Editorials

AIDS virus infection: prognosis and transmission

Acquired immune deficiency syndrome (AIDS) is only a part of a new viral disease in man. There has been confusion and misunderstanding about its nature on a monumental scale amongst public and doctors alike. What is the disease caused by the virus? How is it transmitted? What is the prognosis for those infected?

In the four years since the first cases were reported, much of the natural history of the disease has become clear. It has turned out to be a very different disease from that which it was initially believed to be. However, because of the long interval between infection and death, consideration of the overall prognosis can only be speculative for many years to come. Nevertheless, speculation need not be a mere guess because there is a wealth of evidence from which to make reasonable predictions.

AIDS is the name given to a group of clinical conditions, particularly Kaposi's sarcoma and *Pneumocystis carinii* pneumonia, which were first observed amongst previously healthy homosexual patients in New York and California in 1981. It includes several other life-threatening opportunistic infections, but it was narrowly defined by the Centers for Disease Control (CDC) in Atlanta, Georgia, for the express but limited purpose of epidemiological analysis of a newly observed disease phenomenon in man.

Ever since the term AIDS was first used in mid-1982 it has been widely believed to be a group of disease processes secondary to a defect of cell-mediated immunity. The immune deficiency was assumed to have multiple causation and to affect only homosexual men and intravenous drug abusers because of their unusual lifestyles.

It is now clear that a necessary and sufficient cause of all CDC-defined AIDS is infection with a single, unique virus new to man, variously known as human T-cell lymphotropic virus type 111 (HTLV-111) (Popovic *et al.* 1984), lymphadenopathy/AIDS virus (LAV) (Barré-Sinoussi *et al.* 1983) and AIDS-associated retrovirus (ARV) (Levy *et al.* 1984); for simplicity it will be called the AIDS virus. It is now also clear that homosexuality, promiscuity and drug abuse cannot cause AIDS without infection with the AIDS virus; conversely, infection with the virus is potentially lethal to all men, women and children irrespective of life-style or sexual activity.

The spectrum of disease caused by the AIDS virus is much greater than that covered by the CDC definition of AIDS. A few weeks after infection, the virus commonly causes an acute illness of short duration similar to glandular fever or influenza (Cooper *et al.* 1985), followed by an asymptomatic period lasting many months or years. Later there may be persistent weight loss, intermittent fever, chronic diarrhoea, generalized lymphadenopathy, progressive encephalopathy (Shaw *et al.* 1985), miliary tuberculosis, malaria (Piot *et al.* 1984), bacterial pneumonia or Gram-negative bacterial septicaemia (Jacobs *et al.* 1985), quite apart from the complex opportunistic infections of CDC-defined AIDS. Infection with the AIDS virus is often lethal without the person ever developing CDC-defined AIDS, particularly in Third World countries.

The AIDS virus is a retrovirus of the subfamily Lentivirinae (Gonda *et al.* 1985) of which only three other species are known: the lentiviruses causing maedi-visna in sheep, infectious anaemia in horses, and encephalitis-arthritis in goats. Little is known about these viruses and their pathogenesis, in contrast to the many members of the subfamily Oncornavirinae, which cause leukaemia in man (HTLV-1 and HTLV-11) and neoplastic diseases in many other vertebrates (Weiss 1982).

The association of oncornaviruses with cancer led to a massive study of this subfamily of retroviruses and the diseases they caused during the last twenty years. The lentiviruses have been largely neglected because they appeared irrelevant to disease in man and they could not be transmitted to small laboratory animals. In domestic animals lentivirus infections have proved so lethal and unresponsive to treatment, and vaccines have proved so useless, that slaughter of infected animals has been the universal means of control.

After the AIDS retrovirus was isolated it was incorrectly assumed to be an oncornavirus for nearly two years. The suggestion that the early patients with AIDS represented the start of a pandemic of a slow virus disease in man (Seale 1984*a*) was almost entirely ignored for nearly two years.

The AIDS virus persistently infects a small minority of mature T-helper lymphocytes in the peripheral blood, lymph nodes and spleen; it also persistently infects cells throughout the brain (Shaw *et al.* 1985). In the cells of the blood, and of the brain, it is slowly replicative and in both it can be detected as integrated and as unintegrated pro-

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viral DNA. From both it is persistently expressed as infectious RNA virions.

The implications for antiviral therapy are profound. The integrated pro-viral DNA in the brain becomes a part of the genome of brain cells. Consequently any antiviral agent which merely prevents replication of the virus would have to be continued for life; any agent which destroys all cells containing integrated DNA would have to destroy brain cells.

The AIDS virus is cytopathic to those few lymphocytes in which it replicates (Shaw *et al.* 1984) and may cause mild or profound immune deficiency over a period of months or years. The severity of the immune deficiency fluctuates depending upon the balance between the rate of destruction of T-helper lymphocytes and the rate of their replacement. Severe persistent immune depression commonly leads to lethal opportunistic infections.

The slow cytopathic effect on brain cells is, however, irreversible and cumulative, but takes at least two years to become clinically manifest. Interestingly, the maedi-visna virus of sheep is not cytopathic to the peripheral blood leukocytes in which it replicates, yet infection with the virus still causes progressive brain disease. Infection produces 100% mortality amongst sheep after an asymptomatic period of one to six years, without producing any immune deficiency (Palsson 1976).

The blood and plasma of animals infected with all known lentiviruses remain infectious for life to other animals of the same species (McGuire & Henson 1973). This also appears to be the case with the AIDS virus in man. In animals viraemia persists in spite of high titres of circulating, neutralizing antibodies. In the case of infection with the AIDS virus in man the circulating antibodies appear to have little or no capacity to neutralize the virus (Clavel *et al.* 1985).

In all lentivirus infections in animals, antigenic drift during the lifetime of an infected animal produces a variety of antigenic strains which infect the same animal (Weiss 1982). Different isolates of AIDS virus in man already show great variation in the *env* gene (Ratner *et al.* 1985) which codes for the envelope glycoprotein, the major stimulus for antibody production.

The almost unlimited varieties of antigenic strains of lentiviruses produced by antigenic drift, combined with the inability of antibody produced by the host to eliminate the virus from the circulation, have rendered ineffective all attempts to produce vaccines to prevent lentivirus diseases in animals. Effective protection against infection with the AIDS virus using existing vaccination techniques would seem to be theoretically impossible.

The full range of incubation period between infection and onset of progressive symptomatic disease cannot yet be determined by direct observation, as the upper limit clearly exceeds the number of years since the first cases appeared. Using a mathematical model and cases of transfusion-associated AIDS, researchers at CDC have calculated a range of one to 14 years with a mean of 6 years (Lawrence *et al.* 1985). However, this only applies to CDC-defined AIDS.

Cases of AIDS-virus progressive encephalopathy without severe immune deficiency and without CDC-defined AIDS are now beginning to appear in New York (Siegal 1985). The AIDS virus can kill by causing brain disease without any opportunistic infection and without immune suppression. By analogy with other slow virus infections of the brain, kuru in man and maedi-visna in sheep, a mean incubation period of about 15 years between infection and symptomatic AIDS-virus encephalopathy would be expected, with a range of 2 to over 30 years.

The eventual mortality following infection with a lentivirus like the AIDS virus cannot be ascertained by direct observation till those recently infected have been followed well into the 21st century. In the case of maedi-visna virus infection of sheep, the mortality reaches 100% within about two-thirds of the natural life span of the animal (Palsson 1976). The long-term mortality of horses infected with the infectious anaemia virus is not known.

A highly significant consideration is that the AIDS virus is spreading as a virgin-soil epidemic throughout mankind after crossing the species barrier, probably from a green monkey (Essex 1985). A virus which successfully crosses the host-species barrier is often highly lethal to the new species, though harmless to its natural host. Infection with the myxomatosis virus causes harmless warts in the South American jungle rabbit, but the mortality exceeds 99% in the European rabbit (Fenner & Ratcliffe 1965). The virus of African swine fever does not inconvenience the African wart-hog but it kills nearly all infected European pigs.

Newly recognized animal viruses which have crossed to man in recent years and are blood-borne have caused only limited epidemics. The viruses of Lassa fever, Marburg disease and Ebola haemorrhagic fever normally infect rodents or monkeys in which they are harmless. They kill infected men so quickly, and the immune response of those who survive kills the virus so rapidly after a transient viraemia, that they are incapable of sustaining an epidemic in man.

However, a new virus which produces a persistent viraemia for life, and causes a slow virus encephalopathy after a mean incubation period of many years, would produce a self-sustaining epidemic. Indeed, it would produce a lethal pan-

demic throughout the crowded cities and villages of the Third World of a magnitude unparalleled in human history. This is what the AIDS virus is now doing.

Transmission of the AIDS virus is blood-borne, like hepatitis B virus (HBV). Contrary to popular belief amongst medical scientists, neither virus is characteristically sexually transmitted. Both are very easily transmitted during anal intercourse, particularly male homosexual, because it regularly causes minor or major injuries of, and bleeding from the rectal mucosa (Seale 1984*b*). Similar lesions rarely occur during vaginal intercourse.

The plasma of patients infected with the AIDS virus persistently contains between 10 000 and 100 000 cell-free infectious virions per ml in the presence of circulating antibodies (Levy 1985). Although the plasma of HBV carriers often contains concentrations of virions which are a thousand-fold greater, it is probable that, as with so many viraemic diseases, a single virion introduced directly into the blood will regularly transmit infection. Consequently both virus infections are readily transmitted on multi-use, non-sterile medical needles. They are also easily transmitted by the close, non-sexual contact between cuts, sores and abrasions, and the blood or serum of other people, which commonly occur (particularly in children) in the crowded and unsanitary conditions in which most people on earth live.

Experimental evidence that HBV is easily transmitted in semen or saliva does not exist, although many believe that it does. The experimental evidence that saliva and semen of people infected with the AIDS virus is highly infectious is flawed. Some workers claim to have found cell-free AIDS virions in saliva (Groopman *et al.* 1984) but they have not yet quantified it. Others have been unable to find cell-free virions in saliva (Levy 1985).

As to the infectivity of semen, 19 scientists announced in a paper in *Nature* on 24 January 1985 that 'High titres of cell-free infectious virions can be obtained from AIDS patient semen' (Ratner *et al.* 1985). Close examination of the paper in *Nature*, and the related papers published in *Science* (Zagury *et al.* 1984, Ho *et al.* 1984), showed that they had not found any cell-free infectious virions in semen at all.

The AIDS virus, like HBV, is transmitted in blood. With a persistent viraemia of high titre lasting many years a virus can easily become established as a natural infection of man without being present in significant quantities in any other body fluids.

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References

Barré-Sinoussi F, Chermann J C, Ray F *et al.*
(1983) *Science* **220,** 868–870
Clavel F, Klatzmann O & Montagnier L
(1985) *Lancet* i, 879–880
Cooper D A, Maclean P, Finlayson R *et al.*
(1985) *Lancet* i, 537–540
Essex M
(1985) International Conference on AIDS, 14–17 April 1985, Atlanta. CDC/WHO (in press)
Fenner F & Ratcliffe F N
(1965) Myxomatosis. Cambridge University Press, London
Gonda M A, Wong-Staal F, Gallo R C, Clements J E, Narayan O & Gilden R V
(1985) *Science* **227,** 173–177
Groopman J E, Salahuddin S Z, Sarngadharan M G *et al.*
(1984) *Science* **226,** 447–449
Ho D, Schooley R T, Rota T R *et al.*
(1984) *Science* **226,** 451–453
Jacobs J L, Gold J W M, Murray H W, Roberts R B & Armstrong D
(1985) *Annals of Internal Medicine* **102,** 186–188
Lawrence D N, Lui K J, Bregman D J, Peterman T A & Morgan W M
(1985) International Conference on AIDS, 14–17 April 1985, Atlanta. CDC/WHO (in press)
Levy J A, Hoffman A D, Kramer S M, Landis J A, Shimabukuro J M & Oshiro L S
(1984) *Science* **225,** 840–843
Levy J A
(1985) International Conference on AIDS, 14–17 April 1985, Atlanta. CDC/WHO (in press)
McGuire T C & Henson J B
(1973) In: Perspectives in Virology: VIII. Ed. M Pollard. Academic Press, New York; pp 229–247
Palsson P A
(1976) In: Slow Virus Diseases of Animals and Man. Ed. R H Kimberlin. North-Holland Publishing Company, Amsterdam; pp 17–43
Piot P, Taleman H, Minlangu K B *et al.*
(1984) *Lancet* ii, 65–68
Popovic M, Sarngadharan M G, Read E & Gallo R C
(1984) *Science* **224,** 497–500
Ratner L, Haseltine W, Patarca R *et al.*
(1985) *Nature* **313,** 277–284
Seale J R
(1984*a*) *Zeitschrift für Hautkrankheiten* **59,** 525–528
(1984*b*) *Canadian Medical Association Journal* **130,** 1109–1110
Shaw G M, Hahn B H, Arya S K, Groopman J E, Gallo R C & Wong-Staal F
(1984) *Science* **226,** 1165–1171
Shaw G M, Harper M E, Hahn B H *et al.*
(1985) *Science* **227,** 177–182
Siegal F P
(1985) International Conference on AIDS, 14–17 April 1985, Atlanta. CDC/WHO (in press)
Weiss R A
(1985) In: Virus Persistence. Ed. B W J Mahy *et al.* Cambridge University Press, Cambridge; pp 267–288.
Zagury D, Bernard J, Leibowitch J *et al.*
(1984) *Science* **226,** 449–451