Issue Summary
Blood Products Advisory Committee
October 21-22, 2004
Gaithersburg, MD

Topic II: The Potential Risk of Simian Foamy Virus Transmission by Blood Transfusion

Issue:

Recent data have renewed concern over the potential risk for transfusion transmission of simian foamy virus (SFV) and perhaps other viruses of nonhuman primates. FDA seeks advice from the Blood Products Advisory Committee (BPAC) on the approach that should be taken to address this concern.

Background:

The potential risk of transmission of SFV by blood transfusion is being brought to BPAC for discussion at this time because of a recent report in *The Lancet* that this retrovirus is being transmitted under "natural conditions" from nonhuman primates to the human population in Cameroon. The reported transmission of SFV to humans by non-occupational contact with nonhuman primates not only places a renewed focus on SFV transmission; it also provides yet another example of the working model of retrovirus cross-species transmission. It represents a mechanism by which SFV and other nonhuman primate retroviruses might enter the human population and ultimately the blood supply. This issue is made more urgent by recent research developments related to the possible transmission of SFV to nonhuman primates by blood transfusion, which will be presented by speakers at this advisory committee meeting.

The topic of SFV was discussed at the December 13, 2001 BPAC meeting because of evidence at that time that SFV was being transmitted to some humans with occupational exposure to nonhuman primates. The consensus of the committee was that more data were needed to determine whether SFV presented any risk to the safety of blood transfusions.

Discussion:

<u>Transmission to Humans by Occupational Exposure to Nonhuman Primates</u>
Transmission of SFV to humans due to occupational exposure to infected nonhuman primates has been reported to occur in 2-5% of persons working with nonhuman primates in research institutions and zoos (Heneine et al., 1998; Sandstrom et al., 2000; Switzer et al., 2004); most of the infected persons had histories of scratch or bite injuries caused by the nonhuman primates (Switzer et al., 2004). In the study by Switzer et al., examination of archived serum samples from six of the persons with antibodies to SFV showed that they had had antibodies to SFV for periods ranging from eight to 26 years (mean = 22

years). SFV gene sequences could be amplified from nine of the 10 with antibodies to SFV; sequence analysis indicated that eight isolates were of chimpanzee origin and one was of baboon origin. All ten individuals with antibodies to SFV reported that they were generally in good health. Three wives of infected individuals were shown to have no evidence of SFV infection. None of the 187 workers tested had antibodies to other simian retroviruses.

Transmission to Humans from Nonhuman Primates under "Natural Conditions"

A report of transmission of SFV to humans by non-occupational contact with nonhuman primates (Wolfe, et al., 2004a) and an accompanying commentary (Peeters, 2004) appeared in the March 20, 2004 issue of *The Lancet*. In fact, the exposure was only somewhat "non-occupational" in the generally accepted use of the term "occupational," since the authors felt that the transmission probably occurred as a result of the hunting, preparation, and consumption of food made from tissues of nonhuman primates, sometimes referred to as "bushmeat." Wolfe et al. studied 1,099 residents of a tropical forest area of Cameroon who had regular contact with blood or other body fluids of nonhuman primates. Antibodies to SFV were found in 10 persons; among these 10, SFV was found by RT- PCR in the peripheral blood lymphocytes of three. These three apparently had acquired SFV in three distinctly separate transmissions from nonhuman primates; they were each from different villages, and the sequences of their SFV showed that the SFV in each of them was from a different primate species, each consistent with their individual hunting and food preparation histories (gorilla, mandrill, and *Cercopithecus* spp, respectively). (SFV strains are known to be highly specific for each host species.)

SFV Epidemiology

The prevalence of SFV in the nonhuman primate adult population ranges from 31-61% in the wild (Hussain et al., 2003; Calattini et al., 2004b) and 70-90% in captivity (Hussain et al., 2003). (In contrast, the prevalence of simian immunodeficiency virus [SIV] among nonhuman primates in the wild in the same areas is about 16% and the prevalence of simian T lymphotropic virus [STLV] is about 11% [Peeters, 2004].)

Human-to-human spread of SFV has not yet been shown to occur. Nevertheless, there is clearly primate-to-primate transmission among nonhuman primates in the wild. Transmission between primates is believed to occur by means of saliva, since SFV can be isolated easily from the saliva of infected nonhuman primates. Transmission by bites theoretically could be one mechanism of transmission from captive nonhuman primates to their handlers (Switzer et al, 2004). In support of this theory, a gorilla strain of SFV was detected in two Cameroonian hunters who had separate histories of multiple bite injuries during fights with gorillas (Calattini, et al., 2004 a).

No evidence of transmission of SFV by human-to-human blood transfusion was found in a study of recipients of blood from one donor who was later discovered to have SFV infection (Boneva et al., 2002). Studies of archived specimens from this donor showed that he had been infected with SFV over a nineteen-year period from 1981 to 2000; he had donated blood six times between 1992 and 1997. Lookback studies of two recipients

of his red blood cells, one recipient of his leukocyte-reduced red blood cells, and one recipient of his platelets revealed no cases of transmission of SFV (Boneva et al., 2002). Derivatives made from plasma pools containing this donor's plasma were negative when tested for SFV by RT-PCR (Boneva et al., 2002). Although this study may provide a basis for optimism, its small size and the absence of information about viral load in the blood donor preclude any firm conclusions.

SFV and the Possibility of Pathogenesis in Humans

Recent reports provide strong evidence of persistent SFV infections in humans (Heneine et al., 1998, 2003; Switzer et al., 2004). Studies of stored serum samples have revealed human SFV infections lasting as long as 19 and 26 years (Heneine et al., 1998; Switzer et al., 2004).

Although a putative "human" foamy virus reported in 1971 (Epstein, 2004), isolated from a nasopharyngeal carcinoma from a patient from Kenya, was later shown by sequencing to be the chimpanzee strain of SFV (Wolfe et al., 2004b), no etiologic association between SFV and any human disease has been established so far. Repeated efforts to show an association with nasopharyngeal carcinoma or other human diseases have all been negative (Heneine et al., 2003). All SFV-infected individuals generally report being in good health, although this observation may reflect the fact that studies of human SFV have been conducted mainly among healthy employees of research facilities and zoos. Nevertheless, existing data on health outcomes of SFV are limited and one cannot exclude the possible occurrence of disease after long latency periods (Switzer et al. 2004; Heneine et al. 1998, 2003).

Theoretical Concerns: SFV as a Model for Cross-species Transmission of a Simian Retrovirus

The reported transmission of SFV to humans by non-occupational contact with nonhuman primates not only places a renewed focus on SFV transmission; it also provides yet another example of the working model of retrovirus cross-species transmission, or "species jumping," of which human immunodeficiency virus (HIV) and human T lymphotropic virus (HTLV) are the most significant examples. Two simian immunodeficiency virus (SIV) strains emerged to form HIV types 1 and 2, and two strains of another simian retrovirus, simian T lymphotropic virus (STLV), emerged to form HTLV types I and II. Human diseases associated with infections with these emerging retroviruses were not recognized for many years; in the case of HTLV I, this delay was due in part to the fact that fewer than 5% of persons infected with the virus develop a disease.

The Issue of Possible Blood Donor Exclusion for Nonhuman Primate Exposure

Even though no human disease has been linked definitively to SFV infection, the theoretical concerns described above may lead many people to urge taking precautionary measures. However, such precautionary regulatory measures require careful consideration of risk level and the impact on the availability of needed blood products.

Handlers of nonhuman primates in a laboratory setting are not the only people with close contact with nonhuman primates. In addition, zoo workers, people who have nonhuman primates as pets (there are about 15,000 households with such pets in the U.S.), and bench laboratory scientists and technicians who conduct testing of primate serum and tissues may be at risk for SFV infection. The risk for scientists conducting behavioral studies on nonhuman primates theoretically could be lower than that for scientists conducting other types of studies. It would be a challenge to define precisely which individuals would pose a risk if they donated blood.

Questions for the Committee:

1. In the absence of any known disease association, should FDA be concerned about the potential for transfusion transmission of SFV?

2. Do the recent evidence of SFV infections in humans and of transmissibility of SFV by blood in animal studies heighten concern that known and unknown pathogenic viruses of nonhuman primates could enter the human blood supply?

3. Do the available scientific data warrant possible consideration of donor exclusion criteria for exposure to nonhuman primates? Please discuss the factors that should be considered.

References

Boneva RS, AJ Grindon, SL Orton, et al. (2002). Simian foamy virus infection in a blood donor. Transfusion 42:886-891.

Calattini S, P Mauclère, Tortevoye P, Froment A, Saib A, Gessain A (2004a). Interspecies transmission of simian foamy viruses from chimpanzees and gorillas to Bantous and Pygmees [*sic*] hunters in Southern Cameroon. Proceedings of the 5th International Foamy Virus Conference, Wuerzburg, Germany, July 9-11, 2004, p. 1. (http://www.virologie.uni-wuerzburg.de/index.php?content=11)

Calattini S, E Nerrienet, P Mauclère, Georges-Courbot M-C, Saib A, Gessain A (2004b). Novel simian foamy viruses in wild-caught gorillas, mandrills and chimpanzees from Central Africa. Proceedings of the 5th International Foamy Virus Conference, Wuerzburg, Germany, July 9-11, 2004, p. 1. (http://www.virologie.uni-wuerzburg.de/index.php?content=11)

Epstein MA (2004). Simian retroviral infections in human beings. Lancet 364:138-139 (letter).

Heneine W, WM Switzer, P Sandstrom, et al. (1998). Identification of a human population infected with simian foamy viruses. Nature Medicine 4:403-407.

Heneine W, M Schweizer, P Sandstrom, T Folks (2003). Human infection with foamy viruses. Current Topics in Microbiology and Immunology 277:181-196.

Hussain AI, V Shanmugam, VB Bhullar, et al. (2003). Screening for simian foamy virus infection by using a combined antigen western blot assay: evidence for a wide distribution among Old World primates and identification of four new divergent viruses. Virology 309:248-257.

Peeters M. (2004). Cross-species transmissions of simian retroviruses in Africa and risk for human health. Lancet 363:911-912.

Sandstrom PA, Phan KO, Switzer WM, et al. (2000). Simian foamy virus infection among zoo keepers. Lancet 355:551-552.

Switzer WM, Bhullar V, Shanmugam V, et al. (2004). Frequent simian foamy virus infection in persons occupationally exposed to nonhuman primates. J. of Virology 78: 2780-2789.

Wolfe, ND, WM Switzer, JK Carr, et al. (2004a). Naturally acquired simian retrovirus infections in central African hunters. Lancet 363:932-937.

Wolfe ND, WM Switzer, TM Folks, DS Burke, W Heneine (2004b). Authors' reply. Lancet 364:139-140.