Regular Review

Acquired immune deficiency syndrome

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New patterns of infectious disease are always interesting and sometimes alarming. The appearance of a syndrome with a high mortality and including not one but a whole range of infections is both interesting and alarming.1-3 The interest is heightened by the syndrome including an unusual manifestation of an uncommon form of cancer, Kaposi’s sarcoma.4 The syndrome occurs principally in homosexual men and first surfaced about 1979 in the form of major foci in the urban United States, particularly in New York and California.5-7 Of the first 300 patients described, 291 came from the United States and only nine from six other countries, but several of these had recently been in the United States.8-12 More recently new reports have shown that the disease is now no longer confined to the United States nor entirely to homosexuals, nor to the male sex.13 Pathologically its essential basis is an acquired cellular immune deficiency, but the cause of this deficit at present eludes investigators, and, perhaps for this very reason, the malady excites an interest far beyond the columns of the medical press.14

The clinical picture is difficult to describe, or even to define, because of the diffuseness and incoherence of the syndrome.15 Of the first 300 patients, 290 were men, of whom over four fifths were under 45, and most were homosexuals.2 The 10 women were predominantly heterosexual. Patients may present with a pneumonia eventually diagnosed as due to Pneumocystis carinii or with Kaposi’s sarcoma, or with both. Many patients, however, appear to have had fever, lymphadenopathy, loss of weight, and diarrhea before the principal illness, especially before the pneumocystis pneumonia. Of the 300 patients mentioned above, 135 had pneumocystis pneumonia as the principal illness, 115 had Kaposi’s sarcoma, and 28 had both. The remaining 22 had various opportunistic infections.3 Some two fifths of the earlier patients are now dead, and the overall mortality is expected to reach 70%. A few patients have presented with autoimmune disease, particularly thrombocytopenic purpura, with antibodies directed against the platelets.16 These patients have reduced helper:suppressor T cell ratios. This may be a clinical pathway alternative to the main syndrome, which seems to end in Kaposi’s sarcoma if the patient has not been picked off on the way by a fatal opportunistic infection, of which pneumocystis pneumonia appears to be the commonest. Either pneumocystis pneumonia or Kaposi’s sarcoma may be accompanied by various other infections.

The cardinal feature is the occurrence of infections which test the host’s cellular rather than humoral immunity and which are normally seen only in patients who are naturally or artificially immunocompromised—since their common denominator is the dependence of the host on an effective cellular immunity to combat them. Abnormal or florid forms may also be seen of infections which occur in a more usual guise even in normal people. A striking feature is the range of infectious agents that have been identified. These include protozoa (for example, P carinii17-19 and Entamoeba histolytica; yeasts (for example, Candida albicans and Cryptococcus neoformans); bacteria (for example, Mycobacterium avium-intracellulare20; and viruses (for example, Herpesvirus hominis, genital warts, and cytomegalovirus). Even Kaposi’s sarcoma21 is not entirely out of step with this pattern, because there is growing evidence for its association with a virus,
possibly cytomegalovirus, and it occurs in the train of immuno-
suppressive treatment, particularly in the form seen in these
patients. American Burkitt’s lymphoma has been reported in
one case. In contrast with the defect in cellular immunity, 
antibody mediated immunity to infectious disease appears to 
be working normally in these patients. The severe auto-
immune thrombocytopenic purpura which may figure in 
the overall syndrome is antibody mediated, though its 
ultimate basis is likely to be a defect in T suppressor cells.

Communicability

The most sinister feature of this acquired immune deficiency 
is that it appears to be communicable, perhaps principally by
intimate physical contact. The evidence for this conclusion is 
the explosive occurrence of the syndrome among those who 
have ample and exceptional opportunities for the spread of 
infection from person to person; the few who are not homo-
sexuals can mostly be traced back to such a contact. The 
cellular immune deficiency distorts the clinical picture, so 
that abnormal, florid, and frequently progressive forms of 
infection are seen—for example, with *H. hominis* infection 
occurring as a rectal and anal ulceration; infections occur 
in ostensibly fit people which are usually seen only in the 
immunocompromised. Pneumocystis pneumonia rarely if 
ever occurs in healthy people. Kaposi’s sarcoma is now 
is occurring in the United States more frequently than 
ever before, sometimes in association with pneumocystis 
infection; as a component of this syndrome it appears in a 
more fulminant guise, not just with multiple vascular nodules 
but also with visceral lesions, particularly of the lymph nodes. 
In the past the picture seen so floridly in these patients has 
been observed as a result of congenital immunodeficiencies 
or as a product of the artificial state created by the administra-

tion of immunosuppressive drugs, whereas now it appears to 
come out of the blue. On examining “the blue,” however—
the supposedly previously healthy state—there is more even 
than at first meets the eye. The patients are mostly male 
homosexuals or drug abusers, or both, and they are not so 
physically healthy as has been supposed, particularly in their 
immunological state.

The results of immunological investigations have been 
reported in a substantial number of patients with varying 
types of the syndrome, including pneumocystis pneumonia 
and other opportunistic infections (for example, candidiasis, 
herpesvirus infections, and Kaposi’s sarcoma), and also in 
members of the unaffected homosexual population. Four 
principal immunological features have been identified. Firstly, 
the helper:suppressor cell ratio among the T lymphocytes 
is reversed. Secondly, natural killer cell activity is diminished. 
Thirdly, autoimmune phenomena are seen—for example, 
lupus erythematosus and thrombocytopenic purpura. The 
most striking feature, however, might be described as quantita-
tive rather than qualitative. It is the degree of the immuno-
deficiency which is extraordinary and certainly far beyond 
that seen in patients having long term treatment with steroids, 
cyclophosphamide, or cyclosporin A. This serious disturbance 
of cell mediated immunity contrasts with a largely normal 
humoral immunity. It is reflected in a lymphopenia, in 
defective skin sensitivity to various antigens, and in defective 
lymphocyte transformation. When the lymphocytes come under closer scrutiny a 
deficiency of T lymphocytes is seen, located in the T helper 
and inducer subsets—for example, OKT4—as opposed to the 
T suppressor cytotoxic subsets—for example, OKT8. The 
ratio between the two is reversed from the normal by an 
absolute deficiency of the T helper cells rather than by a 
change in both subsets, though some studies have found that 
the number of suppressor cells was absolutely raised. These 
findings are not surprising in view of the clinical picture, 
but a survey of unaffected homosexuals in New York showed 
that over 80% had a detectable abnormality in the helper: 
suppressor T cell ratio. An attempt was made at treatment 
with thymic extract in one case. In this instance the helper: 
suppressor T cell ratio was restored to normal for a time, but 
the effect was not lasting. This failure suggests that the 
defective T cells are under the influence of some persistent 
agent, or some agent which had a persistent and irreversible 
effect, or perhaps of a combination of factors, both chemical 
and microbial. It is the search for such a cause which is at 
present so baffling, and the choice lies between “recreational” 
drugs, particularly nitrates, and a viral cause, which may 
be a known immunosuppressive virus—for example, cyto-
meagalovirus—or a hypothetical agent yet to be isolated and 
characterised. These possibilities are not mutually exclusive, 
and they may be in action severally or together.

Cause of immunodeficiency

In searching for the cause of the acquired immunodeficiency, 
one fact that needs to be borne in mind is the high prevalence 
of homosexuals in the two areas at first concerned (that is, 
New York and California). This is certainly paralleled by 
increased homosexual social activity in homosexual bars, 
restaurants, and so on, and presumably by increased sexual 
activity. One statistic of note is that the average number of 
men sexual partners for a life time reported by patients is 
1160 as compared with 524 for matched homosexual controls. 
There may, too, be new ventures in the type of “sexual” 
practice. This raises the question of the use of drugs such as 
nitrates—said to be the only group of drugs whose use by 
homosexuals had risen in the 1970s. Nitrates have an effect 
on T lymphocytes, but the part they play in the syndrome is 
uncertain if only because their use by homosexuals, if not 
universal, is widespread. On the other hand, at least one of 
the Danish patients' and two French patients have been 
identified. It is possible that a person may furnish an underlying ecosystem in which they make their individual contribution and in which a virus hitherto 
confined to relatively few individuals could find its way 
around more easily.

So far as microbiological causes are concerned, the difficulty 
is not so much to find a candidate as to evaluate the possible 
contributions of several. Comparison of patients having this 
syndrome with non-affected homosexuals has shown that 
cytomegalovirus is isolated more often from the urine, that 
the antibody titre to cytomegalovirus is above 1/128, that 
there is a raised titre to Epstein-Barr virus, and that there is 
more seropositivity for syphilis. Enteroviruses are also isolated 
more often. Gonorrhoea, hepatitis B, amoebiasis, and 
cytomegalovirus infections may be said to be endemic among 
the heterosexual, as opposed to homosexual, men. The difficulty 
is to decide which, if any, of these infections could have 
contributed. One possible analogy is with the diseases of 
overcrowded poultry or calves, in which two or more pathogens
may be needed to produce a particular syndrome. In those circumstances outbreaks of disease cannot be attributed to any one agent but to simultaneous infection with more than one—a state of affairs facilitated by the opportunities for transfer of micro-organisms from one individual to another.

So far as single organisms are concerned, however, cytomegalovirus has come under the most suspicion. Various viruses of man have an immunosuppressive effect, and cytomegalovirus is one of them. In mice it causes an increased mortality from bacterial and fungal infection, and in man it can produce the T helper:suppressor cell ratio so characteristic of this disease. In addition it is closely associated with classical Kaposi's sarcoma in homosexuals and with pneumocystis pneumonia. In recipients of renal allografts most opportunistic bacterial and fungal infections occur in patients with evidence of concurrent active cytomegalovirus infection, though such cytomegalovirus infections are common in these patients. It might be argued that even if active cytomegalovirus infection causes immunosuppression this is a quite a different matter from a severe irreversible selective loss of T cell function. Nevertheless, there might be a kind of "cascade" effect, with depressed cellular immunity leading to further infection, and so on. The main difficulty in assessing the aetiological role of cytomegalovirus in the homosexuals with acquired immunodeficiency is that (like the use of nitrates) it is rife among them anyway.

Nevertheless, the case for the syndrome being linked with an infectious agent of some kind is strong. Viruses such as hepatitis B virus take good advantage of the homosexual drug abuser ecosystem to make up for the lack of facilities for transfer between humans with a less promiscuous sex life. The most likely picture, and it is at present no more than a conjecture, is that an unrecognised agent, probably a virus, has been enabled by one or more of several circumstances to spread in a way it had previously found impossible. The principal factor is a locus of greatly increased homosexual activity, with a background of specifically and overt homosexual bars, clubs, and so on, combined, perhaps, with the acquisition of new techniques of homosexual activity. This may have been compounded by drug abuse, with the syringe playing its part in boosting parenteral spread from person to person. Certainly this has been found to be a common factor where the disease has appeared in women. A virus—perhaps present in the blood, intestinal secretions, or semen of some carriers—may not until recently have had the chance to "take off." Once on its way, a vicious circle could have been set up in which patients with this acquired immune deficiency are more susceptible to reinfection and further replication and enhanced immunodeficiency. The agent could "jump" from the main cycle if, for example, an infected man has heterosexual intercourse. This model could include also a more or less prolonged symptomless phase after first infection, and there is already evidence that subclinical cellular immunodeficiency is far more common among homosexual men than had been realised until recently.

The question of "newness" of an infectious disease and the emergence of unrecognised agents raise in themselves intriguing issues. These invite comparison with such agents as human T leukaemia virus, Marburg virus, and hepatitis B virus. The first of these is a virus unearthed by present day techniques for a well characterised disease and which must have been in circulation in some form for many years. The Marburg virus, which infected laboratory workers preparing poliovaccine from vervet monkey kidney cell cultures, might not have come to light at all but for the technical procedures requiring extensive processing of kidney cells of this species. To this day, its ultimate origin is uncertain, but it may have been in circulation in the African jungle for centuries, only to make its debut in human medicine in 1967 with a few brief but tantalising occurrences since then. Hepatitis B virus is somewhat nearer home. Human convalescent serum had not been used for prophylaxis against measles and other viral infections until about 1920. At the same time blood transfusion was becoming a practical reality, to be followed soon by the use of freeze dried pooled human plasma. Once these particular procedures became widespread, hepatitis B virus could emerge as a serious problem in infectious disease caused by the human to human transfer of material by this as well as other means, such as improperly sterilised syringes. It was some three decades before its clinical course was realised, however, and even then the nature of the agent was unknown. If it had not been for the use of blood and blood products hepatitis B might well have appeared first, at least in any prominance, as a sexually transmitted disease, brought to light by increasing activity in the homosexual and drug abusing fraternities where it is now so rife.

Unanswered questions

Clearly there are still more questions than answers about this syndrome. What is it? It is a communicable (or "community acquired") cellular immune deficiency. Is it "new"? Yes. Why has it appeared? This is still an open question, best answered by asking two more questions—What is the cause? and Why is it able to cause it? Three answers have been suggested.

Firstly, the "hot bed" theory argues that the traffic in human material in certain quarters by abnormal routes has reached such a level that, combined with the effects of drug abuse of various kinds, the sheer weight of chemical and microbial insult to the body in general, and to T lymphocytes in particular, goes beyond the tolerable limit. Eventually irreparable damage is sustained, which becomes manifest clinically in one or other of the variety of components of the syndrome.

Secondly, the drug theory points to drug abuse as the common denominator between the non-homosexuals and the main mass of patients. Much attention has focused on amyl and butyl nitrite as relative newcomers to the scene, but they are scarcely enough alone to cause all the damage.

Thirdly, the virus theory argues that the apparent communicability of the immune defect points to a microbial origin. Various viruses affect the lymphocytes—for example, measles, cytomegalovirus, and Epstein-Barr virus. That there may be another is not surprising.

The first and second of these theories are worth considering; the factors are undoubtedly relevant. Whether or not an unknown virus, perhaps formerly held at bay by adequate cellular immunity, is a reality is still conjecture. One possibility is the introduction of an animal virus into the homosexual system. The list of those at risk, now that haemophiliacs have been added, and also prisoners, has a familiar ring to those acquainted with the control of hepatitis B.

This brings us to the last question of all. What is to be done? Towards the end of 1982 the tally of cases was 788, but this may be more than the tip of a large and rather chilling iceberg yet to come. Specific treatment for the various aspects of the syndrome has been weighed in the balance and mostly found wanting. Antimicrobial chemotherapy for the infections
has proved ineffective in some cases and somewhat disappointing in many others. Anticancer treatment for Kaposi's sarcoma has been hampered by the leucopenia. The results of attempts at thymic supplantation have not been long lasting, and bone marrow transplantation has been suggested and tried in at least one case.3

The absence of any effective treatment for these patients underlines the importance of a preventive approach. If there is a microbial agent, and if it is present in patients' body fluids and particularly their blood,48 this means that there is a greater need than ever for care in handling human materials49 and in monitoring artificial human to human transfer of any kind. Human blood may carry, among other things, hepatitis B virus, at least two non-A, non-B hepatitis viruses, and cytomegalovirus; and the possibility of transmission of human T cell leukaemia virus in blood has recently been aired.50 Prevention raises issues larger than those simply of cross infection. Ironically, despite all the uncertainties, this disease (like genital herpes, which has also attracted much attention in the American lay press) is essentially preventable. The abandonment of promiscuity, homosexuality, and drug abuse could eventually stop both diseases in their tracks—though that is hardly likely to prove an acceptable solution.

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