THE HUMAN AIDS CONNECTION

SYMPOSIUM ON ANIMAL RETROVIRUSES

ABSTRACTS

December 10th, 1986

Marriott Hotel
Denver, Colorado

Under the Auspices of the American Society of Tropical Veterinary Medicine
Studies on murine, feline, and ungulate retroviruses have provided background and direction for much of the research on human retroviruses and the pathogenesis of leukemia and immunosuppression. The relevance of animal model systems for retroviral induced disease is particularly important because of recently discovered human retroviruses. There are presently four known members of the human T-lymphotropic virus (HTLV) family; at least two of these have been strongly implicated as the etiologic agent of clinically significant human disease. HTLV type I (HTLV-I) has been etiologically linked with the development of a unique human leukemia, termed Adult T-Cell Leukemia/Lymphoma. HTLV type II (HTLV-II) was originally isolated from a T-cell variant of hairy cell leukemia. It is closely related to HTLV-I; however, its role in human disease is still not clear. HTLV type III (HTLV-III), also known as LAV, ARV-2, and HIV, is the cause of AIDS. A Fourth T-lymphotropic virus has recently been isolated from a number of healthy individuals from West Africa and designated HTLV-IV.
SYMPOSIUM ON ANIMAL RETROVIRUSES

JOINTLY ORGANIZED BY
The American Society of Tropical Medicine and Hygiene and The American Society of Tropical Veterinary Medicine.

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SCIENTIFIC PROGRAM
WEDNESDAY AFTERNOON, DECEMBER 10
SYMPOSIUM: ANIMAL RETROVIRUSES
Under the Auspices of the
American Society of Tropical Veterinary Medicine

1:30–6:00 p.m.               Denver Ball Room, Marriott Hotel

Moderator: Myron Essex

Time
1:30    INTRODUCTION. P. Alm, President, American Society of Tropical Veterinary Medicine.
1:35 THE CONTRIBUTION OF RESEARCH ON RETROVIRUSES TO THE UNDERSTANDING OF HUMAN AND ANIMAL DISEASES. M. Essex, Harvard School of Public Health, Boston, MA.

2:15 FELINE LEUKEMIA VIRUS. E. Hoover, Colorado State University, Fort Collins, CO.

2:35 FIELD EXPERIENCE WITH THE FELINE LEUKEMIA VACCINE. M. G. Lewis, R. G. Olsen, Ohio State University, Columbus, OH, and R. Sharpee, Norden Laboratories, Lincoln, NB.


3:15 Coffee Break

3:45 MOLECULAR BIOLOGY OF BOVINE LEUKEMIA VIRUS. A. B. Burny and A. Van Den Broeke, University Libre de Bruxelles, Belgium.

4:05 EQUINE INFECTIOUS ANEMIA. C. J. Issel, L. D. Foil and L. C. Montelaro, Louisiana State University, Baton Rouge, LA.


4:45 SIMIAN RETROVIRUSES. P. J. Kanki, Harvard School of Public Health, Boston, MA.

5:05 PULMONARY ADENOMATOSIS: ETIOLOGY AND PATHOGENESIS. J. C. DeMartini and H. R. Rosadio, Colorado State University, Fort Collins, CO.

5:25 VISNA VIRUS. R. C. Cutlip, NADL, Ames, IA.

5:45 GENERAL DISCUSSION: Question/Answer session between speakers and audience.
Studies on murine, feline, and ungulate retroviruses have provided background and direction for much of the research on human retroviruses and the pathogenesis of leukemia and immunosuppression. The relevance of animal model systems for retroviral induced disease is particularly important because of recently discovered human retroviruses. There are presently four known members of the human T-lymphotropic virus (HTLV) family; at least two of these have been strongly implicated as the etiologic agent of clinically significant human disease. HTLV type I (HTLV-I) has been etiologically linked with the development of a unique human leukemia, termed Adult T-Cell Leukemia/Lymphoma. HTLV type II (HTLV-II) was originally isolated from a T-cell variant of hairy cell leukemia. It is closely related to HTLV-I; however, its role in human disease is still not clear. HTLV type III (HTLV-III), also known as LAV, ARV-2, and HIV, is the cause of AIDS. A fourth T-lymphotropic virus has recently been isolated from a number of healthy individuals from West Africa and designated HTLV-IV.

Retroviruses of cats cause lymphopenia and immunosuppression and represent a major cause of death in that species. Similarly, HTLV-I which is T4 tropic is associated with an increased risk for development of infectious disease in regions where the virus is endemic. Since HTLV-I was also believed to be transmitted by blood and sexual contact we considered the possibility that a variant form of HTLV might cause AIDS. The identification of cross-reactive antibodies to HTLV-I membrane antigen in a third or more of the AIDS patients and in suspicious blood donors that donated to transfusion-associated cases of AIDS eventually led to the recognition of HTLV-III, the causative agent of AIDS.

At present, HTLV-III has the coding capacity for at least 12 proteins. Similar to other retroviruses, there are p55, p24, and p17 gag encoded proteins. We first described the env proteins of HTLV-III as a precursor gp160 and external glycoprotein, gp120 — these being the most immunogenic proteins in people exposed to this virus. They are thus of major value for both blood screening and for
vaccine development. Studies in our lab as well as others have shown that the p27, Tarf product, p23 sor product, p53, p64 RT proteins and p34 endonuclease proteins are immunogenic in certain individuals exposed to this virus. We have therefore speculated that these serologic markers may provide useful information of prognostic value for people infected with the AIDS virus.

It has been recently recognized that the T-lymphotrophic virus family also includes closely related agents that infect non-human primates. Simian T-lymphotrophic Virus type III (STLV-III) has been described in a large number of healthy African green monkeys as well as captive immunodeficient rhesus macaques. STLV-III viruses demonstrate T4 tropism, in vitro growth characteristics and ultra-structural morphology similar to HTLV-III. The major STLV-III viral proteins are all similar in size and serologically cross-reactive with the major viral proteins of HTLV-III. The availability of primate species infected with serologically related STLV-III agents that either resist disease development (African green monkeys) or succumb to an AIDS-type syndrome (rhesus) provides models that should aid in our attempt to develop such vaccines.

The close relationship of STLV-III to HTLV-III raised the possibility that the simian virus may have been transmitted to humans at some time during its evolution. It is therefore possible that a range of viruses exists, perhaps with differing pathogenicity and relatedness to STLV-III. The present data suggest that HTLV-IV shares more common epitopes with STLV-III than with the prototype AIDS virus. Further study of HTLV-IV may contribute to understanding of how the HTLV-III group of viruses originated and how their unique pathogenicity can be prevented.

PATHOGENESIS OF FELINE LEUKEMIA VIRUS-INDUCED CYTOPATHIC DISEASES. Edward A. Hoover, James I. Mullins, Sandra L. Quackenbush, Peter W. Gasper, Ronna E. Dornsife, Julie M. Overbaugh, and Norbert O. Riedel. Department of Pathology, Colorado State University, Fort Collins, CO, and Department of Cancer Biology, Harvard School of Public Health, Boston, MA.

Feline leukemia virus (FeLV) — a naturally occurring contagiously transmitted retrovirus of cats — causes several lethal cytopathic diseases and provides long-standing precedent for the retroviral etiology and pathogenesis of analogous human lympho-hemopoietic disorders, most notably acquired immunodeficiency syndrome and bone marrow aplasias. It is becoming increasingly clear that specific retrovirus-
associated anti-proliferative diseases (e.g., AIDS and aplastic anemia) are caused by specific naturally occurring feline retrovirus genomes. These cytopathic FeLV variants can be molecularly cloned and shown to rapidly reproduce the natural diseases after experimental inoculation into pathogen-free cats. Although the mechanism of lineage-specific cell killing remains to be elucidated, target tissue-specific replication of variant viruses, often as unintegrated viral DNA molecules, both accompanies and prefigures the onset of immunodeficiency syndrome in cats. Other recent studies have identified analogous cytopathic effects of cloned FeLV's in vitro and have provided insight into the retoviral genetic determinants of cell-lineage-specific cytopathic diseases in vivo.

Supported by grants CA-32563, CA-43216, CA-40646, and the Massachusetts AIDS Research Council.

FIELD EXPERIENCE WITH FELINE LEUKEMIA VACCINE.
M. G. Lewis, R. G. Olsen, Ohio State University, Columbus, OH and R. Sharpee, Norden Laboratories, Inc., Lincoln, NB

In 1985 a new vaccine for feline leukemia was first released for commercial use. Field studies have confirmed previous experimental studies in the immune responses and rate of protection from disease observed in the vaccinated cat population. Studies to determine the vaccines mode of action and best route of injection have continued. Recent studies found that although all viral proteins are present in the vaccine preparation, the proteins appear to be in different forms than those seen in the mature virion and that strong antiviral responses appear after challenge. Additional studies find that the vaccine is able to block the establishment of latent infections, with 15/16 previously vaccinated and challenged cats remaining free of virus even after observed transient infections. Studies to determine the most effective route of administration show that a sub-cutaneous route generates both anti-viral and tumor antibody with additional strong virus neutralizing antibody, while intra-muscular injections produce similar responses with inconsistent VN antibody development.

CLINICAL AND IMMUNOLOGIC ASPECTS OF FELINE LEUKEMIA VIRUS-INDUCED IMMUNOSUPPRESSION. G. K. Ogilvie, M. B. Tompkins, W. A. F. Tompkins and S. Daniel, University of Illinois, Urbana-Champaign, IL.

Feline leukemia virus (FeLV) is of great importance to the scientist and to the clinician in that it is capable of inducing hematopoietic
diseases that are either immunosuppressive or neoplastic. The pathogenesis of FeLV immunosuppression syndrome shows similarities to that of the HTLV-III-induced immunodeficiency disease syndrome in humans. In both cases, the viruses appear to interfere with immune regulation via alterations in T-helper lymphocyte distribution or function. A feline T cell, induced by IL-2, has recently been shown to have preferential cytotoxicity for FeLV infected cells. Evaluation of peripheral blood from FeLV infected cats with clinical signs of immunosuppression demonstrated marked immunosuppression in both Tₘ and Tₜ functions. FeLV infected cats without signs of immunosuppression have normal Tₘ and Tₜ functions. The Tₜ suppression may be linked to a failure of IL-2 production. Recent studies of major clinical significance have shown that FeLV immunosuppression can be reversed under certain conditions and with selected immunomodulators. The most promising modulators mediate their effects through IL-2 secretion, or by altering cell functions through cell surface receptors.


Bovine leukemia virus (BLV) is the etiological agent of bovine leukemia. The morphology of the virus (atypical C type), the nucleotide sequence of the proviral DNA, the molecular weight of the viral proteins, the mode of action of the virus via transactivation and its mode of transmission mostly as a cell-bound agent, indicate the BLV, HTLV-I, HTLV-II and STLV-I are closely related. A significant difference is that the target cell for BLV belongs to the B cell lineage whilst the other virus members of the group propagate in T cells. BLV acts as an initiator of cell transformation, the provirus, complete or deleted, being always present in the transformed cell as non-expressed or expressed at a limited rate. Deleted proviruses have always conserved the tat region which encodes the p34 protein, the transactivating product of the tat gene. P34 binds tightly to its specific site, located in the U₃ region of BLV LTR and shows also non-specific binding to other regions of the genomic DNA with a much lower affinity. It is believed that interaction of p34 with some DNA sequences in the genome is the key to cell transformation.

Dissection of BLV gp51 external glycoprotein with monoclonal antibodies shows that the NH₂ moiety of the molecule contains ONE region reactive with antibodies from infected animals.
This unique region has a tendency to unfold in the purified protein and can be subdivided into 3 epitopes using mouse monoclonal antibodies. The 3 epitopes are important for virus infectivity and induction of syncytia. Expression of this polypeptide region at high rate and in the native configuration should constitute the basis for an efficient vaccination protocol.

**EQUINE INFECTIOUS ANEMIA.** C. J. Issel, L. D. Foil and R. C. Montelaro, Louisiana Agricultural Experiment Station, Louisiana State University, Baton Rouge, LA.

There has been a resurgence of interest in equine infectious anemia virus (EIAV) because of its proven relationship to the etiologic agent of AIDS in man, the human immunodeficiency virus (HIV). The complete gene sequence of the cell adapted Wyoming strain of EIAV has been obtained and homologies with HIV documented. Polypeptides and oligonucleotides of the prototype cell adapted strain and antigenic variants derived from it have been compared. These data verify and localize genotypic and phenotypic changes in sequential isolates from chronically infected horses. Control of this disease by immunization remains an important challenge because of the rapid mutation of EIAV and the prevalence of antigenic variants. The biological variation of EIAV within an infected horse occurs at an unprecedented rate. As the novel variants emerge, they replicate and can be found in relatively high titers in plasma for a short time. This viremia usually wanes to undetectable plasma levels following generation of specific immune responses including neutralizing antibody. It is during these bursts of virus replication, usually accompanied by febrile episodes, that mechanical transmission of EIAV is most efficient. The mouthparts of hematophagous insects become contaminated with blood and their rapid transfer to a second host is required to transmit EIAV. The chance of this transmission is directly proportional to the viremia level, the number of interrupted feedings, the time between feedings, and the density of vectors and hosts.

**CAPRINE ARTHRITUS-ENCEPHALITIS SYNDROME:** **ETIOLOGY AND PATHOGENESIS.** W. P. Cheevers, T. C. McGuire and D. P. Knowles. Washington State University, Pullman, WA.

Caprine arthritis-encephalitis (CAE) is a complex disease syndrome of dairy goats, characterized predominantly by progressive arthritis. A retrovirus was isolated by explanation of synovial membrane of an
arthritic goat and shown to produce the disease components of CAE after experimental inoculation of specific-pathogen-free goat kids. CAEV was identified as a member of the subfamily Lentivirinae by electron microscopy, biochemical characterization, and antigenic and genetic comparison to the ovine lentiviruses. Evidence from this laboratory suggests that host restriction of persistent virus, periodic virus replication and interaction of the host immune system with virion-associated surface proteins are important parameters of CAE pathogenesis.

**SIMIAN RETROVIRUSES.** Phyllis Kanki, Department of Cancer Biology, Harvard School of Public Health, Boston, MA.

It has been demonstrated that the family of human T-lymphotropic viruses (HTLV) is closely related to viruses which infect certain non-human primate species. The simian T-lymphotropic viruses (STLV) have been so named because of their similarities to the HTLV viruses. It is therefore not surprising that the study of the biology of STLVs in the simian host has revealed many parallels to what we presently understood about HTLVs and their role in human disease or cancer. The HTLV-1 related virus of Old World primates, STLV-1, is known to be very closely related to the human virus. Additionally, we now know that this virus is associated with lymphoid malignancy and abnormalities in macaque monkeys. This observation closely parallels the etiologic relationship of HTLV-1 and Adult T-cell Leukemia Lymphoma (ATL) in people.

An STLV type III virus has been described in both captive immunodeficient rhesus macaques and healthy wild-caught African green monkeys. Similarities between HTLV type 3 (HTLV-3), the etiologic agent of AIDS, and STLV-3 of macaques and African green monkeys (STLV-3mac and STLV-3AGM) include T4 tropism, in vitro growth characteristics, cross-reactive viral proteins of similar sizes, and association with similar diseases. The major STLV-3 proteins have been identified by RIP-SDS/PAGE and Western blot as gp120/160, gp32, p64, p55, p24, and p15, similar to and cross-reactive with the major env, gag, and pol encoded products of HTLV-3/LAV. As in the case of HTLV-3/LAV infected humans, gp120/160 appears to be the best serologic marker for infection by RIP-SDS/PAGE.

Serologic studies on a variety of African primates indicated that approximately 50% of wild-caught African green monkeys (*Cercopithecus sp.*) were seropositive for STLV-3AGM, whereas chimpanzees, baboons, patas monkeys, and colobus monkeys were seronegative.
STLV-3AGM antibody positive serum samples from *Cercopithecus* sp. have been identified from animal samples as early as 1961.

Studies with STLV-3mac have indicated that this virus is closely linked to an immunodeficiency disease in rhesus monkeys similar to human AIDS. However, in over 600 samples of STLV-3-infected African green monkeys, none has shown evidence of AIDS or an AIDS-related disease. In addition, we recently described a new human virus isolated from healthy West Africans, designated HTLV-4, which is closely related to both HTLV-3/LAV and STLV-3AGM. Most importantly, this new human virus has not been associated with AIDS or an AIDS-related disease. Understanding the biology of HTLV-3/LAV and related viruses in primate species may help us understand the specific viral alterations or viral-host interactions that are involved in the pathogenicity of both HTLV-3/LAV and STLV-3. In addition, further study of HTLV-4 may add important information towards future development of a human AIDS vaccine.

The STLV group of viruses has thus far demonstrated remarkable similarities to their human counterparts. Most striking has been the similarities in viral proteins and the biology of these viruses in the primate hosts. These systems have and will provide valuable data to augment our understanding of HTLVs and the pathogenesis of their associated diseases. Additionally, this animal model system can be readily utilized for the development and testing of HTLV vaccine and therapy.

PULMONARY ADENOMATOSIS OF SHEEP: ETIOLOGY AND PATHOGENESIS. J. C. DeMartini and R. H. Rosadio, Department of Pathology, Colorado State University, Fort Collins, CO.

Pulmonary adenomatosis of sheep (PA, jaagsiekte, sheep pulmonary carcinoma) occurs naturally as a contagious bronchioloalveolar carcinoma in sheep flocks in the Americas, Europe, Africa, and Asia. We have undertaken studies of PA in the USA, where the disease occurs only sporadically, and in Peru, where PA causes an annual loss of about 2% of adult sheep. In both countries, PA has been shown to coexist with ovine lentivirus (OvLV) infection in the same flocks and even in the same animal. The tumor is derived from type II alveolar epithelial cells or non-ciliated bronchiolar cells, and has an approximate 10% rate of metastasis to the pulmonary lymph nodes. In many cases, copious quantities of proteinaceous fluid, presumably surfactant, is produced by the tumor cells and a prominent alveolar
A macrophage response is elicited. Using a tumor homogenate or concentrated lung fluid from North American PA cases injected intratracheally into newborn lambs, the neoplasm was induced within 8 to 30 weeks. Naturally occurring and experimentally induced PA lungs contain a 26 kilodalton protein that reacts in an immunoblotting assay with polyclonal antibody to p27 of Mason Pfizer monkey virus. Inoculated lambs form precipitating antibody to OvLV, develop lymphoid interstitial pneumonia, and yield OvLV upon explant or coculture of lung cells. Evidence implicates a D or B type retrovirus as the cause of PA, but a role for OvLV cannot be excluded. As a pulmonary carcinoma apparently caused by an acutely transforming retrovirus, further studies of the etiology and mechanisms of oncogenesis of PA are warranted.

OVINE PROGRESSIVE PNEUMONIA (MAEDI-VISNA) IN SHEEP. R. C. Cutlip, H. D. Lehmkuhl and M. J. E. Schmerr, National Animal Disease Center, Ames, IA.

Ovine progressive pneumonia (OPP) is a multisystemic disease of sheep caused by a nonocogenic exogenous retrovirus belonging to the Lentiviridae subfamily. Characteristics of the disease are chronic lymphocytic pneumonitis, encephalitis, arthritis, mastitis, and vasculitis associated with progressive wasting, dyspnea, lameness, indurated udder, and rarely paralysis. Any one or all characteristics may be manifest. Transmission of the virus is predominantly through the colostrum to newborn lambs; however, transmission can occur by contact and in utero. Treatment of disease is only symptomatic and prevention of infection is only by avoiding the virus.

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