983) Primary lymphoma of the nervous system associated with acquired immunedeficiency syndrome. *N. Engl. J. Med.* **308**, 45.

STAHL, R.E., FRIEDMAN-KIEN, A., DUBIN, R., MARMOR, M. & ZOLLA-PAZNER, S. (1982) Immunologic abnormalities in homosexual men: relationship to Kaposi's sarcoma. *Am. J. Med.* **73**, 171.

VENET, A., DENNEWALD, G., SANDRON, D., STERN, M., JAUBERT, F. & LEIBOWITCH, J. (1983) Bronchoalveolar lavage in acquired immunodeficiency syndrome. *Lancet*, **ii**, 53.

VIEIRA, J., FRANK, E., SPIRA, T.J. & LANDESMAN, S.H. (1983) Acquired immune deficiency in Haitians: opportunistic infections in previously healthy Haitian immigrants. *N. Engl. J. Med.* **308**, 125.

VOLBERDING, P.A. (1984) Immunoblastic lymphoma in patients with AIDS. *Ann. N.Y. Acad. Sci.* (in press.)

WALLACE, J.I., CORAL, F.S., RIMM, I.J., LANE, H., LEVINE, H., REINHERZ, E.L., SCHLOSSMAN, S.F. & SONNABEND, J. (1982) T-cell ratios in homosexuals. *Lancet*, **i**, 908.

WALLACE, J.I., DOWNES, J., OTT, A., REISE, R., MONROE, J., JORDAN, D., THOMAS, Y., GLICKMAN, E., ROGOZINSKI, L. & CHESS, L. (1983) T-cell ratios in New York City prostitutes. *Lancet*, **i**, 58.

WEBER, J. (1984) 'Ex Africa semper aliquod novi' *N. Engl. J. Med.* (in press.)

WORMSER, G.P., KRUPP, L.B., HANRAHAN, J.P., GAVIS, G., SPIRA, T.J. & CUNNINGHAM-RUNDLES, S. (1983) Acquired immunodeficiency syndrome in male prisoners: new insights into an emerging syndrome. *Ann. Int. Med.* **98**, 297.

ZIEGLER, J.L., DREW, W.L., MINER, R.C., MINTZ, L., ROSENBAUM, E., GERSHON, J., LENNETTE, E.T., GREENSPAN, J., SCHILLITOE, E., BECKSTEAD, J., CASAVANT, C. & YAMAMOTO, K. (1982) Outbreak of Burkitt's-like lymphoma in homosexual men. *Lancet*, **ii**, 631.

ZOLLA-PAZNER, S., WILLIAM, D., EL-SADR, W., STAHL, R. & MARMOR, M. (1984) Beta-2 microglobulin as a marker for AIDS, suspected AIDS and asymptomatic AIDS. *Ann. N.Y. Acad. Sci.* (in press.)