AIDS research

Human and monkey virus puzzles

Peter Newmark

ETHICS and politics vied with virology and epidemiology for attention at the third International Conference on AIDS*. And PWAs (people with AIDS, as those who spoke at the meeting refer to themselves) were as much part of the meeting as HIVs, the human immunodeficiency viruses that cause AIDS. As for the science, although few real surprises emerged, the meeting provided the opportunity to assess what has been learnt in the past year. Here is the briefest of progress reports, with attributions only where identification of a single speaker is appropriate.

DNA sequencing of two isolates of HIV-2, the virus type that predominates in West Africa, has shown them to have over 80 per cent identical but to share only about 40 per cent of their sequences with HIV-1. A much closer relationship is that between HIV-2 and SIV (or STLV-III), the simian immunodeficiency virus, isolated from rhesus macaques and now sequenced. The similarity approaches identity in the case of the HIV-2 isolate called HTLV-IV and the SIV from African green monkeys, but many would interpret that as being a case of mistaken identity rather than a genuine result.

Consensus

In any case, the new consensus is that whereas SIV may have been the recent progenitor of HIV-2, the origin of HIV-1 is a puzzle. Either it has a direct progenitor of monkeys that has yet to be found, or it has evolved from HIV-1 in humans, in which case the viruses must have been in humans for longer than it seems, perhaps confined to a small population in which AIDS went unrecognized.

Any figures on the percentage relationship between different types of immunodeficiency virus have to be taken as first approximations because variations in sequence between different isolates of one type can be considerable. Variants can arise after infection; as many as 14 variants have been identified in one patient at one time, and there is some indication that they differ in biological activity. Variation is mostly by small mutations but there is a suspicion, based on lentivirus research, that recombination may also be possible (Simon Wain-Hobson, Pasteur Institute).

There is also some evidence to suggest that pathogenicity can evolve, at least in experimental animals; a virus (yet to be positively identified as SIV) from a pig-tailed macaque that died of an AIDS-like disease 14 months after being experimentally infected with SIV from sooty mangabey monkeys, killed other pig-tailed macaques and sooty mangabeys within less than two weeks (Harold McClure, Yerkes Primate Research Center). The pathogenicity of HIV-2 remains a matter of controversy. Whereas Luc Montagnier's group (Pasteur Institute) has isolated HIV-2 from about 20 West Africans with typical AIDS and in most cases without any trace of a coinfection with HIV-1, Myron Essex and his colleagues have yet to find any evidence of pathogenicity associated with HIV-2 infections in their surveys and follow-ups of west Africans.

Two apparent relatives of HIV/SIV have emerged elsewhere in the animal kingdom. One causes an AIDS-like disease in cats, and was expected to be a variant of feline leukaemia virus. But by several criteria it is much more like HIV/SIV (Niels Pedersen, University of California, Davis). The other is from cows in which it causes lymphadenopathy (Matthew Gonda, Frederick Cancer Research Facility, Maryland). The cat virus has not yet been sequenced but a partial sequence of the cow virus shows that whereas it is firmly within the lentivirus family, it is probably more closely related to equine infectious anaemia virus than to HIV or SIV.

Experimental gene constructions and deletions have helped to sort out the functions of some of the genes of the HIVs, which have several more genes than most retroviruses or lentiviruses. The confusion over *tat* gene function has been more or less resolved with evidence that the protein it produces can control other genes either transcriptionally or post-transcriptionally, depending on circumstances. The *art* or *trs* gene product is also a positive regulator but only of structural proteins, of which the product of the 3′-ORF (open reading frame) gene may be a negative regulator. Deletion of the *sor* or *A* gene results in mutants with a much reduced ability to infect cells.

Intensive scrutiny of the *env* gene has led to the tentative identification of domains within the envelope protein that are involved in binding to the T4 molecule that acts as the virus receptor on T lymphocytes and, probably, brain cells. Segments of the protein that are recognized by antibodies and by helper T cells have also been identified. The discovery of a suppressible stop codon within the *env* gene of an SIV (James Mullins, Harvard School of Public Health), and its subsequent recognition in some HIV-2 clones, suggests that either full-length or truncated forms of the envelope protein can be made and that their biological activities may differ. This can and will be put to the test.

There is increasing evidence of the presence of antibodies that neutralize HIV in the blood of infected people but the extent to which they will neutralize viruses other than those against which they have been raised remains an area of research, with importance for the attempt to produce broadly protective vaccines. Evidence that there is a T-cell mediated response against HIVs in addition to the B-cell mediated antibody response is mounting, with consistent reports of the presence of cytotoxic T cells directed against the viral envelope protein in infected but asymptomatic individuals.

Immunology and vaccines

Still the only human vaccine tests are those of Daniel Zagury (Universite Pierre and Marie Curie, Paris). He reported that 12 uninfected individuals including himself have now been immunized with a recombinant vaccinia virus that contains the full HIV-I envelope gene and boosted in one of several ways. The most successful boost consisted of the individual's own cells infected with the recombinant vaccinia virus and then inactivated. This produced broadly cross-reactive neutralizing antibodies. More practical boosters are being sought. Ten Africans with AIDS are involved in a trial of post-infection immunization (a procedure advocated by Jonas Salk, see page 473) using their own infected and inactivated cells but Zagury says it is too early to present any results.

Although trials of vaccinia-virus based vaccines in chimpanzees have had disappointing results, an application from Genetic Systems to proceed with human trials is being considered by the US Food and Drugs Administration. A second application is for a trial of a 30 amino-acid synthetic peptide analogue of the p17 product of HIV *gag* gene (Allan Goldstain, George Washington School of Health Sciences, Washington). For optimal presentation of the viral antigens in a vaccine to the immune system, William Jarrett (Glasgow University) advocated the incorporation of the antigens into ISCOMS. This technology has resulted in a fully protective vaccine against feline leukaemia virus and HIV ISCOMS are both good immunogens and non-toxic in gibbons and apes.

No vaccine will be widely available for at least five years. The only drug that is convincingly effective in treating AIDS, AZT (3′-azido-3′-deoxythymidine), is highly toxic. There are now more than 51,000 cases of AIDS in the world and with an estimated 5–10 million people infected, there will be 0.5–3 million cases in the next 5 years. □

Peter Newmark is Deputy Editor of Nature

* III International Conference on AIDS, Washington DC, 1–5 June 1987.