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Animal immunodeficiency viruses

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ABSTRACT

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Feline immunodeficiency virus (FIV) has morphological, physical and biochemical characteristics similar to human immunodeficiency virus (HIV), the cause of AIDS in man. However, it is antigenically and genetically distinct from HIV; an antigenic relatedness with equine infectious anaemia virus has been demonstrated. FIV has been molecularly cloned and sequenced. Diagnostic tests are commercially available and attempts at preparing inactivated, subunit and molecularly engineered vaccines are being made in different laboratories. During FIV infection a transient primary illness can be recognized, with fever, neutropenia and lymphadenopathy. After a long period of clinical normalcy a secondary stage is distinguished with signs of an immunodeficiency-like syndrome. The incubation period for this stage can be as long as 5 years, during which gradual impairment of immune function develops. Many FIV-infected cats are presented for the first time showing vague signs of illness: recurrent fevers, emaciation, lack of appetite, lymphadenopathy, anaemia, leucopenia and behavioural changes. Later, the predominant clinical signs observed are chronic stomatitis/gingivitis, enteritis, upper respiratory tract infections, and infections of the skin. Neoplasias, neurological, immunological and haematological disorder are seen in a smaller proportion. The immunodeficiency-like syndrome is progressive over a period of months to years. Concomitant infection with feline leukaemia virus has been shown to accelerate the progression of disease. In vitro, phenotypic mixing between FIV and an endogenous feline oncovirus (RD114) has been demonstrated which leads to a broadening of the cell spectrum of the lentivirus.

Bovine immunodeficiency virus (BIV) has been isolated only once, and all attempts to obtain additional isolates have failed; it has been recovered from the leucocytes of cattle with persistent lymphocytosis, lymphadenopathy, lesions in the central nervous system, progressive weakness and emaciation. As with the feline representative, BIV also was found to possess a lentivirus morphology and to encode a reverse transcriptase with Mg^{++} preference; it replicates and induces syncytia in a variety of embryonic bovine tissues in vitro. Antigenic analyses have demonstrated a conservation of epitopes between the major core protein of BIV and HIV. The original isolate has been molecularly cloned and sequenced. Besides the three large open reading frames (ORFs) comprising the gag, pol, and env genes common to all replication-competent retroviruses, five additional small ORFs were found. Numerous point mutations and deletions were found, mostly in the env-encoding ORF. These data suggest that, within a single virus isolate, BIV displays extensive genomic variation. When random cattle sera from the Netherlands were tested by indirect immunofluorescence, Western blot and/or radio-immunoprecipitation, 0.7% appeared seropositive; thus BIV infection is not uncommon in one European cattle population.

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INTRODUCTION

Five years ago, Dr. Niels C. Pedersen (Davis, California) reported the discovery of a new retrovirus isolated from diseased cats (Pedersen et al., 1987). Since then this virus has been the subject of intensive research. Already from the first report, where it was referred to as "feline T-lymphotropic lentivirus" (FTLV), it was evident that this virus should become of considerable biomedical importance: not only does it cause an immunodeficiency syndrome in cats, it also shares many physical and biological properties with HIV. The feline immunodeficiency virus (FIV) — as it is now termed — occurs in natural populations of an easily accessible animal species and does not cross species barriers, which has brought its study within reach of many investigators.

Feline viruses have been a major topic of research at the Utrecht Institute of Virology during the last 2 decades. Recently, we focused our interest on FIV, on some aspects of the virus–host interaction in vitro and in vivo — especially the antibody response, on the clinical features of the infection, and on its potential model character for the study of antiviral drugs. Some of these data will be reviewed here.

The chance isolation in 1972 of a new bovine retrovirus that was distinct from leukaemia virus of cattle (Van der Maaten et al., 1972) passed almost unnoticed by the scientific community, until the interest in AIDS revitalized the study of all lentiviruses. In the meanwhile, bovine immunodeficiency virus (BIV) has been well characterized, its genome cloned, sequenced and partially expressed — but still its veterinary significance is unknown. The public may read "No danger seen in cattle virus prevalent in the U.S." (Wall Street Journal, June 3, 1991), but the uneasiness of having a relative of HIV in the human food chain cannot be ignored; it has spawned interest in diagnostic procedures to detect infected cattle. Indeed, seropositive cattle have now also been found in Europe. The problem of non-specific reactions will be reviewed here against the background of published information on BIV.

THE LENTIVIRUSES

Formerly, the family Retroviridae had been divided into three subfamilies based on biological and morphological criteria: the oncovirinae, spumavirinae and lentivirinae (Matthews, 1982). In its 5th Report (Francki et al., 1991), the International Committee on Taxonomy of Viruses explains that the previous classification into subfamilies is no longer appropriate, since the

genera making it up, e.g. the oncovirinae are no more closely related (or similar) to one another than they are to members of other previously designed subfamilies. Two former subfamilies have been converted into the genera
— spumavirus and lentivirus, while the other retroviruses have been accomodated in the
— mammalian Type B Oncovirus group;
— mammalian Type C Retrovirus group (mouse-leukaemia-virus-related group);
— type D Retrovirus group;
— avian Type C Retrovirus group (avian-leucosis-virus-related group); and the
— human T-lymphotropic lentivirus/bovine leukaemia virus group.

The division was intended to reflect the type of disease the viruses cause. Thus oncoviruses are mainly associated with the development of neoplastic disorders, and several representatives have been identified also in cats:

feline leukaemia virus (FeLV), causing neoplastic and degenerative diseases mainly of the haematopoietic system (Jarrett et al., 1964);

feline sarcoma virus (FeSV; Snyder and Theilen, 1969), a defective virus resulting from recombination of FeLV genes with cellular genes; and endogenous RD 114 virus, which is apathogenic and genetically transmitted (McAllister et al., 1972).

Feline immunodeficiency virus (FIV) has been classified as a lentivirus, based on its morphology, biochemical characteristics, nucleotide sequence homology and antigenic cross-reactivities (Pedersen et al., 1987; Yamamoto et al., 1988; Olmstedt et al., 1989; Talbott et al., 1989; Steinmann et al., 1990; Egberink, 1991). Lentiviruses cause chronic, lifelong infections followed by a slowly progressive and degenerative disease (Narayan and Clements, 1989). Several lentiviruses have been known for a long time; most of them are important pathogens in farm animals (Table 1).

Lentiviruses of ungulates, e.g. equine infectious anaemia virus (EIAV) had been described already at the beginning of this century (Vallée and Carré, 1904) although their identification is of a more recent date. The prototype of the genus, maedi-visna virus (MVV) causes chronic progressive pneumonia (maedi) as well as progressive encephalopathy (visna) in sheep (Haase, 1986; Narayan and Clements, 1989). Caprine arthritis/encephalitis virus (CAEV) is closely related to MVV (Weinhold, 1974; Crawford et al., 1980). Bovine immunodeficiency virus was isolated two decades ago from cattle with persistent lymphocytosis and lymphadenopathy (Van der Maaten et al., 1972) and studied intensively only during the last years (Gonda et al., 1987).

Human immunodeficiency virus (HIV), first isolated in 1983, was shown to be the cause of the notorious acquired immunodeficiency syndrome (AIDS) in man (Barré-Sinoussi et al., 1983; Gallo et al., 1984). Later, the search for lentiviruses in primates led to the isolation of simian immunode-

TABLE 1

Major clinical manifestations of lentivirus infections in their natural hosts

Host	Virus	Disease
Sheep	Maedi-visna	Progressive pneumonia
		Encephalomyelitis
		Generalized wasting
Goats	CAEV	Arthritis
		Encephalomyelitis
		Pneumonia
		Wasting
Horse	EIAV	Fever, weight loss
		Anaemia
Cattle	BIV	Lymphadenopathy
		Persistent lymphocytosis
		Wasting
Monkey	SIV	Immunodeficiency
		Neurological syndrome
Human	HIV	Immunodeficiency
		Opportunistic infections
		Lymphadenopathy
		Neurological syndrome
Cat	FIV	Immunodeficiency
		Generalized lymphadenopathy
		Opportunistic infections
		Emaciation
		Neurological syndrome

ficiency viruses (SIV) from several African non human primates (Daniel et al., 1985; Kanki et al., 1985; Fultz et al., 1986; Lowenstine et al., 1986; Murphey-Corb et al., 1986; Tsujimoto et al., 1988). SIV is minimally pathogenic in its natural host but causes immunodeficiency in heterologous monkey species. Another human lentivirus, now known as HIV-2, was isolated from AIDS patients in West-Africa (Clavel et al., 1986) and found to be more closely related to SIV than to HIV-1 (Franchini et al., 1987). The isolation of FIV from cats with an immunodeficiency syndrome was timely. When methods that had been developed to isolate HIV from blood samples of people were applied to cats presented with an immunodeficiency, the virus was discovered.

STRUCTURE OF THE LENTIVIRION

Lentiviruses bud at the plasma membrane, and their core is assembled as budding progresses. However, in syncytia virus buds at intracellular membranes into gross enlarged channels of the endoplasmic reticulum (Gelderblom et al., 1990). Mature virions appear as spherical to ellipsoid particles, 100–125 nm, in diameter. The core is an elongated, bar- or cone-shaped struc-

ture spanning the entire diameter of the virion. Surface projections appear as knobs, about 10 nm in length, and stud the viral membrane; when the virus is manipulated, they are readily lost (Gelderblom, 1991).

The structural proteins are often designated by a numeral representing their molecular weight (Mr, in kilodaltons) preceded by the letter p (for protein) or gp (for glycoprotein). A more descriptive, functional nomenclature has been proposed recently (Leis et al., 1988). A model of a lentivirus particle showing the topology of the major structural proteins is presented in Fig. 1. The lentivirion contains two identical molecules of genomic RNA. To-

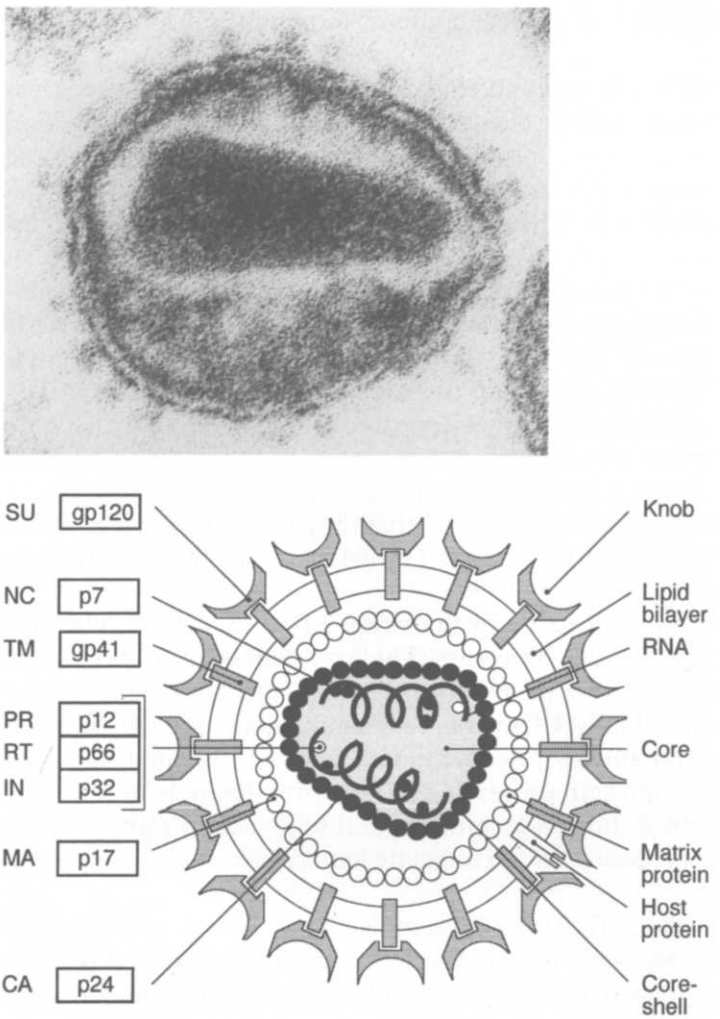

Fig. 1. Electron micrograph (a) and schematic representation (b) of lentivirion architecture (HIV-1). (Micrograph courtesy of H. Gelderblom, Robert Koch Institute, Berlin.

gether with a nucleic acid-associated protein (NC, nucleocapsid protein) it forms the wedge-shaped ribonucleoprotein (RNP) of the virus particle. The genome is a positive-stranded, polyadenylated RNA of 9000–10 000 base pairs. Long terminal repeats, containing characteristic regulatory elements, flank the proviral genome, i.e. the viral genetic information when it is integrated in host-cell DNA. Members of the genus Lentivirus have a more complex genetic structure than other retroviruses. Besides the classic retroviral genes — 5'-gag-pol-env-3' — for proteins to become incorporated into the virion, additional information is located between the pol and env genes and at the 3' terminus. Thus the genome of HIV-1 contains at least six other genes, some of which are involved in the regulation of viral multiplication (Haseltine, 1991).

The proteins coded by gag, pol and env are synthesized as large precursor molecules. The env-precursor is cleaved into the transmembrane portion (TM) and the outer surface glycoprotein (SU). The gag-precursor forms the membrane-associated matrix protein layer (MA) and the viral capsid protein (CA). Enzymes essential for replication, the reverse transcriptase (RT), integrase (IN) and protease (PR) are encoded by the pol gene.

When we analyzed FIV grown and labelled in cat lymphocyte and thymocyte cultures using immunoprecipitation, polypeptides with an apparent Mr of 15, 24, 43, 50, 120 and 160 kilodaltons (kDa) were detected. An additional polypetide of 10 kDa turned up in Western-blot (WB) analysis. The two highest Mr polypeptides sometimes appeared as one band, of which only the smaller polypetide was glysosylated. In the presence of tunicamycin, gp120 was no longer detectable and its unglycosylated precursor of 75 kDa was found instead. Pulse–chase experiments suggested that the gag polypeptides p24 and p15 are cleavage products of both p160 (probably a gag–pol readthrough product) and p50 (Egberink et al., 1990).

Envelope glycoprotein processing of the strain FIV-113 was found to involve two successive proteolytic cleavages. The first cleavage removes an approx. 20 kDa N-terminal presequence from the glycoprotein precursor and takes place post-translationally. Cleavage presumably occurs at a site between amino acid residues 164 and 165, i.e. behind an internally located signal sequence. Thus, FIV glycoprotein processing differs from that in primate lentiviruses as these possess a short N-terminal signal sequence; it rather resembles the processing as proposed for the ungulate lentiviruses (Verschoor et al., 1992).

The original BIV isolate (R29) has been molecularly cloned, and sequence analysis of two functional proviruses revealed a genome 8.4 kb in size. Besides the three large open reading frames (ORFs) comprising the gag, pol, and env genes common to all replication-competent retroviruses, five additional small ORFs were found. The putative protein product of the first major ORF is a p53 protein (the gag-precursor) which is probably processed into

p26, p17 and p14. The non glycosylated envelope precursor of BIV is predicted to be 102 kDa, 145 kDa in its glycosylated form; it is presumably cleaved into a surface protein of 62 kDa and a transmembrane protein of 40 kDa. The small ORFs probably encode non-structural proteins which may play a role in the regulation and pathogenesis of lentivirus infections (Gonda et al., 1987). Numerous point mutations and deletions were found, mostly in the env encoding ORF. These data suggest that, within a single virus isolate, BIV displays extensive genomic variation (Garvey et al., 1990).

During experiments to optimize growth and assay of BIV we found a higher activity of the RT at low concentrations of Mn^{++} ions (20 μM) as compared to Mg^{++} ions; at higher molarities inhibitory effects were seen, as also noted by Gonda et al. (1990a,b). This finding should be considered in view of the importance attributed to cation requirement of the retroviral RT for the construction of phylogenetic trees (Horzinek et al., 1991).

ANTIGENIC RELATIONSHIPS

A non-reciprocal cross-reactivity was observed between the gag gene products p24 of HIV and p26 of EIAV. No antigenic relationships were detected between MVV or CAEV and EIAV or HIV, respectively (Goudsmit et al., 1986). Also, no serologic cross-reactions between FIV and HIV-1, HIV-2, SIV, CAEV and MVV were detected when antibodies from naturally infected hosts were used (Yamamoto et al., 1988). However, rabbit sera to CAEV and MVV were found to react with the putative core protein of FIV (Olmsted et al., 1989).

Analysis by WB using a rabbit serum directed against p26 of EIAV and an anti-EIAV horse serum from a field case of infection revealed a cross-reactivity with p24 of FIV. Cat sera collected late after experimental FIV infection recognized p26 of EIAV indicating a reciprocal cross-reactivity (Egberink et al., 1990).

Based upon the serological cross-reactivity at the gag protein level it was proposed to distinguish two groups within the lentiviruses, one including MVV, CAEV and pleuropneumonia virus (PPV) of sheep, the second group comprising HIV, SIV and EIAV (Goudsmit et al., 1986); based on our results FIV should be included in the second group. Also the major core antigen of BIV is recognized by the rabbit anti-EIAV-p26 serum (Koolen et al., unpubl. observ.). The FIV–EIAV relationship reported above has been determined independently in another laboratory (Steinmann et al., 1990).

HOST-CELL SPECTRUM

Any virus replicates only in a defined range of cells. These may be resistant to infection because they lack the receptor for virion attachment. In vivo,

lentiviruses replicate in cells of the macrophage lineage (Narayan and Clements, 1989). The most important receptor for HIV is the CD4 molecule (Dalgleish et al., 1984; Klatzman et al., 1984), which defines the tropism almost exclusively. The cell spectrum of HIV includes the CD4 helper/inducer T lymphocyte, cells of the monocyte/macrophage lineage, e.g. alveolar macrophages, Langerhans dendritic cells, but also cells of the central nervous system like microglia, astrocytes and endothelial cells (Armstrong and Horne, 1984; Ho et al., 1986; Salahuddin et al., 1986; Patterson and Knight, 1987; Tschachler et al., 1987). Only few cell types without detectable CD4 can be infected (e.g. bone marrow precursor, glial, fetal neural and fibroblastoid cells) suggesting that alternative means of viral entry into cells are sometimes exploited (Folks et al., 1988; Harouse et al., 1989; Tateno et al., 1989).

FIV has been shown to replicate in feline blood mononuclear cells, thymocytes and spleen cells after stimulation with the lectin concanavalin A and interleukin-2 (Yamamoto et al., 1988); T-lymphoblastoid cells chronically infected with FeLV — such as the lines LSA-1 and FL-74 (Yamamoto et al., 1988) — are also susceptible. Monocytes/macrophages are infectable in vitro (Brunner and Pedersen, 1989), as are astrocytes and microglial cells (Koolen and Egberink, 1990; Dow et al., 1990).

The cell spectrum of FIV in vivo is broader than that of HIV in man: FIV infects also CD8 positive lymphocytes (Brown et al., 1991). In vitro, one non-lymphoid cell type, the Crandell line of feline kidney (CRFK) cells can be infected (Yamamoto et al., 1988); one of the possible mechanisms is discussed below.

PHENOTYPIC MIXING

In enveloped viruses, the surface glycoprotein carries determinants that mediate binding of virions to cellular receptors, leading to attachment (adsorption) as the first step of the infection cycle. If cells are infected with two enveloped viruses, the surface glycoproteins of both may be expressed at the cellular membrane and incorporated into the same virion during budding. The progeny virions would thus accomodate glycoproteins not specified by the enclosed genome. This phenomenon is known as pseudotype formation or phenotypic mixing. It can lead to a widening of the host-cell spectrum of one virus due to the glycoprotein of the "mixing partner". The viral genome can thus enter cells other than those normally infectable (via the own receptor-binding protein) and can replicate if there are no other intracellular barriers for virus multiplication. Phenotypic mixing occurs between unrelated viruses as has been shown for mouse mammary tumour or murine leukaemia virus and vesicular stomatitis virus.

Feline immunodeficiency virus released from persistently infected CRFK cells was found to replicate in lines that had been refractory in earlier experi-

ments (Egberink, 1991). These include cells of feline (fcwf), human (HeLa), simian (Cos, VERO), canine (MDCK), rabbit (RK13), and murine (Sac- origin). Replication was demonstrated by immunofluorescence assay (IFA), by the presence of FIPVp24 in the supernatant, by stimulation of a Mg^{++}-dependent RT activity and by the demonstration of lentivirus particles (in MDCK and HeLa cells).

Uninfected CRFK cells harbour an endogenous RD114-like virus, as evidenced by substantial levels of Mn^{++}-dependent RT activity in their supernatant and by intracytoplasmic fluorescence using a homologous immune serum. It is referred to as "RD114-like" because it was found to infect feline cells, while RD114 virus is considered xenotropic. After inoculation of the cell lines listed above with supernatant from CRFK cells, a rise in Mn^{++}-dependent RT activity was found, indicating infection by the RD114-like virus. Phenotypic mixing with the RD114-like virus in the persistently infected CRFK line was postulated to explain the broadening of the cell spectrum of FIV. The phenomenon was not due to genomic recombination nor to mutations in the receptor binding site: after a second passage in HeLa cells no evidence of infection was found, and in MDCK cells only marginal FIVp24 synthesis was observed. However, thymocytes — the standard cell for growing FIV — could still be infected.

Neutralization of the putative mixed pseudotypes was obtained using antisera directed against FIV but not against the RD114-like virus; the reasons for this unexpected finding need to be explored (Egberink, 1991).

EPIDEMIOLOGICAL OBSERVATIONS

Infections with FIV have been found worldwide, their incidence varying from between 1 and 15% in healthy animals to between 3 and 44% in diseased cats (Gruffyd-Jones et al., 1988; IShida et al., 1988, 1989; Lutz et al., 1988; Sabine et al., 1988; Belford et al., 1989; Bennett et al., 1989; Grindem et al., 1989; Hosie et al., 1989; Schuller, 1989; Neu et al., 1989; Povey and Hawkins 1989; Shelton et al., 1989b; Swinney et al., 1989; Yamamoto et al., 1989; Cohen et al., 1990; Rodgers and Baldwin, 1990). The virus infects domestic cats (*Felis catus*) and is species-specific. However, serum samples from several species of wild felids reacted with structural proteins of FIV (Barr et al., 1989; Spencer, personal communication, 1991); these species include the African lion (*Panthera leo*), jaguar (*Panthera onca*), tiger (*Panthera tigris*), bobcat (*Felis rufus floridanus*) and Florida panther (*Felis concolor coryi*). Although the respective "feral" viruses are obviously antigenically related to FIV, their biological properties are unknown. Transmission of the infection to domestic cats with whole lion blood was unsuccessful (H. Lutz, pers. commun.).

Infections with FIV are found mainly in older, free-roaming, male cats. The older age reflects the long latency period between infection and disease. Sev-

eral studies suggest that this period can be more than 5 years (Ishida et al., 1989; Shelton et al., 1989b). FIV can be recovered from blood, serum, plasma, cerebrospinal fluid and saliva of infected cats (Yamamoto et al., 1988; Dow et al., 1990). Horizontal transmission through contact alone probably also occurs (Pedersen et al., 1987; Hosie et al., 1987) but it is inefficient (Shelton et al., 1989b; Yamamoto et al., 1989). Bites seem to be the most efficient mode of transmission, which could explain the higher incidence in male, free-roaming cats. Especially tomcats allowed to roam outdoor express territorial aggression; infection rates in them were 5 to 20 times higher than in animals kept strictly indoors (Hopper et al., 1989; Ishida et al., 1989; Yamamoto et al., 1989).

There is no evidence for venereal transmission (Hosie et al., 1989); infection in utero and through colostrum, milk and maternal grooming is very uncommon (Yamamoto et al., 1988; Pedersen et al., 1989). Transmission from mother to kitten has been publised only once; its mode was not explained (Callahan et al., 1991).

While transmission of FIV between cats by biting is plausible, that of BIV remains enigmatic — the erratic clustering in some farms or regions has been interpreted as evidence for iatrogenic virus delivery (Gonda, pers. commun.). Antibodies against BIV can be detected in calves from 2 weeks after experimental inoculation onwards. Whethstone et al. (1990) were able to demonstrate them for 2.5 years by using both indirect IFA and WB; antibodies were above all directed against p26.

In the USA, these authors also found evidence of BIV infection in about 50% of the sera from a herd with a high incidence of lymphosarcoma and persistent health problems, but none in samples from cattle with other conditions or from healthy animals. The IFA was used in sero-epidemiological surveys by Amborsky et al. (1989) on 235 samples and by Black (pers. commun., 1991) om 1997 random serum specimens predominantly from dairy cattle; the authors report an incidence of about 4% seropositive animals in their collection.

When 957 randomly collected cattle sera from the Netherlands were pretested by indirect IFA and confirmed using WB and/or radio-immunoprecipitation (RIPA), 1.4% appeared seropositive (Horzinek et al., 1991). Thus BIV infection is not uncommon in one European cattle population; this view is supported by results obtained in Switzerland (H. Lutz, pers. commun., 1991) with the aid of recombinant-DNA expression products of the gag gene of BIV (Rasmussen et al., 1990).

In view of the genetic variation of BIV (Garvey et al., 1990) — which nay affect epitopes on all proteins — antibodies in European bovine sera may be of low affinity or even directed against BIV serotypes different from the American strain used in our assays. Isolation of additional bovine lentivirus

strains is mandatory for future progress in this field. Samples from seropositive cattle have been processed with this objective, but so far without success.

CLINICAL OBSERVATIONS

In HIV infection, five clinical stages have been recognized:
(1) the acute stage,
(2) the asymptomatic carrier stage,
(3) the persistent generalized lymphadenopathy (PGL),
(4) the AIDS-related complex (ARC) and
(5) the AIDS stage.

Ishida and Tomoda (1990) distinguish five stages also in FIV infection.

(1) The acute stage is characterized by fever, neutropenia and a generalized lymphadenopathy (Yamamoto et al., 1988; Barlough et al., 1991). These signs differ in severity and are not found in every infected cat. In severely affected cats depression and diarrhoea are also noticed. The fever may persist for several weeks. Normally, neutropenia lasts for 2 to 4 weeks; the generalized lymphadenopathy subsides after 2 to 9 months. Mortality is low at this stage; if the animals are co-infected with FeLV, however, it may increase to 50% (Pedersen et al., 1990).

(2) After the acute stage, a period of years ensues where the cats do not show any clinical signs; nonetheless, virus can be recovered from the blood at all times (Yamamoto et al., 1988).

(3) A distinct PGL phase comparable to that in the HIV infection is not often found in cats. A stage with vague signs like recurrent fevers, weight loss, loss of appetite, leucopenia and anaemia in cats with a generalized lymphadenopathy but without obvious secondary or opportunistic infections could be considered as such.

(4) Most cats will probably be presented to the veterinarian at the time chronic secondary infections have developed. This stage is equivalent to the ARC stage in man (Pedersen et al., 1991, in press). The symptoms most frequently observed are listed in Table 2; they increase in severity over a period of months to years, being the clinical reflection of an immunosuppression that can also be evidenced in vitro (Ackley et al., 1990; Hara et al., 1990; Siebelink et al., 1990; Taniguchi et al., 1990; Barlough et al., 1991).

(5) Finally, the cats may develop a stage comparable with AIDS in man, where anaemia or pancytopenia, weight loss, severe emaciation, chronic disease problems, lymphoid depletion and opportunistic infections are prominent. Most of these animals will die within months. A number of infections of an opportunistic nature have been reported in FIV-infected cats:
— poxvirus infection (Brown et al., 1989)
— feline calici- and herpesvirus infections (Knowles et al., 1989; Neu, 1989; Tenario et al., 1991).

TABLE 2

Symptoms most frequently observed in FIV-infected cats, with the average percentage incidence

Symptom	Percentage
Chronic stomatitis/gingivitis	50
Weight loss	40
Lymphadenopathy	30
Leucopenia/anaemia	30
Chronic upper respiratory tract infections	25
Emaciation	20
Chronic skin disorders	15
Chronic diarrhoea	10

— toxoplasmosis (Witt et al., 1989)
— streptococcus canis (pedersen et al., 1990)
— cryptococcosis and candidiasis (Ishida et al., 1989)
— generalized demodectic and notoedric mange (Chalmers et al., 1989; Ishida et al., 1989; Swinney et al., 1989).
— mycobacteriosis (Ishida et al., 1989; Swinney et al., 1989)
–haemobartonellosis (Ishida et al., 1988; Belford et al., 1989; Grindem et al., 1989; Hopper et al., 1989).

Miscellaneous other clinical features are recognized (Pedersen et al., 1991, in press), e.g. neurological symptoms, which are present in a substantial number of animals. They can be an accompanying trait of other disease problems or the predominant manifestation of the infection (Pedersen et al., 1987; Harbour et al., 1988; Kölbl and Schuller, 1989; Neu et al., 1989; Shelton et al., 1989a,b; Swinney et al., 1989; Yamamoto et al., 1989). Neurological disease is the consequence of a direct viral effect on brain cells (Dow et al., 1990); only rarely other opportunistic infections play a role (Heidel et al., 1990). Frequently observed clinical signs are: compulsive roaming, twitching movements of the face and tongue, dementia and abnormal behaviour (hiding, rage). Although virus can be recovered from many parts of the brain, lesions are mainly found in the cerebral cortex, which explains the nature of the symptoms. Less frequently convulsions, nystagmus, ataxia, tremors and paralysis are observed (Pedersen et al., 1989, Swinney et al., 1989). Many FIV-infected cats without overt symptoms have abnormally slow motor and sensory nerve conduction velocities, suggesting a much higher incidence of brain infection than anticipated (Wheeler et al., 1990). Also, a large proportion of cats without outward neurological abnormalities has microscopical lesions in their central nervous system (Dow et al., 1990).

Several ocular conditions have been found in FIV-infected cats: inflammations, especially of the anterior uveal tract, glaucoma, and a pars-planitis-like disorder (Gruffyd-Jones et al., 1988; English et al., 1990).

Immune-mediated conditions like Coomb's positive anaemia, thrombocytopenias and arthritis have been reported (Hopper et al., 1989).

Also, malignancies occur in FIV-infected cats at rates higher than normal. Lymphosarcomas being often associated with an FeLV infection (Lutz, 1990) have been diagnosed in a number of FeLV-negative, FIV-positive cats (Gruffyd-Jones et al., 1988; Sabine et al., 1988; Belford et al., 1989; Hopper et al., 1989; Ishida et al., 1989 Kölbl and Schuller, 1989; Shelton et al., 1989a, 1990; Yamamoto et al., 1989). Myeloproliferative disorders have been perceived in naturally and experimentally FeLV-negative, FIV-infected cats presented with severe anaemias and leukopenias (Pedersen et al., 1987; Yamamoto et al., 1988, 1989; Belford et al., 1989; Ishida et al., 1989).

Other tumours (i.e. squamous cell and mammary gland tumours) were reported in FIV-positive cats with a higher incidence than normal (Hutson et al., 1991, in press).

Leucopenia, due to an absolute granulocytopenia, lymphopenia, anaemia, and other haematological abnormalities have been encountered in FIV-positive cats, i.e. lymphocytosis and monocytosis. Hypergammaglobulinaemia (in 30%) and elevated levels of serum IgG (in 50%) have been reported (Hopper et al., 1989).

ANTIBODY RESPONSE AND DIAGNOSIS

Lentiviruses persist in their hosts. The carrier state is maintained through the presence of the viral genome in monocyte-macrophage cells and probably in lymphocytes (Narayan and Clements, 1989). With the exception of EIAV, lentiviruses are isolated from the blood throughout the course of disease, also in the presence of a vigorous antibody response. Virus isolation from the blood can be performed for diagnosing FIV infection (Egberink et al., unpubl. observ. Hopper et al., 1989; Ishida et al., 1989; Yamamoto et al., 1989) but the technique is too laborious for routine use. Isolation is easy early after infection and in the terminal stages of the disease while more difficult during the interim period of normalcy (Pedersen et al., 1989).

Because of the persistent nature of the infection, measurement of antibodies is of great diagnostic value. Tests routinely used for their detection are the IFA, using cells persistently infected with FIV (Yamamoto et al., 1988), and the enzyme-linked immunosorbent assay (ELISA) with purified FIV antigens or viral proteins obtained by recombinant DNA techniques (Yamamoto et al., 1988; O'Connor et al., 1989; Reid, pers. commun., 1991).

The WB immunoassay and RIPA can be used for confirmation of results obtained with the other, simpler procedures (Yamamoto et al., 1988; Hosie and Jarrett, 1990; Egberink and Horzinek, 1991). In both methods, the reaction of antibodies with individual FIV-specific proteins is recognized. When purified virus is used in ELISA or WB, antibodies directed against the enve-

lope proteins are usually not detectable: being loosely anchored in the membrane (Gelderblom et al., 1990) the viral "knobs" are lost from the virion due to the hydrostatic force during gradient centrifugation.

Some reports suggest that a substantial number of cats in a population is viraemic but seronegative (Harbour et al., 1988; Hopper et al., 1988, 1989). As in other retrovirus infections the absence of antibody does not imply absence of virus. Whether seronegative viraemic animals play a role in the epidemiology of the infection remains to be shown.

In sequential samples from experimentally infected cats, antibodies against the envelope protein gp120 and the core protein p15 were the first to appear, as shown in RIPA. They could be detected as early as 2 weeks post infection (p.i.) and were followed by antibodies against p24, p43 and p50. By WB assay, anti-p24 and anti-p15 were the first detectable antibodies, 3–5 weeks p.i.; an anti-envelope response was never found in this assay, but was evidenced in RIPA. Using this test, most sera of naturally infected cats were found to recognize the major core protein p24 in addition to one or more minor core proteins. All 40 sera tested precipitated the envelope protein, three reacting exclusively with it (Egberink et al., 1992).

Confirmation of the results of BIV serology is of utmost importance, as experienced during studies on the seroprevalence of the infection in the Netherlands. Had we relied exclusively upon IFA (Horzinek et al., 1991), 6.7% seropositive cattle would have been found. When applying stringent criteria of confirmation by WB and/or RIPA, only 1.4% remained. Individual bands may appear in WB that — from their position in the gel — are taken as BIV-specific; however, bands in the same positions were seen in IFA-negative samples. This observation is at variance with the finding by Whetstone et al. (1991) that WB-positive samples were always positive in IFA. False-positive results can jeopardize both assays which are not really independent, being both based on immunoreactivity. It is the band pattern that should be arbitrated, and reactions with both gag and env gene products should be shown — a fundamental in AIDS serology. While anti-env reactivity has been seen in WB analysis of gradient purified BIV from persistently infected BBK/clone-18 cells using postinoculation serum from an experimental calf, Dutch field sera never showed this reactivity, probably due to reasons of antigen quantity. We have been able to clone BIV-specific sequences from this virus preparation (Sillekens, 1990, unpubl. observ.) which were virtually identical to those published (Gonda et al., 1987).

Quantitative differences in antibody responses to the gag proteins p17 and especially p24 (Lange et al., 1989) have been recognized as a prognostic marker for the course of a HIV infection; as the AIDS phase is approaching, anti-p24 titres tend to decrease. Prognostic markers are indispensable for assessing the life expectancy of a patient and the effect of antiviral drugs. The decline in anti-p24 titre coincides with an increase of p24 antigen in blood.

In the FIV system, a complex-trapping/binding ELISA was developed to quantitate the anti-p24 response. Sera of healthy FIV-infected cats were shown to possess higher anti-p24 titres than those of diseased cats (Egberink et al., 1991).

OUTLOOK

Many lessons can still be learned from animal lentiviruses, although the sheer volume of human lentivirus research is stifling. The most appealing valuable lesson is doubtlessly that the one about the specific deficiencies caused by the eradication of protagonists in the interplay of cells in the immune system. Since its first isolation FIV was recognized as an important feline pathogen. The fact that it causes a disease with conspicuous similarities to human AIDS (Pedersen et al., 1987) has rather emphasized the model character of the infection and perhaps eclipsed its veterinary importance. However, AIDS is a global problem of growing dimensions, and an animal model is badly needed, both for fundamental and applied research. FIV in the cat meets most of the criteria of an acceptable — though not ideal model. The requirements have been expressed during an Informal Consultation convened by the Global Programme on AIDS of the World Health Organization (Esparza and Osmanov, 1990). An ideal animal model:

— should make use of HIV itself;
— should involve a small animal with well-known genetics, immunology and metabolism;
— should involve target cells for the virus that include CD4+cells and macrophages;
— should involve target organs that include blood, lymphoid tissues and brain;
— should mimic the epidemiology of HIV including perinatal transmission;
— should present a disease with a comparatively short incubation period and resemble human AIDS.

The study of FIV pathogenesis, including the mechanism of CD4+ T-cell depletion, of the cofactors involved in disease progression, of neuropathogenesis, of strategies for vaccine development and of anti-lentiviral drugs is now possible. The model character has made FIV and the infection it causes the Number One Topic in feline research. The first International Feline Immunology and Immunodeficiency Workshop (Glasgow, July 1991) and the first World Congress of Feline Immunodeficiency Researchers (Davis, September 1991) reflect the extent of this world-wide interest.

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