AIDS

HIV and Kaposi's sarcoma in mice

Robin A. Weiss

ONLY three months ago, I reported[1] in News and Views on the promise of novel systems for studying aspects of the pathogenesis of the human immunodeficiency virus (HIV) in mice and rabbits. Such is the pace of AIDS research that two new reports have already appeared in the 23 December issue of *Science* to substantiate that promise. I.L. Weissman's and J.M. McCune's group at Stanford has now demonstrated[2] that immunodeficient mice reconstituted with human lymphoid cells can be infected with HIV-2, and M.A. Martin's group at NIH has reported[3] on the fate of transgenic mice inheriting a complete genome of HIV.

Only two species of animal, chimpanzee and man, are readily susceptible to HIV infection, and only man so far produces AIDS symptoms when infected. But mice with severe combined immune deficiency (SCID) will accept engraftment, proliferation and differentiation of human haematopoietic cells. This was recently reported for lymphoid cells[4,5] and has now been extended[6] to myelo-monocytic stem cells in mice recessively homozygous for three distinct immunodeficiency genes, *bg/nu/xid*. In their new work[2], Namikawa *et al.* inoculated HIV directly into human lymphoid xenografts in SCID mice and demonstrate HIV replication. The number of cells expressing HIV by *in situ* hybridization increased progressively up to 8 weeks post-infection, which is when the article went to press. More cells expressed viral RNA than viral antigens, although HIV proteins could be detected, as well as characteristic multinucleated, syncytial cells, especially in the medulla of the implanted human lymph node or thymus fragment. Thus, the authors demonstrate *in vivo* HIV infection of mice carrying human lymphoid tissues. To my mind, the experiments so far described represent a kind of *in vivo* 'organ culture' for HIV infection, and it remains to be seen whether the system will be exploitable for studies of pathogenesis or protection against infection.

Leonard *et al.* have generated[3] transgenic mice incorporating entire, infectious genomic clones of HIV. This has been a controversial project and has required extraordinary levels of containment, lest a mouse should escape and perhaps pass on the HIV genome by breeding with wild mice. Unfortunately, a recent accident with the ventilation system in the containment facility has led to the loss of all the transgenic mice (see *Nature* **336**, 613; 15 December 1988).

The authors show that the HIV genome does become incorporated into the tissues and germ-line of the mice inoculated as pre-implantation embryos with HIV DNA. Curiously, none of the founder mice with proviruses expresses HIV, but one female mouse mated with a nontransgenic animal produced several offspring whose tissues contained infectious HIV particles. These mice developed a runting syndrome, expressed rescuable HIV and died before reaching maturity. The runting was accompanied by severe epidermal hyperplasia, particularly of the non-furry extremities (tail, paws, ears and snout), and by a grossly enlarged spleen, lymph nodes, lymphoid infiltrates of the lung and thymic involution. There was no evidence of opportunistic infections, which is not surprising as the mice were maintained in a germ-free environment. Neither was there gross evidence of neurological dysfunction, nor of HIV expression in the brain. No depletion of $CD4^+$ T lymphocytes was noted, but in the affected lymph nodes there was an increase in $CD8^+$ T cells.

Leonard *et al.* argue that a low level of HIV expression in cells such as macrophages (one of the cell types infected in human AIDS) might be sufficient to elicit the production of cellular factors that contribute to the runting syndrome. This argument may explain how lentiviruses like HIV in humans and visna-maedi virus in sheep can be severely pathogenic with low levels of virus present in the body. It will certainly be interesting to measure the production of proteins such as tumour necrosis factor (made in the macrophages) in these mice. The fact that the skin and lymphoid tissues showing abnormal growth are largely those expressing the HIV genome suggests that, in the main, such indirect factors act locally.

My own view is that transgenic mice expressing HIV genes singly or in combination, rather than the whole genome, will be more informative in probing the complex pathogenesis beyond the immediate destruction of infected cells[7]. Vogel *et al.*[8] have already reported on mice transgenic with the *tat* gene of HIV. These mice also display hyperplastic skin lesions, though these were described as endothelial and spindle cell proliferation, more reminiscent of Kaposi's sarcoma (KS) than the epidermal thickening in the transgenes of Leonard *et al.*[3]. Interestingly, the KS-like lesions in *tat* transgenes occurred predominantly in male mice, just as with KS in humans, whereas the entire HIV genome in transgenes affects both males and females.

Kaposi's sarcoma also features in two papers from R.C. Gallo's laboratory[9,10] that have been heralded for some time by his pronouncements at conferences. Nakamura *et al.*[9] found that certain T-cell lines transformed by human T-cell leukaemia viruses release paracrine growth factors that stimulate the proliferation of KS-derived cells. Interestingly, the KS cells also respond to tumour necrosis factor, so one of the factors that may exacerbate wasting disease may also contribute to KS. Salahuddin *et al.*[10] show that the stimulated KS cells then release their own factors, including strongly angiogenic activity that engenders KS-like proliferation of murine cells upon implantation in nude or beige mice. These findings lend weight to the proposition put forward five years ago by Costa and Rabson[11] that KS in AIDS is not a true malignancy of clonal origin that has become disseminated throughout the

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A MOVEMENT has been started in Norway for the despatch of an Expedition to the North Pole, and it is proposed that the leadership shall be offered to Dr Nansen. Those who are arranging the plans maintain that no other country could furnish such a crew of experienced and hardy ice men as Norway, and that a winter or two in the Arctic regions would affect these men very little. The intention is to reach the Pole by way of Franz Josef's Land, a route advocated by the most experienced Norwegian Arctic travellers. *Ski*, which have played such a prominent part in the Nordenskiöld and Nansen Greenland expeditions, would no doubt again be of great service.

IN THE January number of the *Kew Bulletin* there is a most interesting paper on the coca-plant, to which considerable attention has lately been devoted, mainly because of the valuable properties ascribed to one of its alkaloids, called cocaine, as a local anaesthetic. It appears that since the discovery of the anaesthetic properties of cocaine the demand for coca-leaves in South America has considerably increased for export purposes. A distinct loss in the alkaloids generally has been noticed during the transit of the leaves to this country; and latterly it has become the practice to extract the alkaloids from the leaves in South America, and export to the United States and Europe a crude preparation. The demand for coca-leaves has, therefore, fallen off, and the cultivation of the coca-plant in our tropical colonies will probably never assume large proportions. South America is able to produce such enormous quantities of coca-leaves that the one-eighteenth part would be sufficient to swamp the cocaine markets of the whole world.

From *Nature* **39**, 256; 10 January 1889.