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Animal Models for HIV Infection and AIDS

HIV is a member of the lentivirus subfamily of the retroviruses. Members of the Retroviridae family, or retroviruses, possess enveloped virions containing an RNA genome. The distinctive feature of these viruses, which gave the name to the family, is the presence in the virus particle of a virus-coded RNA-dependent DNA polymerase, or reverse transcriptase; upon infection, this enzyme transcribes the RNA genome into a DNA provirus, which then becomes integrated into the host chromosomal DNA where it may complete the replication cycle by directing the synthesis of infectious virions, or it may express none or only part of its genetic information in a covert infection. Retroviruses are widely distributed in nature and for many years have been known to infect numerous vertebrate species. Human retroviruses have only been recognized since the late 1970s, and now include the human T-lymphotropic virus types I and II (HTLV-I, HTLV-II) and the human immunodeficiency virus (HIV) (*1*).

The Retroviridae family is presently subdivided into three subfamilies (Oncovirinae, Spumavirinae, and Lentivirinae), according to their different biological characteristics, which also coincide with different genomic organization. The Oncovirinae subfamily (onco = Greek "tumor"), the largest one, includes viruses most commonly associated with lymphoproliferative disorders in many animal species. The Oncovirinae genome consists of the structural genes, *gag*, *pol*, and *env*. The *gag* gene (for group-specific antigen) codes for the internal proteins that constitute the "core" of the virion; the *pol* gene (for polymerase) codes for the reverse transcriptase; and the *env* gene codes for the glycoproteins found in

Source: World Health Organization. Animal models for HIV infection and AIDS: Memorandum from a WHO Meeting. *Bulletin of the World Health Organization* 66(5), 1988. The Memorandum is based on the report of an informal WHO Consultation held in Geneva, Switzerland, on 28–30 March 1988. The names of the participants are given on pages 232–233.

the virus envelope. These three genes are flanked by sequences repeated on both ends of the genome, known as long terminal repeats (LTR), which contain regulatory elements for transcription. Morphologically, oncoviruses have been subdivided into three groups, referred to as type B, C, and D particles. Type C oncoviruses include, among others, the murine, avian, and feline leukemia/sarcoma viruses. Type B oncoviruses are represented by the mouse mammary tumor virus. The Mason-Pfizer monkey virus is the prototype of type D retroviruses, and more recently other type D viruses (simian retroviruses, SRV) have been identified as the etiologic agents of a fatal AIDS-like disease in rhesus macaques, known as simian AIDS or SAIDS. The two other known human retroviruses (HTLV-I and HTLV-II), as well as bovine leukemia virus (BLV) and the simian T-lymphotropic virus type I (STLV-I), are generally considered as members of the oncovirus subfamily, but perhaps they should be placed into a new subfamily, based on their unique genomic organization that includes the presence of at least two regulatory genes.

The spumaviruses (spuma=Latin "foam") comprise a number of viruses from many animal species, including man, which are not associated with any pathological entity and are frequently recognized by their ability to induce the formation of foamy vacuolated syncytia in tissue culture.

Lentiviruses (lenti=Latin "slow") are non-oncogenic retroviruses that induce chronic debilitating diseases following long-term persistent infections. The Lentivirinae subfamily at present includes viruses from ungulates (maedi-visna virus of sheep, caprine arthritis-encephalitis virus (CAEV) from goats, equine infectious anemia virus (EIAV) from horses, and bovine immunodeficiency virus (BIV) from cattle), felines (feline immunodeficiency virus (FIV)), and human and nonhuman primates (HIV, simian immunodeficiency viruses (SIV)). The most outstanding characteristic of the genome of the lentivirus subfamily is the presence of a number of accessory genes with regulatory functions. In addition to *gag, pol,* and *env,* at least five other genes (*tat, rev, vif, vpr,* and *nef*) have been identified. Some of these accessory genes are required for virus infectivity, and they regulate the expression of the viral structural proteins.

Several animal model systems for HIV infection and AIDS are now available and can be grouped as follows:

(1) infection of nonhuman primates with lentiviruses (simian immunodeficiency viruses);
(2) HIV infection of nonhuman primates;
(3) infection of nonprimate mammalian hosts with species-specific lentiviruses;
(4) infection with nonlentiviruses that induce immunodeficiency; and
(5) new potential models (2, 3).

SIMIAN IMMUNODEFICIENCY VIRUSES (SIV)

The simian immunodeficiency viruses are a diverse group of nonhuman primate lentiviruses. Based on their antigenic, genetic, and biological characteristics, they represent the closest known relatives to HIV.

SIV was first isolated in 1985 from diseased captive rhesus macaques in a primate center in the United States. The original isolate was called simian T-lymphotropic virus type III (STLV-III), but it is now designated SIVmac. A serologic survey conducted in 1986–1987 in this primate center showed that only three animals (two rhesus and one cyno-

molgus macaque) were infected among the 848 monkeys investigated. This low prevalence of SIV infection raises questions as to whether the isolated viruses actually originated from macaques in the wild or whether, perhaps, captive macaques may have acquired their SIV from some other species in the process of importation or while in captivity.

Known SIV Isolates (*4–7*)

Following the discovery of SIVmac, a number of other nonhuman primate lentiviruses were isolated from:

- multiple species of macaques (*Macaca*)=SIVmac;
- sooty mangabey (*Cercocebus atys*) =SIVsm;
- African green monkey (*Cercopithecus aethiops*)=SIVagm; and
- mandrills (*Papio sphinx*)=SIVmnd.

Natural infection of macaques is rare in captivity and has not been documented in nature, although more extensive serologic surveys need to be conducted to clarify this point. Several isolates of SIVmac have now been obtained in different primate centers, from cynomolgus (*M. fascicularis*), pig-tailed (*M. nemestrina*), and stump-tailed (*M. arctoides*) macaques. Some of these isolations were made from animals experimentally inoculated with tissue samples from a different species of macaque, and their precise origin remains to be elucidated. Macaques from which SIV was isolated very often died with clinical signs and necropsy findings reminiscent of AIDS, including lymphomas and lymphoproliferative diseases.

SIV from sooty mangabeys (SIVsm) was originally identified when rhesus macaques developed immunodeficiency after experimental inoculation with materials obtained from sooty mangabeys. Approximately 75% of sooty mangabeys in a colony were found to be persistently infected with SIVsm, with few manifestations of disease that might be attributed to a lentivirus. On the other hand, infection of mangabeys in their natural habitat in Africa has not been documented, again raising questions as to the origin of this virus.

Early serologic surveys for SIV-reactive antibodies demonstrated that 30% to 50% of green monkeys from Africa harbor a related virus, although a systematic evaluation of the geographical distribution of these antibodies has not been conducted. Curiously, green monkeys present in some islands in the Caribbean, descendants of animals brought to America during the 17th and 18th centuries, have been found to be seronegative. An early putative isolate for African green monkey (STLV-IIIagm) now appears to be a contaminant for SIVmac, but a number of authentic isolates of SIVagm have now been obtained from animals from Kenya and Ethiopia.

Mandrills also appear to be infected in nature, and SIVmnd has been recently isolated from mandrills in Gabon. Natural or experimental infection with SIVagm or SIVmnd does not seem to result in disease, suggesting a lack of pathogenicity in these viruses.

Antibodies that cross-react with HIV or SIV have been found in several other Old World monkey species, suggesting the existence of other primate lentiviruses that remain to be isolated.

Genetic Relatedness of SIV Isolates (*7, 8*)

SIVmac is more closely related to HIV-2 than to HIV-1. It shares 75% overall nucleotide identity with HIV-2, and only 40% with HIV-1. Nucleotide conservation between HIV-1 and HIV-2 is approxi-

mately 40%, mostly within the *gag* and *pol* genes.

SIVmac isolates derived from a single primate colony display some degree of variation in their nucleotide sequence. Restriction endonuclease mapping of SIVmac derived from five rhesus and one cynomolgus macaques showed that all isolates were closely related, but nevertheless distinguishable from each other, with the isolate from the cynomolgus macaque being the most different.

Antigenic and genetic analysis of SIVagm and SIVmnd have indicated that they are newly identified members of the HIV/SIV group of primate lentiviruses. SIVagm *gag* products are antigenically related to those of HIV-1, HIV-2, and SIVmac. On the other hand, their *env* products are related to those of HIV-2 and SIVmac, but not (or scarcely) with those of HIV-1. Nucleotide sequence analyses have indicated that SIVmac and SIVagm are related, but quite distinct from each other and distinct from HIV-1 and HIV-2.

SIV from mandrills appears to be approximately equidistant from HIV-1, HIV-2, SIVagm, and SIVmac. SIV from mangabeys appear distinct from SIVmac and SIVagm, but precise information is lacking. Likewise, little information is available on the heterogeneity of isolates from a given species or genus obtained at different locations.

Experimental Inoculations (*2, 5, 6, 9*)

SIV infection in macaques induces an immunodeficiency syndrome similar to that of human AIDS and is becoming increasingly important as a model not only of infection but also of disease. The two systems that have been most explored are infection of rhesus macaques with SIVmac or with SIVsm.

Infection of rhesus macaques with SIVmac results in persistent infection leading to death in the majority of inoculated animals. The median time of death was 266 days, with a range of 62 to 1,061 days. No correlation has been observed between the dose of virus and clinical outcome, but the ability of macaques to survive correlated directly with the strength of the antibody response. Macaques that died displayed clinical symptoms and necropsy findings similar to AIDS in humans. They exhibited diarrhea, wasting, and decreases in the number of peripheral T4 lymphocytes and mitogen proliferative responses. Opportunistic infections (*Pneumocystis carinii*, cytomegalovirus, *Cryptosporidium*, *Candida*, adenovirus, and *Mycobacterium avium-intracellulare*) have been a common feature. Fifty percent of macaques have died with a characteristic granulomatous encephalitis, similar to that seen in humans.

A new approach to studying the biological properties of SIVmac isolates is the use of infectious molecular clones. At least three such infectious clones have been obtained from SIVmac (SIVmac 251, SIVmac 239, and SIVmac 142), and they may prove to be particularly useful in defining determinants of pathogenicity through in vitro experiments with molecular clones and mutants derived from them.

Experimental infection of the rhesus macaque (an Asian monkey) with SIV from the sooty mangabey (an African primate) demonstrated that this virus, although associated with no apparent disease in its species of origin, can induce an immunodeficiency disease in an alternate host which, in many respects, parallels that of acquired immunodeficiency disease (AIDS) in man. More than 70% of juvenile rhesus monkeys inoculated with a pathogenic strain of SIVsm (delta strain) died within six months of infection. In general, the simian disease parallels AIDS, but with some notable differences. Generalized lymphadenopathy

was usually apparent within one month after the inoculation. This condition may persist for months, but usually regresses before the animal's death. The immediate cause of death in the majority of infected monkeys was apparently diarrhea which did not respond to appropriate antibiotic and supportive therapy. Much of the diarrhea associated with SIVsm infection was due to *Shigella* or *Campylobacter,* common pathogens in rhesus monkeys. A retroviral encephalitis morphologically very similar to that observed in AIDS was a frequent finding. B-cell lymphomas associated with an Epstein-Barr–like herpesvirus also occurred in immunosuppressed monkeys. Infection with multiple opportunistic agents was a common finding, with cytomegalovirus being the most frequent viral opportunistic agent observed, often contributing to or being the immediate cause of death. Several protozoan opportunists have also been identified, including *Cryptosporidium* and *Pneumocystis carinii.* Syncytial cells were most commonly found in the lymph nodes and central nervous system of infected monkeys, but have also been seen in other tissues. The presence of giant cells in the tissues of infected individuals appears to be a marker for both SIV and HIV infection, since in monkeys and humans these cells express viral proteins and certain virus particles. Other lesions observed were peribronchiolar lymphoid infiltrates, hepatic lesions, and a prominent erythematous rash.

An interesting observation is that different virus isolates, although related, may vary in both pathogenic potential and the spectrum of disease they induce. Some correlations have been found between the pathogenic potential of these isolates and their ability to productively infect primary monocytes, and one strain was associated with a high incidence of central nervous system infection. As with the SIVmac–rhesus model, pathogenicity is relatively independent of dose. On the other hand, changes in lymphocyte subsets (particularly in the helper-inducer subset of T-lymphocytes), a decline in SIV-specific antibody, and virus-specific antigenemia are prognostic for disease progression. Inoculated animals that remained clinically healthy respond to SIV infection with antibodies to both *gag*- and *env*-related SIV proteins which persist throughout the course of infection. In infected animals displaying immunological alterations, a disproportionate loss of *gag*-specific, relative to *env*-specific, antibodies was observed in the terminal stages of the disease. This decline uniformly coincided with the emergence of viral antigen in serum. These changes are apparent months before any change in the clinical picture can be noted and thus are useful prognostic indicators for disease progression. This observation is consistent with that reported in HIV-infected humans wherein a loss of detectable HIV *gag*-specific antibody coincident with antigenemia was noted in patients progressing from ARC (AIDS-related complex) to AIDS. The striking exception to the SIV antibody response previously described involves animals that develop retroviral-associated encephalopathy. The clinical course of the disease in monkeys with encephalopathy varies from acute (death within eight to nine weeks after inoculation) to chronic (survival for five to seven months). SIV-specific antibodies in all of these animals were either markedly reduced, when compared to other SIV-infected animals, or notably absent, regardless of the time course of the disease. Moreover, lack of detectable SIV antibody corresponds to persistent, recurrent, or progressively increasing levels of SIV antigen in the serum.

Studies similar to those described above have been conducted at another primate center, using a different isolate of SIVsm (strain SMM Yerkes). Twelve rhe-

sus macaques have now been infected for 20 to 33 months, and five of the animals died of an AIDS-like disease between 14 and 28 months after inoculation. Characteristics of the disease in macaques that died following infection include weight loss, diarrhea, lymphadenopathy, pneumonia, hepatosplenomegaly, ataxia, anemia, neutropenia, lymphopenia with preferential loss of $CD4^+$ cells, thrombocytopenia, and hyper- and hypogammaglobulinemia. Histopathologic analysis revealed that most of the tissues from some animals, including lymph node, spleen, lung, and brain, contained multinucleated giant cells. Following inoculation, most of the animals developed antibodies to *env*- and *gag*-encoded proteins between three and six weeks after virus inoculation and, in agreement with findings in SIV-infected mangabeys, few or no neutralizing antibodies were detected in serum from the rhesus macaques up to 18 months after infection. Loss of antibodies to specific proteins, primarily *gag*-encoded, was detected, but owing to the limited number of animals that have died to date, it has not been possible to determine whether a specific antibody profile will be predictive of more severe disease and death. It was found, however, that cell-free virus can be recovered from the serum of animals that have more frequent and persistent symptoms of disease, but not from those animals that remain well or show only intermittent signs of disease.

SIVsm was also used to inoculate a pig-tailed macaque, which unlike the inoculated rhesus macaques, was found to develop neutralizing antibodies at six months after infection. The pig-tailed macaque had essentially no antibodies to *gag* gene products at any time after infection and was sacrificed 14 months after inoculation because of a deteriorating clinical condition and signs of neurologic disease. At the time of death, virus was recovered from peripheral blood mononuclear cells (PBMC) and from multiple tissues, including the brain. The concentration of cell-free virus increased from 10 fifty percent-tissue-culture-infectious doses per milliliter ($TCID_{50}$/ml) at six months after infection to 10^2 TCID-50/ml at 10 months and to 10^4 at the time of sacrifice. Virus isolated at the time of death was used to inoculate additional macaques and SIV-seronegative mangabeys, and resulted in death within 13 days of inoculation in eight out of nine macaques and three out of four mangabeys. The acute deaths were due to severe mucoid diarrhea that led to dehydration and electrolyte imbalance. An interesting observation was that both of two SIV-SMM virus-positive and seropositive mangabey monkeys were protected from the lethal effect of the SIVsm variant (designated SMM-PBj14). Investigations are now being conducted to demonstrate definitively that it is in fact SIVsm that is killing the animals with this rapidity. If validated, the use of a highly virulent strain of SIV may provide a rapid assay system for screening drugs or vaccines for efficacy in the prevention not only of infection but also of disease.

Potential Uses of the SIV Model

The potential use of the SIV model for the study of human AIDS derives from the many similarities of these viruses with HIV. Both viruses have the same morphology and morphogenesis typical of lentiviruses and exhibit tropism for cells bearing the CD4 antigen. Conservation of some critical epitopes of CD4 in a variety of primate species allows the in vitro infection of their lymphocytes with HIV. Infection of $CD4^+$ cells with HIV or SIV can be cytopathic for these cells. As described before, SIV can cause an AIDS-like disease in selected species of nonhuman primates, and the induced disease is

remarkably similar to AIDS in humans. However, Kaposi's sarcoma has not been described in SIV-infected primates, and the spectrum of opportunistic agents observed following SIV-induced immunosuppression is slightly different from that in HIV-infected humans. There are many conserved epitopes in the major viral antigens of SIV and HIV, and the existence of these epitopes permitted early serologic identification of the existence of HIV-related viruses in nonhuman primates.

The nucleotide sequence and genomic organization of SIV is closely related to those of HIV-2. However, SIVmac and SIVagm, as well as HIV-2, have an additional gene, *vpx*, which is not present in HIV-1. This gene appears to be expressed in the SIV virus, is immunogenic, and apparently is dispensable for the replication of the virus in vitro. The *vpr* gene, which is present in HIV-1, HIV-2, and SIVmac, does not appear to be present in at least one isolate of SIVagm. Comparisons of the genomic structure of pathogenic and nonpathogenic SIV isolates may be important to understanding the molecular basis of the pathogenicity of HIV. Another major molecular difference between HIV-1 and SIV is that SIV (SIVmac and SIVagm) often has a premature stop codon in *env*, resulting in a truncated form of transmembrane glycoprotein. This premature translation termination signal has also been observed in HIV-2.

Continued use of the SIV model will be important in three areas of AIDS research:

(1) To better understand the natural history and evolution of primate lentiviruses. Information is needed regarding species in the wild that harbor SIV as well as the precise genetic make-up of these viruses.

(2) To define the pathogenesis of AIDS, such as mechanisms of persistence, host tropisms, and determinants of neuropathogenicity.

(3) To develop AIDS vaccines and treatment strategies. Comparison of vaccine approaches can be more easily achieved using SIV in readily available macaques than by using HIV in rare chimpanzees.

Studies in all these areas are dependent on more fundamental research, including investigations of virus-host interactions and characterization of the immune system of the nonhuman primate host.

HIV INFECTION OF NONHUMAN PRIMATES

The ideal model for AIDS would be one in which HIV infects and induces an AIDS-like disease in a common experimental animal. Thus far, in addition to humans, only chimpanzees and gibbon apes have been found to be susceptible to HIV infection. Only very limited numbers of these animals are available to researchers.

The ability of HIV to infect in vitro the lymphocytes of a number of primate species indicates that further investigation, particularly with common New World primates, may be warranted.

Experimental Infection of Chimpanzees (*10, 11*)

Several groups have demonstrated that chimpanzees can be readily infected with some strains of HIV-1. Infections are easily established by intravenous inoculation of human tissue homogenates, HIV-1-infected PBMC, or cell-free HIV-1, or by application of cell-free virus to vaginal mucosa. It appears that only small numbers of virus particles are needed to es-

tablish infection in chimpanzees, but strain differences may exist. It has been documented that 40 $TCID_{50}$ of HIV-1 (strain HTLV-IIIB) established infection in both of two chimpanzees, but only one of two animals became infected with 4 $TCID_{50}$ of the same pool of viruses.

Within two weeks of inoculation of the LAV-1 strain of HIV-1, virus can be recovered from PBMC of chimpanzees, irrespective of the inoculum or route of inoculation, and once an animal is infected, virus can be recovered on a routine basis from PBMC. In contrast, cell-free virus has only been obtained from animals during the first six weeks after infection. Virus has also been obtained from one of two bone marrow samples, but not from a limited number of saliva or spinal fluid samples that were tested.

Early after infection (the first two to three months), 10^3 to 10^4 infectious PBMC per 10^7 PBMC can be detected. Over the ensuing months, this number drops to a baseline level of one to 10 infectious PBMC per 10^7 PBMC, which persists for extended periods. Thus, there appears to be an early phase of viremia, corresponding to high numbers of infectious cells, which gradually disappears as HIV-1–specific antibody titers increase; however, the decrease in numbers of infectious PBMC or cell-free virus has not yet been shown to result from immune clearance. HIV-1–specific antibodies are detectable in serum of chimpanzees by enzyme immunoassay (EIA), immunoblot, and radioimmunoprecipitation (RIP) assay within approximately four weeks of virus inoculation. Short-lived low-titered (less than 100) IgM responses to HIV-1 have been detected in about one-half of infected chimpanzees, but IgG titers, as determined by EIA, developed rapidly and stabilized about six months after infection at titers ranging from 25,000 to 500,000. Antibodies to *env* and *gag* gene products are detectable at approximately the same time (three to five weeks after infection) while antibodies to *pol* gene products are delayed by weeks to a few months. More recently, antibodies to the putative regulatory protein encoded by the *nef* gene have been detected either coincident with antibodies to *env* and *gag* proteins, or even earlier. It is interesting to mention that experimental inoculation of a chimpanzee with the ARV-2/SF2 isolate of HIV resulted in a less-efficient infection, with virus being recovered by PBMC only after five months after the inoculation. In this animal, antibodies to the *nef* gene product were detected within two weeks after inoculation, whereas antibodies to other proteins were not detected until three months later.

Antibodies that mediate complement-dependent lysis of HIV-infected cells have been demonstrated in infected chimpanzees; these antibodies are generated relatively early after infection and are capable of lysing cells infected with diverse strains of HIV, analogous to cross-reactivity that has been observed for neutralizing antibodies.

All persistently infected animals possess PBMC that proliferate and incorporate thymidine when incubated with purified HIV antigen; this reactivity occurs as a dose-dependent response. In contrast, not all animals have cells capable of lysing HIV-infected cells. Using as target cells autologous or heterologous EBV-transformed B-cells infected with recombinant vaccinia viruses expressing various HIV genes, PBMC from chimpanzees infected with HIV-1 for various periods of time were used as effectors. While PBMC from most infected animals exhibited HIV-specific cytotoxic activity, they killed not only autologous but also heterologous cells to the same extent. These data indicate that the killing may be effected by antigen-specific, non-major histocompatibility complex–restricted natural

killer (NK) or lymphokine-activated killer (LAK) cells.

Thus far, no AIDS-like disease has been shown to occur in HIV-1 infected chimpanzees. However, evidence of minimal disease has been documented. During the first six months after inoculation of juvenile chimpanzees, the rate of weight gain in the animals showed a significant decrease. In addition to transient mild thrombocytopenia in one animal, substantial lymphadenopathy was observed in two animals that received large doses of HIV-1. Histopathologic analysis of biopsy material from inguinal lymph nodes of these animals with lymphadenopathy showed marked follicular hyperplasia and irregularly shaped germinal centers, similar to what is seen in human tissue sections from HIV-infected persons. Interestingly, one chimpanzee that had no cellular cytotoxic activity (but whose PBMC did proliferate in response to antigen) has been infected with HIV-1 for four years and has lost antibodies to p24 over the last two years. This animal has exhibited no signs of disease or hematological abnormalities. A second animal, infected for more than three and one half years also has lost antibodies to p24, as determined by radioimmunoprecipitation assay. These animals are being closely monitored to see whether loss of antibodies to p24 in chimpanzees will parallel the human situation where this phenomenon correlates with onset of antigenemia and progression to disease. In addition, a third chimpanzee infected for more than three years has developed persistent lymphopenia with loss of $CD4^+$ cells. Perhaps, as apparently is the case with humans infected with HIV, the major cofactor for the development of AIDS in chimpanzees is time.

Attempts to infect nonhuman primate species with HIV-2 isolates have been partially successful, and some animals have been chronically infected for more than one year. Seroconversion and virus recovery have been documented, but no evidence of hematological abnormality or disease has been observed. Efforts are continuing, by serial passage, to obtain an HIV-2 strain adapted for growth in macaques.

Immunization of Chimpanzees with Prototype Vaccines (*12*)

Immunization of chimpanzees has been attempted with a variety of antigens: recombinant vaccinia viruses expressing HIV-1 antigens, HIV-1 glycoprotein subunit preparations, purified HIV-1 antigens expressed in different eukaryotic or prokaryotic systems, inactivated HIV-1 virions, and synthetic peptides. Immunization has resulted in the priming of HIV-specific T-cells, and in the development of antibodies detectable by ELISA, immunoblot, and radioimmunoprecipitation. However, sera from the immunized chimpanzees had weak, if any, neutralizing activity against HIV-1. Chimpanzees that were subsequently challenged with HIV-1 were not protected against the development of viral infection.

The following are examples of the approaches being used to develop prototype vaccines which are being evaluated in chimpanzees:

(a) Because the external glycoprotein gp120 specifically binds to the CD4 molecule on the surface of T4-positive cells (the initial event in the infectious process), it is generally assumed that an immune response against this protein may serve to inhibit virus replication. Also, since gp120 is expressed on the surface of virus-infected cells, an effective T-cell–directed immune response to gp120 may be effective in eliminating cells infected with HIV.

Native gp120, purified by immunoaf-

finity from membranes of cells infected with HIV-1 (strain HTLV-IIIB), has been used to immunize chimpanzees. Precipitating antibodies were maximum at two weeks after subsequent boosters, but rapidly decayed after each immunization. Neutralizing antibodies were produced, but they were only effective against the homologous virus and did not neutralize a different strain of HIV-1 (HTLV-IIIRF). Two chimpanzees were selected for challenge two weeks after a fifth dose of gp120 formulated in alum, receiving 40 or 400 $TCID_{50}$. Virus was isolated from both animals and both developed antibodies to p24, indicating an active infection.

(b) It is likely that neutralizing antibodies to HIV, which have been demonstrated in certain HIV-infected humans, may prevent extracellular spread of the virus, but the virus can also spread from infected to uninfected cells by cell fusion and can thereby escape neutralizing antibodies. Antibodies that can lyse HIV-infected cells by antibody-dependent cell-mediated cytotoxicity have recently been detected in healthy individuals who are HIV-seropositive and in patients who have developed AIDS.

T-cell-mediated immunity, which has been found to be very important in protection against disease or death caused by a variety of envelope viruses in animals, may help eradicate HIV-infected cells which can express HIV antigens before spreading virus to uninfected cells. HIV-specific T-helper cells may produce lymphokines, such as interleukin-2 (IL-2), to expand HIV-specific cytotoxic T-cells or which could activate other effector cells such as natural killer cells or macrophages to lyse HIV-infected cells.

Immunization of nonhuman primates with a recombinant vaccinia virus that expressed HIV envelope glycoproteins did induce HIV-specific T-helper cells in macaques and chimpanzees and also primed HIV-specific cytotoxic T-cells in chimpanzees. T-cells from chimpanzees infected with HIV for three months to three years showed strong proliferative responses to HIV. Some HIV-infected healthy humans also have T-cells that recognize HIV antigens by proliferating and/or by lysing autologous HIV-infected cells. In this regard, it will be interesting and important to determine whether there is an inverse relationship between the level and functional types of HIV-specific T-cell responses with the subsequent development of disease in HIV-infected humans. If this is observed, it will add further rationale for developing AIDS vaccines that can induce strong HIV-specific T-cell-mediated immunity in man, as well as rationale for attempting to augment HIV-specific T-cell immunity in humans already infected with the virus before they develop immunosuppression.

(c) Prototype live recombinant vaccines have also been prepared by inserting the genes encoding either the HIV-1 (strain LAV-BRU) envelope glycoprotein gp160 and/or core proteins p24, p18, or the complete *gag* protein or nonstructural proteins *nef* or *vif* into a vaccinia virus genome. Resulting recombinant viruses were injected into chimpanzees by the intradermal route or by scarification. The chimpanzees showed a transient but significant proliferative response to HIV or gp160, but not to p24, after two injections of or scarifications with vaccinia virus recombinants. Most animals were also seropositive to HIV-1 by ELISA. Immune responses were enhanced after the boost with recombinant vaccinia virus-infected cells. Antibodies specific for HIV core antigens were also generated.

Prospects for the Future

Experimental infection of chimpanzees with HIV-1 is a reliable model of infection by the human virus. If the evidence sug-

gesting that chimpanzees infected with HIV may develop disease is borne out, it may be possible to identify factors that influence disease progression.

With the development of the simian immunodeficiency model, chimpanzees could be reserved for second-phase testing of more promising candidate vaccines. Preparations with increased immunogenicity, using different immunization vehicles, such as immunostimulatory complexes (ISCOMs), are currently being evaluated as possible means for inducing a broader-reacting immune response that is maintained for a longer period of time after vaccination.

LENTIVIRUSES FROM NONPRIMATE MAMMALIAN HOSTS

The term lentivirus ("slow virus") was applied first to the etiologic agent of maedi-visna disease complex of sheep, the classic example of "slow virus disease." Slow viruses have long incubation periods, with a gradual onset and slowly progressive course of disease that invariably ends in cachexia and death. However, visna virus is not T-lymphotropic and does not cause immunodeficiency.

Other mammalian viruses with biophysical properties similar to maedi-visna virus have been recognized in nature and placed in the lentivirus subfamily. Two recent additions to this subfamily are bovine immunodeficiency-like virus (BIV) and feline immunodeficiency virus (FIV; formerly called FTLV). BIV and FIV are distinct from the previously known bovine (BLV) and feline (FeLV) leukemia viruses, which are members of the oncovirus subfamily. The nonprimate lentiviruses are restricted in their host range and are not known to infect primates, including humans.

Visna virus replicates in lymphocytes and macrophages in vivo, resulting in life-long infection in the host. Virus replication continues throughout the infection at a minimally productive rate, a phenomenon that, by definition, emphasizes the ineffectiveness of immunologic mechanisms in eliminating the agents. Enigmas that apply to all lentivirus infections are the nature of the factor(s) that trigger the onset of disease after prolonged periods of subclinical infection and the paradox of virus–host interactions in which the virus replicates at a minimal rate and yet somehow leads to progressive wasting disease.

Pathogenic Mechanisms of Nonprimate Lentiviruses (*13*)

Studies on the closely-related visna and caprine arthritis-encephalitis viruses suggest that the infection of macrophages plays a pivotal role in the mechanism of virus persistence and in the clinical syndromes that these animals succumb to. HIV also infects macrophages, and as studies on the pathogenesis of AIDS unfold, these cells are coming under increased scrutiny as candidates with probably as great a role in the human disease as they have in the diseases of sheep and goats. The close similarity between the animal lentiviruses and HIV suggests that the interaction between the lentiviruses and host cells may provide relevant information and a better understanding of the biology of the human pathogen.

The lentiviruses show distinct differences in their interaction with macrophages and with nonmacrophage cell types. These latter cells may be fibroblasts in the visna virus system or helper T-lymphocytes in the HIV system. In the visna system, the interactions between virus and fibroblasts and virus and macrophages can be summarized as follows:

(a) *Visna virus/fibroblast interactions.*

Visna virus causes fusion of fibroblasts "from without" in a pH-independent manner, reminiscent of paramyxovirus/cell interactions. This suggests that the viral genome is introduced into these cells after fusion of the viral envelope with the plasma membrane of the cell. Initial fusion between virus and fibroblasts is followed by progressive fusion of contiguous cells. Antibodies that inhibit this fusion process usually neutralize infectivity of the virus. However, when antigenic variant viruses are used in these experiments, polyclonal antibodies induced by the parental virus prevent fusion by the variant virus but do not neutralize infectivity of the latter agent. Thus, infection in fibroblasts may occur independently of cell-to-cell fusion. Maturation of progeny virus in fibroblasts occurs at the plasma membrane by a budding process. Treatment of cells with neutralizing antibodies at this stage of the virus life-cycle results in accumulation of virus particles at various stages of budding at the cell surface and "capping off" of these viral aggregates.

(b) *Visna virus/macrophage interactions.* Lentiviruses do not cause "fusion from without" in macrophages, irrespective of the multiplicity of inoculation (up to 10^3 plaque-forming units per cell). This indicates that virus enters these cells by a nonfusing process, perhaps by endocytosis, after binding to a specific receptor, or by random phagocytosis of the particles. Virus preincubated with antibodies is endocytosed faster than non-antibody-treated virus. Both neutralizing and non-neutralizing antibodies accelerate the early events in the virus life-cycle including binding and uncoating of the virus within the macrophage. When neutralizing antibodies are used, virus is internalized and uncoated rapidly, but no RNA transcripts are produced. Antibodies which bind to viral envelope antigens but do not neutralize infectivity enhance the infection because these immunoglobulins facilitate entry of large numbers of infectious virus particles into the macrophages. This disparity in speed of entry of virus into the cells between antibody-treated virus and virus alone does not occur when $F(ab)_2$ fragments of the antibodies are used instead of intact immunoglobulins. This provides indirect evidence that when virus particles are reacted with antibody molecules, complexes may be endocytosed by macrophages via Fc receptors on the surface of these cells. Thus, infection in the macrophage may occur by three mechanisms: (1) entry into the cell following virus attachment to specific receptors; (2) entry into cells by phagocytosis of virus particles; and (3) entry into cells by phagocytosis of immune complexes via the Fc receptors of the cell. Virus maturation in macrophages occurs within the cytoplasm of the cell by budding off of membranes of intracytoplasmic vacuoles and accumulation within these vacuoles. Only minimal budding of virus particles occurs at the plasma membrane of these cells.

The envelope of lentiviruses consists of a large, heavily glycosylated glycoprotein structure that is encoded by the *env* gene. Oligosaccharide chains with numerous terminal sialic acid molecules are attached to the *env* protein backbone by O and N linkages. These carbohydrate molecules create an outer shell on the virus and cause reduction in the affinity of binding of neutralizing antibodies to virus particles. Treatment of virions with neuraminidase removes the sialic acid molecules, which results in improvement in the kinetics of neutralization. In fact, some sera which have no apparent neutralizing activity (they have infection-enhancing properties) will neutralize neuraminidase-treated virus. The distinction between neutralizing and nonneutralizing antibodies may therefore reside

in the avidity of binding between Ig molecules and virus particles. Neutralizing antibodies may bind more tightly to the virus particles than the nonneutralizing antibodies. Since virus neutralization is the net result of two competing systems—virus binding to cells and virus binding to antibodies—any delay in binding between virus and antibodies would increase the chances of infection in the host cell. This is particularly important because the affinity of virus for cellular attachment sites is very high. The mere demonstration of neutralizing antibodies in sera is therefore not enough to indicate protective properties because such antibodies may be "slow" in causing neutralization or even enhance infection in macrophages.

Although virus morphogenesis occurs within the cytoplasm of the macrophages, these cells express viral antigens on their plasma membranes, preceding by two or three days the synthesis of virus particles. One of these antigens is a fusion determinant of visna virus. Cells with receptors for the fusion determinant are readily recruited into multinucleated syncytia. The fusion process represents a potential mechanism for the macrophage to disseminate infectivity by a transfection mechanism. Such a process does not require virus particles to cause infection because viral RNA, transfected into neighboring cells by the fusion process, would be enough to initiate the virus lifecycle without participation by infectious virions. Recent experiments have suggested that high levels of antifusion antibodies (not necessarily neutralizing) may protect animals against massive dissemination of virus in vivo and thus help them to remain clinically normal, albeit infected. A relevant question here is: are anti-fusion antibodies important in protecting against disease? This concept may be important in a vaccine-therapy approach where the idea would be not to prevent infection as a true vaccine does, but rather to boost production of antibodies to the fusion proteins of the virus. The object would be to limit the rate of virus dissemination and thus keep the infection within controllable limits.

Virus-infected macrophages present viral antigens to lymphocytes within restriction limits of major histocompatibility complex antigens. One of the viral antigens is associated with Ia antigens on the surface of the infected macrophage. The viral antigen is distinct from the structural fusion determinant of visna virus and is recognized within the context of Ia by T-lymphocytes of sheep and goats, resulting in production of an interferon. This interferon has a number of effects on the mononuclear cell population, including induction of expression of Ia and production of prostaglandin E2 by macrophages, suppression of proliferation of mononuclear cells, and inhibition of virus gene expression. It has been proposed that maintenance of macrophages in a state of continuous antigen presentation may increase the potential for creating immunopathologic or possible autoimmune reactions.

In summary, lentiviruses have evolved an unusual relationship with the chief defense cell of the body. The infected macrophage not only regulates the amount of virus particles produced during infection, but is also the major disseminator of virus in nature (infected macrophages in colostrum and inflammatory respiratory exudates), for the spread of the virus within the body, and for induction of immunopathologic processes. Therapeutic interventions aimed at preventing infection or reducing the severity of pathologic lesions will have to focus on the infected macrophage in its role as a virus-producing cell and also as an infected antigen-presenting cell. Such interventions will have to be performed with the understanding that this therapy,

which may prevent virus replication, may enhance immunologic reactivity and pathology, and vice versa.

Feline Immunodeficiency Virus (FIV) (*14*)

FIV, previously known as feline T-lymphotropic lentivirus (FTLV), causes a persistent immunodeficiency syndrome characterized by oral, gastrointestinal, and upper respiratory diseases. The pathology most frequently observed is gingivitis, periodontitis, chronic proliferative and ulcerative stomatitis, anorexia and emaciation, chronic diarrhea and dehydration, chronic rhinitis, conjunctivitis, and upper respiratory infections. Other clinical signs observed in the infected cats are lymphadenopathy, neurologic abnormalities, chronic abscesses, fever, and chronic microbial infections.

Serologic surveys conducted in different parts of the world have shown that 14% to 30% of cats with a history of chronic infections are infected with FIV, although coinfection with FeLV is common.

The initial isolation of FIV was derived by co-cultivating peripheral blood lymphocytes (PBL) from infected cats with concanavalin-A (Con-A)-stimulated PBL from specific-pathogen-free (SPF) cats. The virus induced giant cells and cell death in these cultures. The virus isolate replicated in primary T-spleen cells as well as in stimulated thymus cells, feline T-lymphoblastoid cell lines (FL74, LSA-1), and Crandell feline kidney cells. FIV is highly species-specific and does not seem to replicate in a variety of human, canine, and rodent cell lines tested.

FIV has the typical morphology of lentiviruses and possesses a Mg^{++}-dependent reverse transcriptase. In Western blot analysis, FIV antigens do not cross-react with those of SIV, HIV-1, HIV-2, maedi-visna, or caprine arthritis-encephalitis virus. Molecular cloning and detailed analysis of the FIV genome remain to be done.

Experimental infection of SPF kittens resulted in life-long persistent infection. Antibodies are detectable by ELISA or Western blot as early as two weeks after infection. A generalized lymphadenopathy appears in all experimentally infected cats, beginning three to five weeks post-inoculation; peak lymph node enlargement occurs two to eight weeks later, and slowly resolves after two to nine months. An absolute neutropenia, often associated with a leukopenia, occurs in many of the cats, beginning about two to five weeks post-inoculation and persisting for four to nine weeks before disappearing. FIV has been reisolated from the brain, spleen, bone marrow, PBL, mesenteric and submandibular lymph nodes, saliva, and cerebrospinal fluid.

Blastogenic responses to T-cell mitogens are depressed during the initial clinical phase of illness (fever, neutropenia) in experimentally infected kittens. Suppression of lymphocyte mitogenesis lasted for several weeks before reversing itself. Lymphocyte blastogenesis then increased above normal levels during the subsequent two to nine months of the lymphadenopathy stage, and it returned to normal as the lymphadenopathy disappeared. A variable decrease in lymphocyte blastogenesis reappeared in the AIDS phase of the illness.

Attempts to demonstrate experimentally horizontal transmission by prolonged intimate contact have failed. However, FIV appears to be transmitted by bites (through infected saliva).

Bovine Immunodeficiency-like Virus (BIV) (*15*)

BIV was originally isolated in 1969 from leukocytes of a cow with persistent lym-

phocytosis, lymphadenopathy, lesions of the central nervous system, progressive weakness, and emaciation. However, the extent of BIV natural infection remains to be determined.

Experimental infection with BIV of colostrum-deprived calves reared in isolation causes a mild lymphocytosis and lymphadenopathy early in the infection (within 3 to 12 weeks after inoculation), which is similar to the persistent generalized lymphadenopathy considered to be part of the AIDS-related complex (ARC). The subcutaneous palpable nodes are of the hemolymph type and are particularly noticeable in the cervical region. Histological examination of these swollen nodes reveals a follicular hyperplasia of the germinal centers without signs of lymphosarcoma. The hyperplasia can be specifically attributed to an increase in the number of small lymphocytes.

BIV can grow in a number of primary cell cultures derived from first-trimester bovine fetuses, although the cell of choice has been spleen. At present, established cell lines of bovine origin have not been permissive for viral replication, but a fetal canine thymus cell line (Cf2th) is susceptible and may provide a good source of antigen for diagnostic tests.

The cytopathic or syncytia-inducing capability of BIV is similar to that seen in HIV and other lentiviruses in their host cells. BIV has a reverse transcriptase which shows a significant preference for Mg^{++}. Electron microscopy of infected cultures reveals virus particles with a lentivirus morphology. Polyacrylamide-gel electrophoresis of concentrated purified virus reveals a major band of relative molecular mass (M_r) 26,000 (p26) corresponding to the major core protein. Preliminary studies of BIV proteins, recognized by bovine antibodies from naturally or experimentally infected cattle, have shown putative transmembrane protein with a relative molecular mass of 32,000 to 42,000 and an exterior envelope glycoprotein as a doublet of M_r 120,000 and 160,000, by radioimmunoprecipitation and Western blotting. Immunofluorescence assays of HIV-infected lymphocytes using polyvalent anti-BIV serum demonstrated the presence of cross-reacting epitopes; these shared determinants were localized in Western blots to the major core proteins, p24 and p26, of HIV and BIV, respectively.

BIV has recently been molecularly cloned, and two infectious proviruses (clones 106 and 127) have been obtained for future detailed studies. Clone 106 has been completely sequenced. Overall, the genome looks much like that of HIV with the exception that it is smaller (8,875 base pairs). The *env* gene region is larger and has a significant number of glycosylation sites. Restriction enzyme comparisons of the two infectious clones suggest a hyperavailability of *env* sequences, as seen in other lentiviruses. There is an intergenic region between the *pol* and *env* genes in which several open reading frames can be found that may functionally correspond to the *vif*, *tat* and *rev*, and *vpx* genes found in HIV and/or SIV. An additional open reading frame exists at the 3′ LTR. Detailed analyses of the structure, function, and relationship of the predicted coding regions are presently under study.

Potential Uses of Nonprimate Lentivirus Models

The nonprimate lentivirus animal models offer several advantages, e.g., they are natural infections common throughout the world and, because of their species-specificity, working with these agents does not require biohazard containment for human protection. These animal models are potentially useful for dissecting the complex biology of

HIV infection, including mechanisms for induction of protective immunity.

Once validated, the FIV model has the following advantages: inexpensive, short incubation period, animals available in large supply, various clinical stages from field cases, and specific-pathogen-free animals. This model could also be used for the preliminary screening of large numbers of potentially useful antiviral agents.

OTHER VIRUSES AND MODELS

Nonlentiviruses That Induce Immunodeficiency

Included in this category are feline leukemia virus (FeLV) and the macaque type D retroviruses (SRV) associated with simian AIDS (SAIDS).

In addition to subclinical infection and tumors which generally take a long time to develop, FeLV can be responsible for a wide spectrum of chronic nonneoplastic conditions in cats including immunosuppression, wasting, severe diarrhea, and anemia. Similarly, type D retroviruses have been shown to be associated with immunodeficiency and chronic wasting syndromes, opportunistic infections, necrotizing gingivitis, and retroperitoneal fibromatosis in primate colonies.

Experience with several animal retroviruses underpins the rationale for selecting the HIV envelope as the antigen for use in many of the candidate AIDS vaccines. An experimental bovine leukemia virus (BLV) vaccine is being tested, and extensive studies of murine leukemia virus have shown that vaccines incorporating the envelope glycoprotein may prevent infection. A commercial vaccine against FeLV, which includes envelope glycoprotein, protects most cats from FeLV infection and disease.

A killed whole-virus preparation has been shown to confer protection against the type-D SRV infection. This would allow for the comparison of vaccine strategies in this model, using different recombinant and other subunit candidate vaccines. Type-D simian retroviruses are common in macaque colonies, a situation that has to be understood and controlled in order to develop further the more relevant SIV model.

New Potential Models: Transgenic Mice

A characteristic feature of HIV infection is the long asymptomatic phase following initial exposure to the virus. During this period, a positive serology may be the only evidence of infection in an individual with no clinical evidence of disease. It is very likely, however, that multiple copies of integrated provirus DNA are present in infected persons, some of which may be functionally repressed, incapable of performing the production of progeny virions. This latent or persistent phase of HIV infection has been modeled by constructing two types of transgenic mice in which gene expression is regulated by the HIV long terminal repeats (LTR).

The first model consists of the HIV LTR linked to the bacterial gene, chloramphenicol acetyl transferase (CAT). The CAT gene has been ligated to a number of eukaryotic and viral promoter elements and its expression monitored following transfection into mammalian cells. Four founder strains of mice were established carrying two to eight copies of the HIV LTR-CAT construction. High levels of constructive CAT expression were monitored in the thymus, tail, heart, and eye of all four transgenic mouse strains; lower levels were detected in spleen, small intestine, and liver. Although no HIV LTR-directed CAT activity was detectable in circulating lymphocytes or bone marrow-derived macrophages, aug-

mented (20–30-fold) expression was observed when these cells were activated in vitro with mitogens or recombinant cytokines such as IL-2, colony-stimulating factor (CSF-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Upon further examination, the elevated CAT expression in mouse tail was localized to the skin. Fractionation of skin constituents revealed very high levels of CAT in epidermal Langerhans cells (LC) and not in keratinocytes. The former are highly differentiated dendritic cells of monocyte macrophage lineage, comprising 2% to 5% of epidermal cells. Functionally, LC are thought to be the most peripheral limb of the immune system, representing the cell type that initially encounters microorganisms/foreign bodies at the portal of entry. LC are considered to be highly differentiated monocytes (macrophages which originate in the bone marrow). Several reports describe the depletion of LC in AIDS patients. It is noteworthy that HIV LTR-directed CAT synthesis occurred in transgenic animals that had never been exposed to the HIV transactivating regulatory protein, *tat*. These findings therefore imply the existence of tissue-specific regulatory factors that are able to modulate the expression of an integrated HIV LTR.

In a second group of experiments, transgenic mice were constructed containing an infectious molecular clone of HIV. Thirteen founder animals, ranging in age from 7 to 16 weeks and containing 2 to 60 copies of HIV, have been obtained. Thus far, all 13 animals are healthy and have exhibited no manifestations of disease. Two animals seroconverted and synthesized antibodies that react with HIV *env* and *gag* proteins. One of these (a female animal), containing two copies of the HIV provirus, was mated to nontransgenic FVB male mice; two litters have been obtained. Approximately 50% (9/19) of F-1 animals developed a unique syndrome and died. The clinicopathologic features of the affected animals include runting, scaling, and fissuring of the skin on the tail, feet, and ears (microscopically characterized by hyperkeratosis and acanthosis), thymic atrophy (about 20% the size of the thymus in nontransgenic littermates), lymphadenopathy, and lymphocytic infiltrates in the spleen, lung, and intestine. Animals developed symptoms at 12 to 14 days of age and died approximately two weeks later. Affected animals invariably carried the HIV provirus, whereas healthy littermates were not transgenic.

CONCLUSIONS AND RECOMMENDATIONS

The consultation clearly indicated that there are a number of potentially useful animal models for HIV infection and disease. Three major models were discussed: simian immunodeficiency viruses (SIV), nonprimate lentiviruses, and HIV infection of nonhuman primates.

Simian immunodeficiency viruses comprise a diverse group of nonhuman lentiviruses, closely related to HIV. They have been isolated from macaques, sooty mangabeys, African green monkeys, and mandrills. The last two species are known to be infected in their natural habitats. SIV shares a number of molecular and biological characteristics with HIV and causes an AIDS-like disease in selected nonhuman primates. The SIV model will be important to understand the pathogenesis of the disease and will facilitate the evaluation of AIDS candidate vaccines and treatment strategies.

The nonprimate lentiviruses include a number of persistent viruses that cause chronic debilitating diseases and sometimes immunodeficiency in different animal species. These viruses are not known to infect primates, including humans.

The nonprimate models, particularly the bovine and feline lentiviruses, could be used for dissecting the complex biology of HIV infection, including the mechanism for induction of protective immunity. A major advantage is that infection with these viruses is common throughout the world, and working with them does not require biohazard containment for human protection. Lentiviruses from small animals could be used for the preliminary screening of large numbers of potentially useful antiviral agents.

Chimpanzees are susceptible to infection with HIV-1 and exhibit a humoral immune response similar to that seen in human HIV infection. At 48 months postinfection, no chimpanzee was found to have developed the clinical features of AIDS, but changes in the HIV antibody profiles, predictive of the disease in humans, are now being observed. Immunization of chimpanzees with a variety of candidate vaccines has resulted in the forming of HIV-specific T-cells and in the development of antibodies, although with little or no detectable neutralizing activity. Immunized chimpanzees that were challenged with HIV-1 were not protected, and more effective immunogens are now being evaluated.

The participants' recommendations to WHO were:

(a) To promote further research on animal models, including HIV, SIV, and nonprimate lentivirus models, with emphasis on the mechanisms of pathogenesis, potential measures for protective immunity and therapy, and studies on the diversity and natural history of primate lentiviruses. Ongoing basic and applied research with SIV should be accelerated and new avenues for its use should be explored.

(b) To assist in the establishment of primate research facilities and in the coordination of international collaborative efforts between investigators in different countries. Critical for this effort is the need for new facilities with adequate biosafety containment.

(c) To continue to facilitate exchange of information pertinent to animal models for HIV and SIV infections through sponsorship of scientific and technical meetings and publication of technical reports.

(d) To assist in efforts to optimize the development and use of primate and nonprimate lentivirus models, including the development of ancillary reagent and test systems, such as a repository of relevant antibodies to characterize viruses and target cells. WHO should facilitate the availability of these reagents by establishing reference centers for animal lentiviruses.

(e) To develop recommendations on the use of relevant animal models for HIV infection in the evaluation of candidate vaccines and therapeutic agents.

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World AIDS Summit in London

The World Summit of Ministers of Health on Programs for AIDS Prevention was held in London from 26 to 28 January 1988. The conference was attended by health ministers from 148 countries, representing 95% of the world's population. The meeting, jointly sponsored by the World Health Organization and the British Government, marked the first time that so many nations had come together to discuss the topic of AIDS on a political, rather than scientific or medical, level.

In a series of short speeches and informal discussions, the health ministers shared statistics on the incidence of infection in their countries and reviewed the programs for public information, prevention, and treatment that they had developed. Among the messages brought to light were (1) that the spread of AIDS can be prevented through national information programs, (2) that health care workers must be educated for the struggle against AIDS, and (3) that effective means must be sought to inform and educate specific groups whose behaviors place them at high risk of infection.

According to Dr. Halfdan Mahler, WHO's former Director-General, the most important contribution of the conference was that political and medical leaders had adopted the "revolutionary" concept that the spread of information can slow the spread of the disease by persuading people to alter high-risk behaviors. Until recently, Dr. Mahler said, "information and communication had been to a large extent stonewalled by the health professionals, including myself. We now have to relearn that communications is decisive in fighting such a global threat as AIDS." In a declaration that was issued at the close of the three-day conference, the representatives agreed that information and education about AIDS were the most important components of national control programs, in the absence of a vaccine or cure.

Dr. Jonathan Mann, head of the WHO Global Program on AIDS, said that the most important aspect of the declaration adopted by the delegates was its rejection of discrimination against those infected with the virus or suffering from the disease. In addition, Dr. Mann and others at the conference argued that there is no evidence that widespread screening for the infection, particularly on a mandatory basis, would contribute to stemming its spread.

The text of the declaration, which was

Sources: Karen DeYoung, Global AIDS conference ends with call for action, *The Washington Post*, 29 January 1988; *and* London Declaration on AIDS Prevention, World Summit of Ministers of Health on Programs for AIDS Prevention, 28 January 1988.