BMJ

LONDON, SATURDAY 13 MAY 1989

Origin of HIV

Either from primates or from a non-pathogenic human virus

Sir Fred Hoyle believes HIV to be of extraterrestrial origin, though some claim that it has escaped from a germ warfare laboratory. Lack of supporting evidence precludes serious discussion of such bizarre hypotheses. This review deals with the theories on the origin of HIV that are scientifically plausible.

HIV belongs to the family of retroviruses, which are distinguishable from other RNA viruses because they replicate through a DNA intermediate by means of an enzyme, reverse transcriptase.[1] HIV-I and HIV-II are further classified as lentiviruses or "slow" viruses.[2,3] Symptoms induced in animals by lentiviruses include a gradual degeneration of the central nervous system, wasting and progressive pneumonia in sheep (visna virus), arthritis in goats (caprine arthritis encephalitis virus), anaemia in horses (equine infectious anaemia virus), and immunodeficiency syndromes (bovine, feline, and simian immunodeficiency viruses).[3] Like HIV the prototype virus of this group, visna virus, has a latent period before the onset of disease and gives rise to respiratory and neurological manifestations; the genomes of the viruses are clearly related.[4]

The isolation of the first non-human primate (simian) immunodeficiency virus in 1985 (SIV_{MAC}) from a rhesus macaque (*Macaca mulatta*)[5] fuelled speculation that human AIDS originated in monkeys. This seemed reasonable as this virus is related to HIV antigenically and in its biological properties and can induce a disease like AIDS in macaques. The genomic sequence of SIV_{MAC} seems to be closer in nucleotide sequence homology to that of HIV-II (75%) than to that of HIV-I (40%).[6,7] But natural infection with SIV_{MAC} is rare among captive macaques and it has never been detected in wild macaques, which raises questions about its origin. For example, the infected macaques may have acquired this virus either from other species while held in captivity or in the course of being imported to primate centres.

Several other isolates of simian immunodeficiency viruses have since been obtained from captive and free living Old World monkeys,[8-11] but the only simian immunodeficiency viruses other than SIV_{MAC} whose genome has been cloned and sequenced are from monkeys caught in the wild. They are SIV_{AGM} from African green monkeys (*Cercopithecus aethiops*) caught in Kenya and Ethiopia and SIV_{MND} from wild mandrills (*Papio mandrillus sphinx*) inhabiting Gabon, the Cameroons, and the Congo.[12,13] Interestingly, neither of these viruses seems to cause disease in its natural host.[14] Detailed genetic comparison of SIV_{AGM} with HIV-I, HIV-II, and SIV_{MAC} shows that SIV_{AGM} is a novel lentivirus whose relation to HIV-I and HIV-II is no closer than that between these two human viruses[12]; only SIV_{MAC} and HIV-II are closely related.[7] Similar analysis of SIV_{MND} suggests that it is equidistantly related to HIV-I, HIV-II, SIV_{MAC}, and SIV_{AGM}.[15] In other words, the three simian immunodeficiency viruses that have been molecularly characterised bear little relation to each other. SIV_{AGM} and SIV_{MND} probably coexisted harmlessly with their hosts long before the human AIDS epidemic began. The remarkable sequence divergence between SIV_{MAC}, SIV_{MND}, and the human immunodeficiency viruses had been interpreted as evidence against any one of the simian viruses being a direct progenitor of the human viruses, but recent studies have suggested that the genomic sequences of isolates of SIV_{AGM} are much more variable than hitherto assumed. Therefore, SIV_{AGM} isolates may exist whose genomic sequences are close enough to either HIV-I or HIV-II to support the theory of a closer evolutionary relation between the human and simian viruses.[16]

Another simian lentivirus, SIV_{SM} from sooty mangabeys (*Cerocebus atys*), a species indigenous to west and central Africa, has been isolated from healthy captive sooty mangabeys in two primate centres in the United States and is the aetiological agent of a disease like AIDS in rhesus macaques.[10,11] Complete sequence data, which would disclose the extent of its relation to the human immunodeficiency viruses, are not yet available.

If HIV has been transmitted from monkeys to man extensive changes must have taken place for the virus to evolve from the known animal lentivirus to HIV, but recombination of several other retroviruses may have contributed to the evolution of HIV.[17] Recombinational events—that is, the emergence of new viruses containing genetic elements of different progenitor viruses that infect a cell simultaneously—have been shown experimentally with other closely related retroviruses. For example, D type retroviruses have been postulated to originate from recombination between B and C type retroviruses. Evidence cited in support of recombination includes a few islands of homology between the HIV-I env gene and that of the murine mammary tumour virus and Moloney murine leukaemia virus.[18-20]

Another theory on the origin of HIV is based on the knowledge that many host species have lentiviruses that have evolved with them and which sometimes may not cause

disease in their hosts. This theory postulates that HIV has recently evolved from a non-pathogenic human ancestor lentivirus which would have had to be sufficiently different not to induce antibodies reactive in standard HIV tests or to have been confined until recently to small remote populations. These possibilities are not mutually exclusive. To date there is no evidence for such a "missing link." The serological and molecular techniques used to look for viruses like HIV in normal subjects may not, however, reliably detect even quite close ancestors. Occasionally antibodies to HIV core proteins are found in normal subjects,[21] which might point to the existence of an unknown human lentivirus—but this is speculative.

If HIV was transmitted to man from monkeys how could this have happened? Transmission might have been possible through bites, scratches, medicines, or ritual preparations obtained from other primates. Irrespective of whether HIV was transmitted to humans from primates or whether it evolved from an ancestor lentivirus in man, when could this have happened? The earliest retrospectively identified cases of AIDS occurred in the 1960s,[22 23] and a comparison of the genomic sequence variability among several strains of HIV-I, HIV-II, and SIV_{MAC} suggests that about 40 years would have been long enough for the differences observed between HIV-I and HIV-II to have evolved.[24 25] It is therefore possible, but by no means certain, that HIV evolved towards becoming a pathogenic virus or spread into human populations, or both, within the past few decades.

Where did HIV come from? Very early cases of AIDS (retrospectively identified) seem to have originated in Africa.[22 23] There have been unconfirmed reports that related viruses may occur in other parts of the world. The extent to which rapid political, social, and cultural changes that have occurred in African society during this century could have played a part in the spread of HIV is impossible to specify, although some of the features of the AIDS epidemic —for example, its spread through prostitution—are certainly linked to rapid urbanisation.

The origin of HIV remains a mystery. Attempts to solve it may disclose information about the evolution of lentiviruses in different species and, perhaps, lead to the discovery of as yet unknown lentiviruses in humans. The future prevention of AIDS is the real challenge, but understanding the origins of HIV and the reasons why simian immunodeficiency viruses are not pathogenic in their natural hosts may eventually help in controlling HIV.

We acknowledge the help of Professor Robin A Weiss, director of the Institute of Cancer Research, in preparing this article.

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Institutional review boards

Britain should consider the US example of more controlled ethics committees

The American counterpart to the British research ethics committee is the institutional review board. The principal function of these committees is to review proposals to conduct research in humans to assure conformity with ethical standards. Although the leading international code of research ethics, the World Medical Assembly's Declaration of Helsinki, charges these bodies to provide only "consideration, comment, and guidance," in both the United States and the United Kingdom they have the authority to approve or disapprove plans to conduct research.

Although the goals of ethical review in the United States and Britain are identical, there are some striking contrasts in the means employed to pursue them. In the United States, but not in Britain, ethical review and approval is required by national law for most types of clinical research; virtually all research institutions have negotiated agreements with the federal government that extend the requirement for ethical review to all clinical research.[1] Federal regulations specify minimum requirements for membership, functions, and operations of the institutional review board.

The ethical criteria for approval of research by institutional review boards are set forth in considerable detail in federal regulations. The review boards have the authority to monitor the conduct of research to assure compliance with ethical standards; if they detect either non-compliance or "unexpected serious harm to subjects" they are empowered to suspend or terminate the research. By regulation, institutional review boards are required to report to institutional officials and to the federal government "any serious or continuing non-compliance by investigators" with the boards' requirements.

Applications to the United States Department of Health and Human Services for grants or contracts to support