

human beings have occurred in the past 45 years, and only four resulted in significant human-to-human transmission (HIV-1 groups M and O and HIV-2 groups A and B). The closest HIV relatives to SIVs are HIV-1 group N and HIV-2 groups C–G. Each is extremely rare: only six patients are known to have been infected with HIV-1 group N and only single individuals by HIV-2 groups C–G.^{2,3} Most SIVs are therefore epidemiological failures in human beings.

In central and west Africa, human exposure to retroviruses through hunting and butchering is ancient, but the AIDS epidemic emerged only in the second half of the 20th century, supporting a theory that some factor or factors intervened in the spread of SIV and its emergence as HIV in human populations. These factors could be deforestation, increase of urbanisation and travel in the 20th century, or increase in use of unsafe injections and transfusions. This factor might promote viral adaptation through serial passages⁴ or favour adaptation by other mechanisms such as recombination. However, all theories remain unproven.

Experimental or accidental transmission of SIVs to different species is often cleared by the new host, showing that SIV only and not AIDS is spread.⁴ When SIVsm (SIV of sooty mangabey origin) was accidentally transmitted to human beings in laboratories in the USA, one infection was cleared and the second (a human infection with SIVsmB670), caused a persistent asymptomatic infection. Macaques inoculated with SIVhu isolated from this person failed to develop productive infection.⁵ This study shows that SIVsm, the source of HIV-2,^{2,3} is of low pathogenicity in human beings. Finally, it has been repeatedly reported that most SIVs will replicate in human peripheral blood mononuclear cells (PBMCs). This is an overstatement since most SIVs are only known from DNA sequences and no infection of human PBMCs has been done.^{2,3} Thus, only four SIVs out of the 13 reported in *Cercopithecus* monkeys have been isolated, and only one of them (SIVhoest) is known to grow on human PBMCs.

SIV infections in their natural hosts are generally non-pathogenic and immuno-

deficiency is rare. In zoonotic infections that result in zoonosis (eg, rabies) the animal source is often susceptible to the disease.

In these days of AIDS, avian influenza, Ebola, and SARS, the question of what launches new epidemics and pandemics is extremely important. The somewhat shocking answer is that we actually know nothing about the factors that launch animal viruses into epidemics or pandemics. Equally important is the question as to why most animal viruses fail to launch sustained human-to-human transmission. These are critically important questions that are being bypassed. When we think zoonosis, we should think of diseases such as rabies. There is no evidence that a person can contract AIDS from a monkey or chimpanzee. There is still a missing link.

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Nathan Wolfe and colleagues¹ provide good and intriguing evidence for the natural transmission of simian foamy viruses to forest-dwelling people in west Africa engaged in hunting or butchering bush meat including that from various species of non-human primates. 61% of those interviewed from several locations reported contact with ape or monkey blood, and of this group of more than 1000 individuals, 1% had antibodies to simian foamy viruses, with the virus confirmed by PCR in three of them. Since the foamy viruses involved were

from three different host species, natural transmission to humans beings cannot be a rare event. As the authors rightly comment, such transmission of simian retroviruses belonging to a group other than immunodeficiency viruses raises important issues in relation to the possible range of zoonoses that could emerge. However, the findings have implications, which have not been pointed out, for another aspect of foamy virus studies—ie, the significance of earlier reports of the isolation of foamy viruses direct from human beings.

The first isolation of a human foamy virus (HFV) was made from a biopsy sample of a nasopharyngeal carcinoma after cell growth in vitro for about 15 weeks.² At a time predating sequence information and PCR, there was no evidence for the infectious agent either in the original biopsy or the cultures before the virus caused a cytopathic change. Early neutralisation tests with a panel of antisera specific for various animal foamy viruses showed that the isolate had some slight antigenic relatedness to simian foamy virus 6. As a result of this finding, of later work showing sequence homology of HFV with foamy viruses isolated from chimpanzees,³ and of subsequent failure to confirm new HFV infections,⁴ it came to be believed that the isolate was not derived from the human starting material but was a laboratory contaminant, despite the fact that no monkey cells were held in the laboratory where the isolation took place.

Nasopharyngeal carcinoma has been recognised for a great many years as having an exceptionally high incidence among southern Chinese individuals,⁵ but it is perhaps less well known that a moderately high incidence is seen among the Kikuyu and other tribes of the Kenyan highlands.⁵ In the context of the first isolation of foamy virus from a human source,² it is worth recalling that the nasopharyngeal carcinoma yielding the biopsy sample used for the experiment was removed from an African patient in Kenyatta National Hospital in Nairobi. The consumption of bush meat takes place among several groups in east Africa, and in certain circumstances this source of protein has

been used by the military. Although it is not now possible to ascertain the habits or activities of the Kenyan patient as concerns bush meat, the paper by Wolfe and colleagues supplies a basis to explain and thereby validate the original conclusion that the first human-derived foamy virus indeed came from an infected individual.

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Authors' reply

The emergence of new pandemics can be conceptualised as a series of steps leading from contact to global spread. Exposure to infected animal tissues leads to cross-species transmission (ie, primary infection), primary infections spread locally, and local epidemics lead to pandemics. The viruses in the primary infection and local epidemic stages have the potential for global spread, but will probably be of limited public-health significance since most primary infections are poorly adapted to new hosts, and can require time to evolve adaptations for spread.¹ Studying the epidemiology of primary infections and local spread or “viral chatter”, and predicting which patterns of chatter are likely to lead to pandemics, are the primary objectives of the study of disease emergence.

It is important to distinguish between causal explanations at different stages of emergence. Factors that influence the frequency of primary infections are

often different from those that contribute to viral adaptation and spread. For example, it is possible that hunting provides a mechanism for primary SIV infections, but that normal contact between human beings is not sufficient to initiate subsequent spread. In addition, some phenomena, such as deforestation, can exert multiple effects: deforestation might increase the frequency of primary infections by facilitating hunting at the same time as increasing the probability of global spread by connecting rural and urban communities, and thereby decreasing the probability of local extinction.²

It is also important to distinguish between the process of how a virus emerges and whether or not a new virus causes disease. Pathogenic viruses (eg, HIV) and largely non-pathogenic viruses (eg, GB virus C [hepatitis G virus]) can emerge globally. Although the significance of the simian foamy virus (SFV) chatter documented in our study is unknown, the discovery of three new primary retroviral infections is notable. The greater the frequency and diversity of primary infections, the greater the possibility that one of the primary infections will be harmful or lead to more substantial spread. SFV is a marker of primary retroviral infections as well as a unique model with an unknown public-health outcome that could range from benign endpoint to epidemic spread. Studies that follow up SFV-infected individuals are the next step to addressing these issues.

The basic ingredients for cross-species transmission of SIV to people are present. Rural central African populations are highly exposed to the blood and body fluids of non-human primates,³ and the primates that they hunt have a high prevalence of SIV. The fact that primary SIV infections have not been seen might be due to methodological limitations. Existing studies are limited to serology and PCR, which limit discoveries to viruses that fall into known groups. The advent of more comprehensive (ie, pan-retrovirus) diagnostics would probably lead to the discovery of more primary retroviral infections. In addition, our study shows that enriching collections

with behavioural data and the systematic collection of plasma and peripheral-blood mononuclear cells from all participants can improve the ability to detect primary retroviral infections relative to more general survey work.⁴ Whether collections such as ours will yield evidence of similar findings in other groups of retroviruses, and thereby identify the missing link, remains to be seen.

M A Epstein rightly comments that the first isolation of a human foamy virus (HFV, now referred to as prototype foamy virus) from a nasopharyngeal carcinoma of a Kenyan patient in 1971 could represent a cross-species infection of a human being with SFV. The sequence homology of the virus to chimpanzee-type SFV (SFVcpz) and the reported consumption of bush meat among groups in east Africa further support the possible primate origin of the infection. Our recent data⁵ confirm that HFV is a variant SFVcpz strain, and show further its high relatedness to SFV from the chimpanzee subspecies *Pan troglodytes schweinfurthii* that is prevalent in east Africa. Although it would have been desirable to have additional serological or molecular evidence of SFV infection in this patient, the isolation of HFV probably represents the first report of a cross-species SFV infection and implies that human infection with SFV is widespread in Africa and has been occurring for decades. These observations reiterate the importance of studies to define the public-health consequences of SFV infections in human beings.

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