

## For Debate . . .

### AIDS: an old disease from Africa?

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Many possible causes for the acquired immunodeficiency syndrome (AIDS) have been proposed since its first recognition in American homosexual men.<sup>1,2</sup> Investigation has centred on the search for an infectious agent (or agents), most probably viral,<sup>3</sup> and suggested aetiologies have included hepatitis B virus or a hepatitis B virus associated particle,<sup>4,5</sup> cytomegalovirus,<sup>6</sup> African swine fever virus,<sup>7</sup> and human T cell leukaemia virus.<sup>8</sup> Recently, major interest was aroused by the French discovery of lymphadenopathy associated virus,<sup>9</sup> isolated from a case of the homosexual lymphadenopathy syndrome, and by the American recognition in patients with AIDS of retroviruses belonging to the group of human T lymphotropic retroviruses collectively designated HTLV-III.<sup>10</sup> Any suggested aetiology must explain the epidemiology and clinical manifestations of AIDS. Why homosexuals, drug users, and haemophiliacs? What is the link with Haiti? Why Kaposi's sarcoma? Is this a new disease? Why has it appeared now, and where has it come from?

This report proposes that the infectious agent causing AIDS, whatever its nature, is endemic and unrecognised in parts of sub-Saharan Africa, from where it recently disseminated into external populations. No other explanation unifies the confusing observations on the syndrome. At very least, the common features of AIDS and the pattern of disease in equatorial Africa demand intensive research. Although the possibility that AIDS originated in Africa has been widely mentioned, this hypothesis has not previously been examined in detail.

#### Is AIDS a new disease?

Previous unrecognised infectious diseases often cause alarm, as witnessed by reactions to legionnaires' disease and the toxic shock syndrome. We have no evidence that any recently described infection is caused by a genuinely new agent.

In rural Africa diagnosis is often inexact. Fever is readily attributed to malaria without confirmation,<sup>11</sup> and pneumonia is often assumed to be pneumococcal or tuberculous. Lack of facilities and the sheer volume of patients generally preclude more than basic investigation. Infections of all kinds are endemic and the major cause of death.<sup>12,13</sup> In such a situation immunodeficiency would go unrecognised.

Useful analogies can be drawn between the sudden appearance of AIDS and the recent recognition of some African viral haemorrhagic fevers. Only three outbreaks of Marburg virus disease have been documented, the first in laboratory workers in Europe,<sup>14</sup> the second in South Africa,<sup>15</sup> and the third in Kenya.<sup>16</sup> The index case each time was a white person. Seroepidemiological studies indicate that infection must be occurring all the time,<sup>17</sup> but it is recognised only with access to highly advanced virological investigation, unavailable to rural Africans.

Ebola virus remained undetected until the magnitude of epidemics

in southern Sudan<sup>18</sup> and northern Zaire<sup>19</sup> attracted the world's attention. Sexual promiscuity is thought to have been important in the initial spread of this disease outside hospital (D H Smith, personal communication). Here, then, was a "new" African virus causing epidemics with high mortality, capable of being spread sexually.

The final analogy is with Lassa fever, first described in a missionary nurse in north eastern Nigeria.<sup>20</sup> Despite initial alarm surrounding this disease,<sup>21</sup> subclinical infection is now realised to be common.<sup>22</sup> Just as deaths from Lassa fever are atypical, so full blown immune deficiency may be unrepresentative of infection with the AIDS agent. The AIDS agent may exist in stable equilibrium with its rural African environment, but in a new population its expression may be altered by various factors including different innate susceptibility. Measles exemplifies this, being a generally mild infection that is nevertheless capable of decimating populations not previously exposed to it.

Like the viral haemorrhagic fevers, AIDS is an impressive disease that would not go unrecognised in the West. As the concept of genuinely new infectious organisms has no supporting evidence the AIDS agent has presumably existed undetected—in the same way as have these other infections in rural tropical Africa.

#### AIDS, Kaposi's sarcoma, and African medicine

Extensive use of drugs that suppress cellular immunity, in transplantation, oncology, and autoimmune disorders, has resulted in a few cases but not an epidemic of Kaposi's sarcoma. The tumour must have a specific aetiology, rather than just developing under conditions of impaired tumour surveillance. As Kaposi's sarcoma was a feature in about one third of reported cases of AIDS,<sup>3</sup> it would seem mandatory to look for AIDS where Kaposi's sarcoma has its highest incidence in the world, equatorial Africa.

There are few published studies examining immunological function in African patients with Kaposi's sarcoma. Although classical African Kaposi's sarcoma is an indolent tumour, the neoplasm in patients with AIDS tends to be more malignant.<sup>23</sup> An aggressive variety of Kaposi's sarcoma is seen in African children and young adults in whom lymph nodes and viscera are affected, and such patients, perhaps a tenth of all cases, have been shown to have impaired cell mediated immunity.<sup>24</sup> A recent Zambian study showed that patients with classical Kaposi's sarcoma had decreased ratios of T helper cells to T suppressor cells, as do patients with AIDS, as well as various serological changes common in AIDS.<sup>25</sup> The validity of patient and control matching in this study was questioned by other experienced workers.<sup>26</sup> The relevance of African Kaposi's sarcoma to AIDS is an important question, and it is surprising that the whole issue of the African tumour and its immunology has not received more attention.

Kaposi's sarcoma is most common in eastern and western Zaire, Rwanda and Burundi, western Uganda, Tanzania, Malawi, and Kenya, in roughly that order.<sup>27</sup> The great regional variation in prevalence and the finding of time-space clustering in Uganda's West Nile District<sup>28</sup> support an infectious aetiology. Cytomegalovirus antigen and specific DNA have been found in Kaposi's sarcoma tissue<sup>28</sup> (and cytomegalovirus infection is ubiquitous in patients with AIDS), but a firm oncogenic role for the virus has not been proved. Immunosuppression by an AIDS agent may be required before the specific factor causing Kaposi's sarcoma can induce its effects. Other long term complications of tropical infections—for example, tropical splenomegaly syndrome and hepatocellular carcinoma—occur outside Africa, but Kaposi's sarcoma in high prevalence is geographically restricted to the above areas. This observation must be relevant.

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Other tumours complicating AIDS include Burkitt's lymphoma as well as Hodgkin's and non-Hodgkin's lymphoma.<sup>3 29</sup> Burkitt's lymphoma has always been rare in non-tropical settings. Although endemic foci exist elsewhere, Burkitt's lymphoma is most common in areas constituting a band across Africa, the "lymphoma belt."<sup>30 31</sup> By otherwise strange coincidence, the "lymphoma belt," 15° north and south of the equator, encompasses the areas described above where Kaposi's sarcoma is endemic. There is strong evidence that the Epstein-Barr virus, a common infective agent in patients with AIDS, is causally relevant in African Burkitt's lymphoma,<sup>32</sup> but the importance of modulating influences such as stable malaria<sup>33</sup> or some other unidentified agent remains uncertain.

Lymphomas other than Burkitt's are also strikingly prevalent in the same geographical region. In Kenya lymphoma is the third most common solid tumour after carcinomas of the skin and cervix.<sup>34</sup> A disproportionately high prevalence of lymphoma has also been documented in Uganda.<sup>35</sup> The neoplastic complications of AIDS have much in common with patterns of cancer in equatorial Africa, and the similarities deserve further study.

Patients with AIDS have a high prevalence of enteric infections not typical in other Western immunosuppressed patients. *Entamoeba*, *Giardia*, *Cryptosporidium*, *Ascaris*, *Trichuris*, *Salmonella*, and *Shigella* are some of the pathogens documented in AIDS<sup>36</sup> but unusual in other immunosuppressed patients. Presumably many of these infections in AIDS arise from exposure to faecal material in the context of sexual activity centred on the gastrointestinal tract. Such infections, common also with poor living conditions in rural Africa, may serve to enhance immune deficiency. To what extent *Pneumocystis* occurs in the tropics is not certain. Lung biopsy is usually required for diagnosis, and few hospitals can perform it.

### The Haitian connection

The high prevalence of AIDS in Haitians, in many of whom homosexuality and drug abuse have not been obvious factors, has not been explained. Definite cases of AIDS have occurred in Haiti since 1979, and the opinion of experienced Haitian workers must be accepted that Kaposi's sarcoma was seen only once before 1979 in that country.<sup>36</sup> As the tumour is most often diagnosed on inspection and biopsy specimens are readily taken, appreciable underdiagnosis is unlikely. The present outbreak of Kaposi's sarcoma and opportunistic infections in the United States began in 1978,<sup>3 37</sup> although isolated cases may have occurred even earlier. AIDS in the United States would seem to antedate that in Haiti.

The ecology of Haiti resembles that of other Caribbean countries, and there is no reason why any endemic viral disease should localise itself to one island. If AIDS were traditionally endemic in Haiti one would have expected it also to occur in the neighbouring Dominican Republic, but this has apparently not been the case.

AIDS was probably introduced to Haiti by vacationing American homosexuals for whom the island was a fashionable resort in the late 1970s. It is easy to see how in a poor country a young man, not necessarily primarily homosexual, might become intimately involved with an affluent group of foreigners.<sup>38</sup> Once thus established AIDS could spread in a small population with relaxed attitudes towards heterosexual relations and a strong sense of community among members emigrating to the American mainland. Interestingly, Haitian born patients with AIDS are the only group in the United States in whom AIDS has become proportionately less prevalent compared with others at high risk.<sup>39</sup>

The incubation period of AIDS is thought to be one or more years. The first American cases are likely to have become infected in the early to mid-1970s, a time when tourism from the United States to Africa was developing as a result of heightened cultural interest. There now exists an increasing number of well documented cases of AIDS in black Africans,<sup>40-45</sup> mainly Zaireans, in whom obvious risk factors were lacking. One case dates back to 1977,<sup>43</sup> a year before the first reported American cases. In addition, the case has been reported of a Danish surgeon who almost certainly died of AIDS in 1977, having first become ill in Zaire in 1976.<sup>46</sup> In continental Europe heterosexual black Africans and their sexual partners now constitute an important risk group for AIDS.<sup>44</sup> A detailed report from Belgium documented AIDS or its prodrome in 23 patients from central Africa who had no history of homosexuality, drug abuse, or blood transfusions.<sup>45</sup> Half of these patients went to Belgium specifically for medical treatment, and the others had been living outside Africa for only a short time. A case report from England has also documented AIDS and Kaposi's sarcoma in a Ugandan woman without obvious risk factors.<sup>47</sup> It must be

concluded that these patients contracted the condition in Africa. The hypothesis that AIDS is an African disease best explains the ethnic and temporal descriptions of the syndrome.

### Homosexuals, heroin, haemophiliacs, hepatitis, and human T lymphotropic retroviruses

About four fifths of patients with AIDS have some serological marker of past or current infection with hepatitis B virus, and this virus was earlier seriously proposed as the causative agent.<sup>4 5</sup> Although the evidence is against hepatitis B virus or an associated particle having a causative role, hepatitis B virus provides an excellent epidemiological model of transmission. If hepatitis B virus were the cause full blown AIDS would have been recognised in areas of the world where infection with hepatitis B virus is endemic and advanced medical care is available, as in the Far East. Also, the hypothesis of hepatitis B virus as a causative agent does not explain why AIDS has surfaced at the present time while "serum hepatitis" was recognised long before its virology was understood.<sup>48</sup>

The elusive nature of the AIDS agent is no surprise to clinicians familiar with non-A, non-B hepatitis. Infection with hepatitis B virus shows how a virus can spread through three apparently distinct groups—namely, homosexuals, haemophiliacs, and drug users. The commercial nature of blood donation in the United States<sup>49</sup> and the greater interaction there than in Europe between the homosexual and drug using communities may in part explain why AIDS has been particularly a North American problem.

Infection with hepatitis B virus is endemic in patients with AIDS as well as in the condition's putative African source. In Kenya 12.2% of adults living in rural areas have been found to have hepatitis B surface antigen in serum, while 80% show some marker of previous exposure to hepatitis B virus.<sup>50</sup> It is not clear how hepatitis B virus infection maintains its high prevalence in Africa. Unlike in the Far East, vertical transmission is not thought to be a major factor.<sup>51</sup> The mode of transmission of hepatitis B virus clearly differs in Africa from in Western patients with AIDS, and the same would be true for the AIDS agent itself.

Experience in hepatitis and venereology clinics suggests that fear of AIDS has affected homosexual behaviour.<sup>52 53</sup> This could result in future reduction of hepatitis B virus infection as well as of AIDS without the two being causally related.

Recently retroviruses have been favoured as the possible cause of AIDS.<sup>54</sup> These agents were suggested because some retroviruses cause immune deficiency and tumours in animals and because antibodies to certain retroviruses have been commonly detected in patients with AIDS. In addition, some agents in the HTLV group specifically disturb T cell function and are capable of being spread by intimate personal contact. The French discovery of lymphadenopathy associated virus<sup>9</sup> and subsequent description in AIDS of immune deficiency associated virus,<sup>55</sup> along with the American finding of HTLV-III agents in patients with AIDS,<sup>10</sup> make retroviruses the leading contenders at present for a causal role.

Despite recent advances,<sup>9 10 54-57</sup> inadequate data exist as yet to incriminate retroviruses unquestionably as the cause of AIDS. It is still uncertain whether HTLV-III, lymphadenopathy associated virus, and immune deficiency associated virus are identical agents. Not all patients with AIDS who have been studied had detectable markers of these viral infections. Most importantly, association is not proof of cause, and these agents, like cytomegalovirus, might possibly turn out to be coincidental passengers in these multiply infected patients.

There is a need for international seroepidemiological studies of infection with HTLV-III and allied agents, including in African patients with AIDS and in areas in which Kaposi's sarcoma is endemic. Infection with HTLV-I is common in patients with AIDS but is also common in the Orient, where AIDS has not declared itself. Essential evidence for a causal role for HTLV-III will be the prospective showing of an increased relative risk of developing AIDS in people infected with this virus and, ultimately, reduction in the incidence of AIDS after prevention of HTLV-III infection. Finally, any causal agent must explain the epidemiology of AIDS and its sudden appearance in the West.

### Conclusions

AIDS is almost certainly caused by an infectious agent independent and distinct from hepatitis B virus but transmitted in similar fashion. Although attention is currently focused on a

number of lymphotropic retroviruses as the aetiological agent, the origin, epidemiology, and clinical manifestations of the syndrome have not been explained. The concept of a new disease is untenable. The association with Haiti has caused confusion. AIDS in the United States antedated that in Haiti, and the disease was probably introduced into the Haitian population by American homosexuals. It is suggested that the first Americans with AIDS acquired the condition in the early 1970s in Africa. AIDS is being increasingly recognised in black Africans, and the early African cases preceded the first documented American cases by several years.

The hypothesis that AIDS originated in rural equatorial Africa best explains the sudden emergence and clinical features of the syndrome. The clinical spectrum of AIDS, with Kaposi's sarcoma, Burkitt's lymphoma, other lymphomas, enteric infections, and other parasitic diseases, is strikingly reminiscent of the pattern of disease in sub-Saharan Africa. Inadequate attention has been paid to the geographical pathology of the diverse manifestations of this "new" syndrome.

The arguments put forward are my own, but I thank various colleagues for discussion. I am grateful to Ruth Nao for secretarial help.

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**AIDS: an old disease from Africa?**

SIR,—We disagree with some of Dr K M De Cock's statements in his article (4 August, p 306). We believe that with the present available data on the acquired immune deficiency syndrome (AIDS) in Africa it is too early, and it could be dangerous, to put forward any hypothesis concerning the origin of this syndrome. Human and economic problems arose in Haiti because it was initially suggested that AIDS originated from Haiti and that all Haitians had to be considered as an AIDS risk group. It is more likely that AIDS was introduced to Haiti by holidaying American homosexuals.

Dr De Cock's theory that AIDS was present in Africa before it was present in the United States is based mainly on two case reports of AIDS patients, originating in Zaire in 1976 and 1977 (retrospective diagnosis). A retrospective diagnosis of AIDS was suggested in a European patient who developed a similar syndrome in 1959,<sup>1</sup> and the diagnosis of AIDS could also have been possible in a previously healthy 49 year old black American man, born in Haiti, who died in 1959 from *Pneumocystis carinii* pneumonia.<sup>2</sup> Cases of central nervous system cryptococcosis without underlying disease have occurred sporadically in different parts of the world for many years. Perhaps some of these patients were really suffering from AIDS. Human T lymphotropic retroviruses (HTLV III) or lymphadenopathy virus serology or both performed on serum obtained before 1975 from United States homosexuals and Africans may give a more reliable indication of the origin of the syndrome.

Dr De Cock suggests that AIDS originated in rural Africa, but a recent study in Rwanda seems to show that the disease occurs more often in an urban environment (as in the United States and Haiti).<sup>3</sup>

Homosexuality is a taboo subject in equatorial Africa, as it is in Haiti, and it is hard to get information about an African's sexual life. We are treating a Belgian homosexual who has AIDS. He has been living in Zaire for more than 20 years and has had many African sexual partners, nearly all of them bisexuals who engaged in homosexual relationships for material profit. He also had sexual partners in Europe and in Brazil and had numerous European friends in Zaire who had had similar homosexual relationships with black Africans. In an epidemiological study of AIDS in Africa special attention should

be given to the sexual habits of the patients. Although present data strongly suggest that AIDS in Africa is transmitted through heterosexual contact,<sup>3,4</sup> the possibility has to be kept in mind that homosexual men could have introduced AIDS into Africa in a similar way as may have happened in Haiti.

Risk groups probably also exist in Africa, but it would be unfair with our present knowledge to consider all black Africans and their sexual partners as an AIDS risk group, as has been suggested.<sup>5</sup>

As to the relevance of African Kaposi's sarcoma to AIDS, the geographical distributions of Kaposi's sarcoma and AIDS in Africa seem to be different. More and more evidence is accumulating that the classical endemic African Kaposi's sarcoma is clinically, immunologically, and epidemiologically different from the aggressive Kaposi's sarcoma of the patients with AIDS. Kaposi's sarcoma is found in African AIDS patients in a rate much below the rate of Kaposi's sarcoma in homosexual AIDS patients.<sup>3,4,6</sup>

We agree that AIDS may not be a new disease, but the present outbreak of AIDS in equatorial Africa is certainly a new phenomenon. Certain opportunistic infections would not have gone unrecognized in certain well equipped hospitals in African countries. Indeed a spectacular increase in cases of cryptococcal meningitis has been observed in Kinshasa since 1981, before any link with AIDS was suspected.<sup>7</sup> Oesophageal candidiasis has increased sharply since mid-1983 in Kigali, where 300 oesophagoscopies a year have been performed since 1979.<sup>3</sup> Studies on the epidemiology of AIDS and its relation to Kaposi's sarcoma in different parts of Africa are under way.

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### AIDS: an old disease from Africa?

SIR,—I would like to reply to some of the thoughtful points raised by Dr R Colebunders and others (22 September, p 765) in response to my article (4 August, p 306). No certainty exists about the origin of the acquired immune deficiency syndrome (AIDS). The causative agent, however, must have come from somewhere, and the discovery of its origin would greatly increase our understanding of the syndrome. That AIDS is an African disease is a more plausible hypothesis than any other that has been proposed. The Belgian workers must see at least some merit in it, or they would not be carrying out such extensive research on AIDS in central Africa.

It is true that only a few cases of possible AIDS in Africans were reported before the current Western epidemic.<sup>1,2</sup> This is inevitable, since the syndrome has only recently been defined, and retrospective diagnosis is fraught with difficulty. Nevertheless, these early African cases of opportunistic infections in previously healthy people sound very much like real cases of AIDS. Such cases would not have gone unreported in the West. Without well documented cases elsewhere, it is difficult to see how AIDS could have been introduced into central Africa from outside.

Sporadic cases of obscure infections such as central nervous system cryptococcosis have certainly occurred world wide. There is a great difference, however, between occasional and isolated cases of unusual infections and the current epidemic of AIDS. To suggest that isolated instances of cryptococcosis might have been cases of AIDS is speculative. Again, the question arises: where would such infections with the AIDS agent have come from? Apart from their geographical links with the current African outbreak, the early African cases were also characterised by multiple opportunistic infections rather than individual ones.<sup>1,2</sup>

Dr Colebunders and his colleagues comment that AIDS in Rwanda has been recognised most often in an urban environment.<sup>3</sup> Sexual promiscuity and prostitution seem risk factors. These observations do not exclude a rural origin for the disease. Hospitals in developing countries are often concentrated in urban centres, and epidemiological conclusions drawn from hospital records can be notoriously misleading. It is easy to see how promiscuity and prostitution could amplify the spread of a sexually transmitted disease like AIDS within a city population. The epidemics of AIDS in Kinshasa<sup>4</sup> and Kigali<sup>5</sup> may be new phenomena, but that simply suggests that the AIDS agent has only recently entered these cities. Yellow fever offers an example of a condition with a rural origin which can produce epidemics in urban populations.

Too much may have been made of the fact that most Western patients with AIDS are homosexuals. A virus is unlikely to infect selectively on the basis of race, nationality, or sexual preference. The risk factors for AIDS are not being homosexual, African, or Haitian; they are having sexual intercourse with, or being exposed to blood from, another individual infected with the AIDS agent. A high carrier rate of hepatitis B virus infection among male homosexuals is the result of sexual promiscuity within an enclosed ecosystem, as well as male predisposition to becoming a carrier. It does not result simply from homosexuality. Your correspondents' suggestion that homosexuals may have introduced AIDS into Africa seems improbable. Homosexuality has existed throughout history, but the AIDS epidemic is new. It is more likely that the AIDS agent has recently gained entry into the homosexual community, and that homosexual practices have since then amplified its spread.

The Belgian workers comment that classical Kaposi's sarcoma is clinically, immunologically, and epidemiologically different from the more aggressive variety seen in AIDS. With their extensive African contacts they have experience and information not generally available, but I am aware of only one published report on the relation (if any) between classical Kaposi's sarcoma and AIDS.<sup>6</sup> Reports from Zambia suggest that aggressive Kaposi's sarcoma is being seen more often,<sup>6</sup> and that Zambian patients with the tumour have reversed ratios of T helper to T suppressor cells.<sup>6</sup> Some patients, especially children, have always had the aggressive variety of Kaposi's sarcoma,<sup>7</sup> and immunological abnormalities have been noted in such cases.<sup>8,9</sup> Studies to establish the relevance of classical Kaposi's sarcoma to AIDS should have a high priority. Your correspondents observe that the prevalence of Kaposi's sarcoma in African AIDS is lower than in homosexual patients. The same is true when one compares AIDS in American heterosexuals and children with that in homosexuals.<sup>10</sup>

My final point is more general. Kaposi's sarcoma was described in Africa as early as 1934,<sup>11</sup> and its high incidence is well documented.<sup>1,2</sup> It is a poor reflection on the outlook of Western medicine that it took an outbreak of a relatively small number of cases in American homosexuals for anyone to take any notice. The AIDS epidemic is yet another illustration of the importance of the study of geographical medicine. With their historical connections in central Africa, the workers from the Institute of Tropical Medicine in Antwerp are in a unique position to carry out important investigations. We should wish them well, and await their findings with interest.

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