HUMAN T-CELL LYMPHOTROPIC VIRUSES

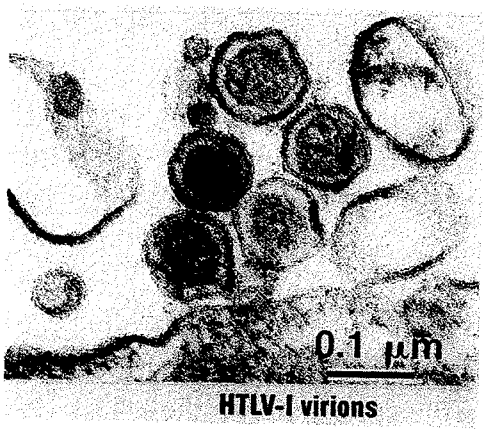
1. Exposure Data

1.1 Structure, taxonomy and biology

1.1.1 *Structure*

The structure of retroviruses is reviewed in the monograph on human immunodeficiency viruses (HIV) in this volume. The human T-cell lymphotropic (T-cell leukaemia/lymphoma) viruses (HTLV) are enveloped viruses with a diameter of approximately 80–100 nm (Figure 1). The HTLV virions contain two covalently bound genomic RNA strands, which are complexed with the viral enzymes reverse transcriptase (RT; with associated RNase H activity), integrase and protease and the capsid proteins. The outer part of the virions consists of a membrane-associated matrix protein and a lipid layer intersected by the envelope proteins (Gelderblom, 1991).

Figure 1. An electron micrograph of HTLV-I virus



Courtesy of Dr Bernard Kramarsky, Advanced Biotechnologies, Inc., Columbia, MD, USA

1.1.2 *Taxonomy and phylogeny*

Traditionally, retroviruses (family *Retroviridae*) have been classified according to a combination of criteria including disease association, morphology and cytopathic effects *in vitro*. On this basis three subfamilies were defined. The oncoviruses (Greek, *onkos* = mass, swelling) consist of four morphological subtypes which are associated with tumours in naturally or experimentally infected animals, and non-oncogenic related viruses. The second group, the lentiviruses (Latin, *lentus* = slow), cause a variety of diseases including immunodeficiency and wasting syndromes, usually after a long period

of clinical latency. The third subfamily, the spumaviruses (Latin, *spuma* = foam), so called because of the characteristic 'foamy' appearance induced in infected cells *in vitro*, have not been conclusively linked to any disease. More recently, the International Committee on the Taxonomy of Viruses has divided the *Retroviridae* family into seven genera on the basis of genetic structure. The lentiviruses and spumaviruses each constitute a genus; the oncoviruses have been subdivided into five genera (Coffin, 1996). The HTLVs form one of these genera, along with the related bovine and simian viruses (see Section 1.1.4), and in turn can be divided into type I (HTLV-I) and type II (HTLV-II) according to their genetic composition and serotype. The genotypes of HTLV types I and II are related to each other; within these types, genetic variability is greater in the type I group. By the use of the polymerase chain reaction (PCR) and sequencing, strain variation within types has been characterized in viruses from humans residing in different geographical areas.

The term HTLV-III was assigned to a virus which was later defined as HIV-1 (see the monograph in this volume).

Three subtypes of HTLV-I (known as clades (Myers *et al.*, 1993), which are defined as groups of viral strains with common nucleotides at any given position in the DNA sequence analysed) can be recognized using several analytical methods and by studying different viral genes (Figure 2) (Koralnik *et al.*, 1994).

The cosmopolitan clade (HTLV-I_{Cosm}), found in many populations across the world (also known as HTLV-IA), represents a very homogeneous group of viruses. In the New World, HTLV-I_{Cosm} was probably introduced by the slave trade (Gallo *et al.*, 1983; Gessain *et al.*, 1992a; Koralnik *et al.*, 1994) (see Figure 2).

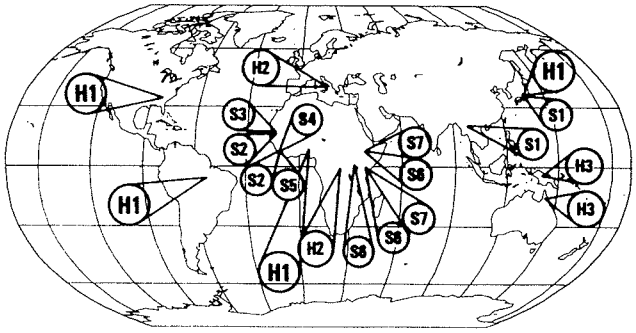
The second clade (HTLV-I_{Zaire}), also known as HTLV-IB, was identified in central African populations in the Zairian basin (Figure 2) (Gessain *et al.*, 1992a).

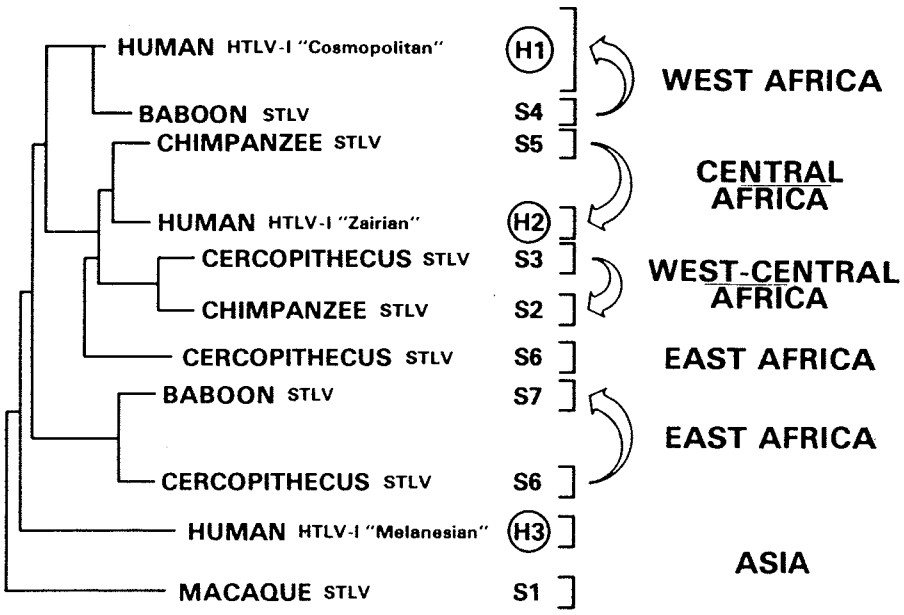
The third clade (HTLV-I_{Mel}) was identified in inhabitants of Papua-New Guinea and the Solomon Islands and later in Australian Aboriginals (Bastian *et al.*, 1993; Gessain *et al.*, 1993). Phylogenetic analysis has shown that this clade (also known as HTLV-IC) and HTLV-I_{Cosm} probably evolved independently from a common ancestor (Figure 2). Analysis of sequence variations among these viral strains suggests that the HTLV-I_{Mel} clade diverged earliest, before the split between the HTLV-I_{Zaire} and HTLV-I_{Cosm} groups.

Two other subgroups have been proposed within the HTLV-I_{Cosm} clade, but rigorous phylogenetic analysis does not appear to support this notion.

Phylogenetically, HTLV-II separates into three clades: IIa, IIb and IIc. HTLV-IIa and b can be further divided into several subgroups (Dube *et al.*,1993; Neel *et al.*, 1994; Eiraku *et al.*, 1995; Gessain *et al.*, 1995a; Switzer *et al.*, 1995; Biggar *et al.*, 1996; Eiraku *et al.*, 1996). Approximately 70% of HTLV-II from intravenous drug users has been found to be HTLV-IIa. Amerindian tribes from Central and North America have the distinct type IIb, whereas remote Amazonian tribes harbour mainly subtype IIa (Biggar *et al.*, 1996; Eiraku *et al.*, 1996). These findings suggest that ancestral Amerindians who migrated to the New World brought at least two and possibly three genetic subtypes of HTLV-II (Neel *et al.*, 1994; Biggar *et al.*, 1996; Eiraku *et al.*, 1996).

Figure 2. Relationships between HTLV and STLV clades





Top: Geographical origin of the samples studied. H1 corresponds to the HTLV-I_{Cosm} clade, H2 to the HTLV-I_{Zaire} and H3 to HTLV-I_{Mel}. The simian clades (S) are numbered according to the species of origin and their geographical origin.
Based on the data presented by Koralnik *et al.* (1994)

1.1.3 *Host range*

HTLV-I and HTLV-II have been isolated from humans (Poiesz *et al.*, 1980; Kalyanaraman *et al.*, 1982). Under experimental conditions, both HTLV-I and HTLV-II infect rabbits (Miyoshi *et al.*, 1985; Cockerell *et al.*, 1991) and HTLV-I can also infect rats (Yoshiki *et al.*, 1987; Ibrahim *et al.*, 1994). Among non-human primates, HTLV-I isolates have been shown to infect rhesus macaques (*Macaca mulatta*) (Lerche *et al.*, 1987), cynomolgus monkeys (*M. fascicularis*) and squirrel monkeys (*Saimiri sciureus*) (Yamamoto *et al.*, 1984; Nakamura *et al.*, 1986). (See also Section 3).

1.1.4 *Related non-human primate viruses*

Viruses related to HTLV have been isolated from non-human primates. These are known as simian T-cell lymphotropic viruses (STLVs). DNA analysis of STLV-I strains of African and Asian origin has led to several conclusions. STLV-I from a single species can be sorted into genetically distinct clades. The distribution of STLV-I phylogenetic clades from *Cercopithecus aethiops* (African green monkey), *Pan troglodytes* (the common chimpanzee) and *Papio* (baboon) (respectively S3 and S6; S2 and S5; S4 and S7 in Figure 2) indicates that these retroviruses did not evolve within each species and suggests interspecies transfer within the primate genera, including man.

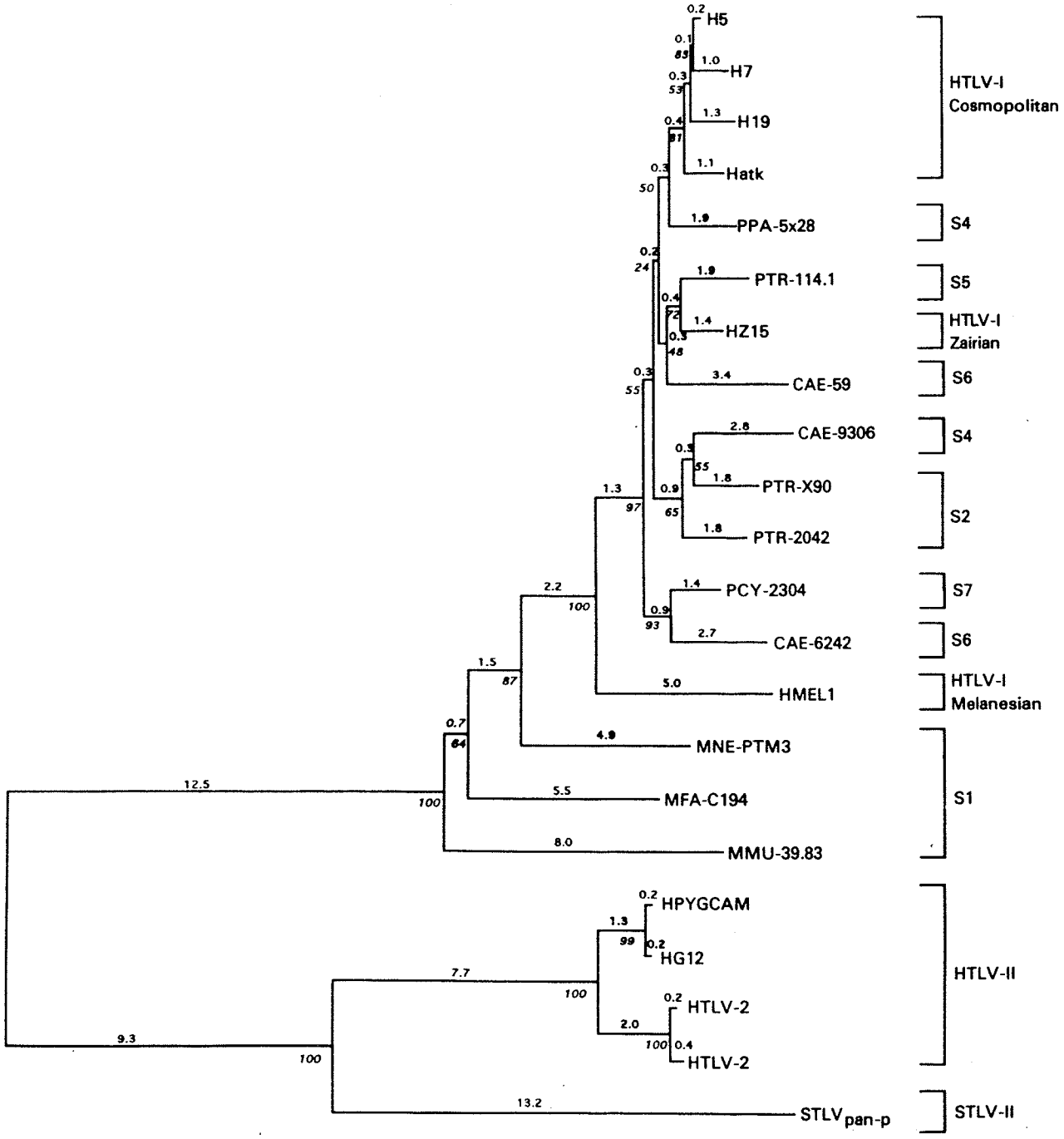
The human HTLV-I_{Zaire} and the common chimpanzee clade S5 are closely related (Figure 2), suggesting that the human clade may have resulted from cross-species transmission of chimpanzee STLV-I to humans. Two additional examples of interspecies transmission which are suggested by the phylogenetic analysis of STLV-I from African primates with different geographical origins (Koralnik *et al.*, 1994) are shown in Figure 2. In the equatorial region of Africa, the STLV-I clades S2, S3 and S5 and HTLV-I_{Zaire} are grouped by geographical region rather than species. Similarly, STLV-I clades S6 and S7 cluster in the eastern part of the continent. In addition, viral strains obtained from a West African baboon also cluster with the HTLV-I_{Cosm} clade.

The S1 clade, from Asia, contains heterogeneous members and is closely related to HTLV-I_{Mel}. These results indicate the evolution of three clades in the human species and suggest that at least three independent introductions of HTLV-I into humans occurred during the evolution of these retroviruses. A simple interpretation of the global dissemination of these retroviruses might be the following. Ancestors of HTLV-I and STLV-I entered primates in Asia and were transmitted to several species. Primates infected with STLVs migrated to Africa, where the viruses were transmitted to local primate genera (*Cercopithecus, Papio, Pan* and humans). Meanwhile, HTLV-I_{Mel} emerged by a separate primate-to-human transfer in Melanesia. More recent human migratory patterns, including the slave trade, led to the dissemination of the cosmopolitan HTLV-I clade worldwide. This hypothesis implies the existence of STLV for over 30 000 000 years, at least since the end of the Oligocene epoch and the beginning of the Miocene era, when the continents were linked, favouring contacts between primate species (Martin, 1990).

The recent description of STLVs in two species of African primates, the pygmy chimpanzees (*Pan paniscus*) and baboons from Ethiopia, adds further complexity to our picture of the evolution of the STLVs and HTLVs. Two closely related viruses (Giri *et al.*, 1994; Liu *et al.*, 1994) isolated from pygmy chimpanzees that live exclusively in central Africa (Kano, 1984; de Waal, 1995) are nearer to HTLV-II than to HTLV-I (Giri *et al.*, 1994; Liu *et al.*, 1994). This finding, in addition to the discovery of sporadic cases of HTLV-II infection in human pygmies (Goubau *et al.*, 1992; Gessain *et al.*, 1995a), raises questions concerning the origin and evolution of HTLV-II, previously thought to be a New World virus. Another STLV, designated primate T-lymphotropic virus-L (PTLV-L) (Goubau *et al.*, 1994), appears to be phylogenetically equidistant between HTLV-I and HTLV-II.

The observations of interspecies transmission of these phylogenetically distinct viruses among non-human primates (Saksena *et al.*, 1994) (see Section 3.2) and of indeterminate serological profiles of HTLVs (see Section 1.2) found in some human populations raise the question of the existence of other HTLV-related viruses in addition to HTLV-I and HTLV-II in humans (see also Figure 3).

Figure 3. Phylogenetic analysis of HTLV-I/STLV-I and HTLV-II/STLV-II



The DNA sequence of a 522 bp envelope fragment from various STLV and HTLV strains was used in a neighbour-joining analysis to define their phylogenetic relationship.
Adapted from Koralnik *et al.* (1994)

1.1.5 *Target tissue (*in vitro *and* in vivo*)*

HTLV-I infects $CD4^+$ T-cells and occasionally $CD8^+$ T-cells *in vitro* (Markham *et al.*, 1983; Popovic *et al.*, 1983) and, less efficiently, other cells including macrophages, B-cells and glial cells (Longo *et al.*, 1984; Hoffman *et al.*, 1992; Koralnik *et al.*, 1992a). *In vivo*, HTLV-I is mainly, if not exclusively, associated with $CD4^+$ T-cells (Richardson *et al.*, 1990). HTLV-II infects mainly $CD8^+$ T-cells *in vitro* and almost exclusively $CD8^+$ T-cells *in vivo* (Rosenblatt *et al.*, 1988a; Hall *et al.*, 1994).

1.1.6 *Genomic structure and properties of gene products*

The HTLV-I genome (Seiki *et al.*, 1983) of approximately 9 kb encodes structural proteins (Gag and Env), enzymes (RT, integrase and protease) and regulatory proteins (Tax and Rex). The two long terminal repeats (LTR) located at the 5′ and 3′ ends of the viral genome contain the viral promoter and other regulatory elements. HTLV-I increases its complexity by alternative splicing of viral messenger ribonucleic acid (mRNA) in the region at the 3′ end of the genome known as pX (Seiki *et al.*, 1985; Aldovini *et al.*, 1986; Nagashima *et al.*, 1986; Furukawa *et al.*, 1991; Orita *et al.*, 1991; Berneman *et al.*, 1992a; Koralnik *et al.*, 1992b; Orita *et al.*, 1993), which contains at least four open-reading frames (Gitlin *et al.*, 1993), and possibly by the use of an internal promoter (Nosaka *et al.*, 1993). The regulatory proteins Tax and Rex are derived from this region. Rex, a post-transcriptional regulator of viral expression (Kiyokawa *et al.*, 1985; Hidaka *et al.*, 1988; Inoue *et al.*, 1991), and Tax, the viral transactivator of transcription (Sodroski *et al.*, 1984; Cann *et al.*, 1985; Felber *et al.*, 1985), are both encoded by double-spliced polycistronic mRNAs in open reading frames III and IV.

Tax, the 42 kDa viral transactivator, is a nuclear phosphoprotein which exerts its effect on the Tax-responsive elements (TRE-1 and TRE-2) located in the U3 region of the viral LTR (Sodroski *et al.*, 1984; Felber *et al.*, 1985). Tax does not bind directly to TRE-1 or TRE-2, but activates other transcriptional factors which do so. Members of the cyclic AMP (c-AMP)-responsive element-binding proteins and activating transcription factor (CREB/ATF) family (leucine zipper protein) have been shown to interact with TRE-1 (a 21-bp repeated element) (Jeang *et al.*, 1988a; Willems *et al.*, 1992a; Suzuki *et al.*, 1993; Adam *et al.*, 1994), whereas TRE-2 contains binding sites for other transcriptional factors such as Sp1, TIF-1, Ets1 and Myb (Bosselut *et al.*, 1990; Gitlin *et al.*, 1991; Bosselut *et al.*, 1992; Franchini, 1995) (reviewed in Gitlin *et al.*, 1993; Yoshida, 1994). In addition to this complex transactivation of the viral LTR U3 region, Tax also positively transactivates cellular genes. Tax-mediated transactivation pathways and the resulting effects on cellular gene expression are discussed in detail in Section 4.3.

Rex (Kiyokawa *et al.*, 1985; Nagashima *et al.*, 1986; Hidaka *et al.*, 1988; Inoue *et al.*, 1991), generated by the same double-spliced mRNA that encodes Tax, is a 27 kDa nucleolar phosphoprotein which regulates the balance of single- and double-spliced versus unspliced viral mRNAs necessary for viral replication. Rex stimulates the expression of both the single-spliced mRNA for the envelope gene and the unspliced viral genomic RNA for the Gag/Pol proteins. However, it inhibits the splicing and transport of double-spliced mRNAs which encode for Rex itself, Tax and the other

alternatively spliced mRNAs in the pX region. The effect of Rex on mRNA level is exerted *in trans* on the *cis*-acting Rex response element (Rex RE), a highly stable RNA stem-loop structure in the U3/R region of the 3′ LTR (Seiki *et al.*, 1985; Yoshida & Seiki, 1987; Hanly *et al.*, 1989). Since the Rex RE stem structure is present in all viral mRNAs, the differential regulation of spliced versus unspliced mRNA by Rex also relies on other *cis* elements in the viral genome (Black *et al.*, 1994a). Rex also stabilizes the mRNA for the interleukin (IL)-2Rα chain by acting *in trans* on the coding sequence of the IL-2Rα chain gene (Kanamori *et al.*, 1990), as well as indirectly potentiating IL-2 gene expression in concert with Tax (McGuire *et al.*, 1993).

1.1.7 *Other genes encoded by open reading frames I, II and III in the HTLV-I pX region*

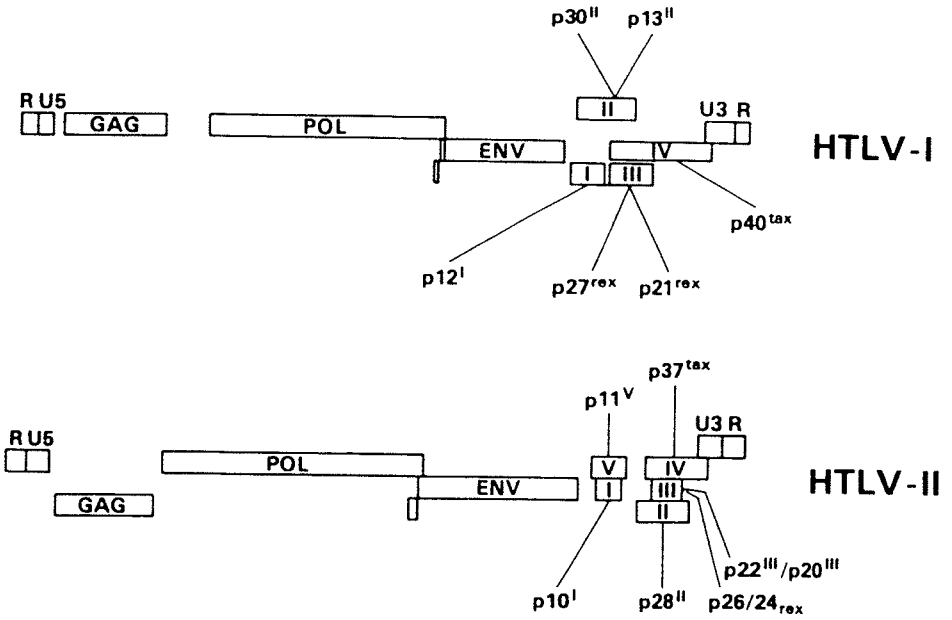
The double-spliced mRNA that encodes Tax and Rex also encodes another protein, $p21^{rexIII}$, a cytoplasmic protein of unknown function (Furukawa *et al.*, 1991), that has been identified in several HTLV-I-infected cell lines. Transcripts for $p21^{rexIII}$ have been found to be highly expressed also in uncultured adult T-cell leukaemia/lymphoma (ATLL) samples (Berneman *et al.*, 1992b). Three other proteins are encoded by alternative splicing of the pX region and transcripts for these mRNAs have been demonstrated in infected cells *in vitro* and in *ex-vivo* samples from healthy individuals as well as from patients with ATLL and tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM) (Berneman *et al.*, 1992b; Ciminale *et al.*, 1992; Koralnik *et al.*, 1992b; Orita *et al.*, 1993). Double- and single-spliced mRNAs from open reading frame I encode a single protein of 12 kDa ($p12^{I}$) in transfected cells (Koralnik *et al.*, 1993).

The $p13^{II}$ and $p30^{II}$ proteins, encoded by open reading frame II in the pX region, are expressed in the nucleus and nucleoli, respectively, of transfected cells (Koralnik *et al.*, 1993). Neither $p13^{II}$ nor $p30^{II}$ influences the activity of the regulatory genes *tax* and *rex* (Roithmann *et al.*, 1994).

Four additional proteins are expressed in HTLV-II from open-reading frames I, II, III and V (Ciminale *et al.*, 1995). Schematic representations of the most recent genomic maps of HTLV-I and HTLV-II are presented in Figure 4.

Spliced genes from the pX region of the bovine leukaemia virus (BLV) have also been described. This distant relative of HTLV causes B-cell leukaemia in cattle (Alexandersen *et al.*, 1993; Kettmann *et al.*, 1994), of which the clinical stages mirror those of HTLV-I-induced ATLL in humans (see Section 3.3). BLV encodes genes functionally equivalent to Tax and Rex and other proteins from the pX region. In a leukaemogenic BLV molecular clone, deletion of the R3 and G4 open reading frames (which are topologically equivalent to HTLV-I open reading frames I and II) results in an attenuated viral phenotype *in vivo* (Willems *et al.*, 1994) (see also Section 3.3.2). Whether there is a biological relationship between these proteins encoded by the BLV and HTLV-I pX region is uncertain. In the case of HTLV-II, deletion of the region encoding these proteins but sparing the *tax* and *rex* genes does not alter its ability to immortalize T-cells *in vitro* (Green *et al.*, 1995).

Figure 4. Schematic representation of the genomic structure of HTLV-I and HTLV-II



From Franchini (1995)

1.2 Methods of detection

The confirmed presence of HTLV-I or HTLV-II antibodies is considered to represent current infection, because, as with other human retroviruses, once acquired, infection is lifelong. This has been confirmed by virological and molecular studies.

1.2.1 *Serological detection of specific antibodies*

Two successive steps are generally necessary to demonstrate the presence of specific antibodies against HTLV-I or HTLV-II in serum, plasma, cerebrospinal fluid or other body fluids (Verdier *et al.*, 1990; Lal & Heinene, 1996). The first is a screening assay, while the second is a confirmatory test which can also discriminate between antibodies directed specifically against HTLV-I or HTLV-II. The screening assays include enzyme-linked immunosorbent assay (ELISA), particle agglutination assay and immunofluorescence. All three methods can be used quantitatively (Gessain *et al.*, 1988).

Commercial ELISA tests use, either alone or in combination, disrupted purified virions or specific peptides and recombinant proteins of HTLV-I or HTLV-II (Chen *et al.*, 1990; Lillehoj *et al.*, 1990; Lal *et al.*, 1991; Washitani *et al.*, 1991; Bonis *et al.*, 1993; Rudolph *et al.*, 1993, 1994; Lal, 1996). The specificity and sensitivity of these assays have been defined (Kline *et al.*, 1991; Wiktor *et al.*, 1991; Cossen *et al.*, 1992; Karopolous *et al.*, 1993; Jang *et al.* 1995). The use of additional specific peptides or recombinant proteins in earlier assays has increased their specificity.

The particle agglutination test uses gelatin particles sensitized with HTLV-I antigens (Ikeda *et al.*, 1984; Fujino *et al.*, 1991).

The indirect immunofluorescence test uses HTLV-I- and HTLV-II-producing cell lines as antigens (Aoki *et al.*, 1985; Gallo *et al.*, 1991).

Confirmatory assays use western blot, radioimmuno-precipitation and immunofluorescence. All commercial western blots contain disrupted purified HTLV-I virions (Gallo *et al.*, 1994a). Generally, HTLV-I and HTLV-II induce antibodies directed against Gag proteins (p19 and p24) and their p53 precursor and Env glycoproteins (gp21 and gp46). Due to significant differences between HTLV-I and HTLV-II in the sequences of p19 and p24, HTLV-I-infected serum generally exhibits a stronger reactivity against p19 than against p24, while the opposite is true for HTLV-II (Wiktor *et al.*, 1990). Some of these western blot assays have been supplemented by the addition of native gp46 specific to HTLV-I or recombinant gp21, recognized by both anti-HTLV-I and anti-HTLV-II antibodies (Lal *et al.*, 1992a,b; Kleinman *et al.*, 1994; Hadlock *et al.*, 1995). HTLV-I and HTLV-II antibodies can be discriminated by the addition of synthetic specific peptides from the gp46 of HTLV-I (MTA1) and HTLV-II (K55) (Lipka *et al.*, 1990; Hadlock *et al.*, 1992; Lipka *et al.*, 1992; Roberts *et al.*, 1993).

A WHO working committee (WHO, 1990) proposed that confirmation of HTLV-I seropositivity must be based upon reactivity both to at least one *gag*-encoded protein (p19, p24) and to one or two *env*-encoded glycoproteins (gp21, gp46). However, more stringent criteria for HTLV-I and HTLV-II serodiagnosis have been proposed (HTLV European Research Network, 1996).

Indirect immunofluorescence has been used as a confirmatory assay to discriminate between HTLV-I and HTLV-II infection (Gallo *et al.*, 1991).

Radioimmuno-precipitation is more sensitive than western blot, but is rarely used as a confirmatory assay because it is time-consuming, expensive and uses radioactive material. It has been useful in the detection of gp21 and gp46 seroreactivities in some unusual sero-indeterminate western blot patterns (Aboulafia *et al.*, 1993; Gallo *et al.*, 1994b).

Most of the immunoglobulins detected are IgG (Lal *et al.*, 1993), but IgA and IgM can also be detected at certain periods of infection (Robert-Guroff *et al.*, 1981; Manns *et al.*, 1991, 1994).

Several algorithms have been used for the detection and confirmation of HTLV-I- or HTLV-II-positive serum specimens at blood banks in Japan (Aoki *et al.*, 1985), the United States (Busch *et al.*, 1994) and Europe (Tosswill *et al.*, 1992; Taylor, 1996). However, some of the assays used for screening are less sensitive for HTLV-II than for HTLV-I and several studies have shown that HTLV-II may go undetected in blood donors (Hjelle *et al.*, 1993; Weiss, 1994; Zehender *et al.*, 1996).

1.2.2 *Detection and characterization of viral nucleic acids*

HTLV-I and HTLV-II are mainly cell-associated viruses. PCR allows the direct detection of proviral DNA sequences of HTLV-I or HTLV-II in cellular DNA (Ehrlich *et al.*, 1990), which is usually obtained from peripheral blood mononuclear cells (PBMCs) found not only in blood but also in semen, breast milk and other body fluids (Iwahara *et al.*, 1990). Primer pairs specific for HTLV-I and/or HTLV-II have been

developed from the *pol* and *tax* regions (Ehrlich *et al.*, 1990). The genetic variability of both HTLV-I and HTLV-II is sufficiently low to permit the detection of the great majority of the existing viral strains.

Single-round PCR with 30/35 cycles can detect specific HTLV-I or HTLV-II proviral sequences in the DNA of PBMCs of persons with ATLL or TSP/HAM and in most healthy carriers. However, nested PCR is required for the detection of HTLV-I proviral sequences in a few individuals with a low viral level. The viral DNA can be sequenced either directly after PCR (Komurian *et al.*, 1991) or after cloning in one of several possible vectors (Gessain *et al.*, 1993). A simpler method to determine HTLV-I or HTLV-II viral subtype involves restriction fragment length polymorphism (RFLP) analysis of either LTR or the *env* gene (Ureta-Vidal *et al.*, 1994).

The clonal integration of provirus(es) in ATLL cells can be demonstrated by Southern blot analysis (Yamaguchi *et al.*, 1984) and/or inverse PCR (Takemoto *et al.*, 1994).

In-vivo expression of HTLV-I or HTLV-II viral antigens is very low. Detection of viral RNA can generally be achieved only by very sensitive methods such as RT/PCR or in-situ hybridization (Gessain *et al.*, 1991). In-situ PCR has recently been applied to HTLV-I infection (Levin *et al.*, 1996).

Quantification of the proviral copy number in the DNA of PBMCs can be achieved by several techniques (Tachibana *et al.*, 1992; Matsumura *et al.*, 1993; Cimarelli *et al.*, 1995; Miyata *et al.*, 1995; Morand-Joubert *et al.*, 1995) (see Section 4.3.1).

1.2.3 *Isolation of HTLV-I and HTLV-II*

Culture, in the presence of IL-2, of PBMCs from HTLV-I- or HTLV-II-infected individuals can lead, usually after several months, to the establishment of long-term T-cell lines which are either $CD4^+$ or $CD8^+$ cells expressing markers of activation (CD25, HLA-DR) (Gessain *et al.*, 1990a; Dezzutti *et al.*, 1993). These clonal T-cell lines, which can also be established by co-culture of PBMCs with phytohaemagglutinin-stimulated cord blood, produce viral particles, visible by electron microscopy, and viral antigens, as demonstrated by specific immunofluorescence using either polyclonal or monoclonal antibodies directed against p19 (Robert-Guroff *et al.*, 1981), p24 (Gessain *et al.*, 1990b) or gp46 (Edouard *et al.*, 1994). These cell lines release viral Gag antigens into the culture supernatant, detectable by an antigen capture assay. The use of the BJAB cell line is very useful to isolate HTLV-II from cultured PBMCs of a patient co-infected with HTLV-II and HIV (Hall *et al.*, 1992).

1.2.4 *Sero-indeterminate HTLV-I western blots*

There are difficulties in interpreting some western blots of HTLV-I or HTLV-II in serum specimens, particularly those from tropical areas (Weber *et al.*, 1989; Verdier *et al.*, 1990; Gessain *et al.*, 1995a). A high percentage of western blots of specimens from equatorial Africa and Melanesia exhibit indeterminate patterns, with reactivities to '*gag*-encoded proteins' p19, and/or p24 and/or p53 and/or proteins of uncertain origin (p26, p28, p32 and p36), but without reactivity to Env glycoproteins gp21 and gp46 (Garin *et al.*, 1994). As a consequence, a number of studies have overestimated the

HTLV-I seroprevalence in these regions (Biggar *et al.*, 1985; Brabin *et al.*, 1989; Garin *et al.*, 1994). In an effort to standardize results, more stringent criteria for western blot positivity have been proposed by WHO (1990) and by the Centers for Disease Control and Prevention (CDC) (1992).

With commercial HTLV-I western blot kits that contain only low amounts of native glycoprotein (gp21, gp46), only persons with high HTLV-I titres, such as patients with TSP/HAM, exhibit a clear Env reactivity. Despite significant progress in specificity of western blot assays, some problems remain; for example, the low specificity of sero-reactivity directed against the recombinant Env gp21 leads to false-positive inter-pretations. A modified version of this recombinant antigen with higher specificity is now available (Varma *et al.*, 1995). The WHO and the CDC diagnostic guidelines need to be further validated for samples originating from tropical areas (Gessain *et al.*, 1995b).

1.2.5 *Seronegative HTLV-I-infected individuals*

A few individuals have been described who are seronegative for both HTLV-I and HTLV-II, but in whom fragments of HTLV-I provirus in their PBMCs have been detected by PCR. In some West Indian HTLV-I-seronegative patients with a clinical TSP/HAM syndrome, some investigators have demonstrated the presence of HTLV-I-related sequences in their PBMC DNA. In most such cases, the detected sequences were small fragments of the *tax* and/or *pol* genes. Recently, an HTLV-I-seronegative TSP/HAM patient harbouring a defective HTLV-I virus in his PBMCs was reported (Daenke *et al.*, 1994). However, most studies indicate that, in healthy individuals, this is very rare, even in HTLV-I endemic areas. Thus, several studies performed in Japan, in the Caribbean region and in the United States have failed to detect HTLV-I proviral sequences in the DNA of PBMCs from seronegative subjects, even children born to HTLV-I-seropositive parents. The possibility of a cryptic infection in which HTLV-I resides elsewhere than in the peripheral blood remains, however, a possibility.

The issue of detection of proviral HTLV sequences in seronegative patients with cutaneous T-cell lymphomas other than ATLL is discussed in Section 2.1.2.

1.3 Epidemiology of HTLV infection

1.3.1 *HTLV- I transmission*

Three modes of transmission have been demonstrated for HTLV-I.

(*a*) *Mother-to-child transmission*

Mother-to-child transmission represents a major mode of transmission of HTLV-I in endemic areas, mainly due to breast-feeding beyond six months (Hino, 1990a; Tajima *et al.*, 1990a; Takahashi *et al.*, 1991; Monplaisir *et al.*, 1993; Wiktor *et al.*, 1993; Hino *et al.*, 1994), after which time the protective IgG maternal antibodies decline (Takahashi *et al.*, 1991). Seroconversion (the development of detectable specific antibodies to the virus in the serum) in children occurs between 18 and 24 months of age (Takahashi *et al.*, 1991). Depending on the population studied, 10–25% of breast-fed children from

HTLV-I-seropositive mothers become infected with the virus (Ando *et al.*, 1987; Hino *et al.*, 1987a,b; Hino, 1990a; Tajima *et al.*, 1990a; Takahashi *et al.*, 1991; Ando *et al.*, 1993; Monplaisir *et al.*, 1993; Hino *et al.*, 1994). This transmission is linked to the presence of HTLV-I provirus in mononuclear cells in breast milk (Kinoshita *et al.*, 1984, 1985a). Maternal factors associated with transmission, which correlate with high HTLV-I viral load, are: high HTLV-I antibody titres directed against the whole virus, presence of anti-Tax antibodies and in-vitro maternal HTLV-I antigen expression in short-term culture (Sugiyama *et al.*, 1986; Hino *et al.*, 1987a; Sawada *et al.*, 1989; Kashiwagi *et al.*, 1990; Wiktor *et al.*, 1993). Other factors include the presence of antibodies directed against certain immunogenic epitopes of the gp46 envelope glycoprotein and maternal age > 30 years (Wiktor *et al.*, 1993).

Strong evidence that breast-feeding plays the predominant role in mother-to-child transmission comes from Japanese studies in which advice to HTLV-I-seropositive mothers not to breast-feed their babies resulted in a significant decrease in mother-to-child transmission of the virus, albeit with unexplained regional variation (Ando *et al.*, 1987; Hino *et al.*, 1987a; Tsuji *et al.*, 1990; Hino *et al.*, 1994; Katamine *et al.*, 1994). Thus in Nagasaki prefecture, the risk of the maternal transmission was reduced from 20–30% to 3% by bottle feeding (Hino *et al.*, 1994; Takezaki *et al.*, 1996), whereas in Okinawa prefecture about 13% of bottle-fed children (all under 10 years of age and none transfused) born to carrier mothers were infected by HTLV-I. Evidence against transplacental transmission comes from a study in which none of seven children with HTLV-I proviral DNA-positive cord blood cells seroconverted by 24–48 months. The observation that none of the cord blood samples of nine formula-fed children, who were later confirmed to be infected, was positive for HTLV-I suggests that intrauterine infection was not the cause of viral transmission (Katamine *et al.*, 1994).

There are no data on the role of vaginal delivery in HTLV-I transmission.

(b) Sexual transmission

HTLV-I is sexually transmissible and this transmission is more efficient from men to women than the reverse (Tajima *et al.*, 1982; Kajiyama *et al.*, 1986; Stuver *et al.*, 1993; Take *et al.*, 1993; Figueroa *et al.*, 1995; Takezaki *et al.*, 1995). The risk for transmission, over 10 years, from seropositive husbands to wives has been calculated at 60%, whereas that for transmission from wives to husbands was only 0.4% (Kajiyama *et al.*, 1986). Another study reported that over 50% of the wives of HTLV-I seropositive husbands were infected within one to four years after marriage (Take *et al.*, 1993). Female prostitutes of Fukuoka (Japan) had a significantly higher seroprevalence of HTLV-I antibodies than various control populations (Nakashima *et al.*, 1995). In prostitutes in Peru, HTLV-I seropositivity was linked to duration of prostitution, lack of consistent condom use and past infection with *Chlamydia trachomatis* (Wignall *et al.*, 1992; Gotuzzo *et al.*, 1994). In a group of 409 Zairian prostitutes from Kinshasa, the annual incidence of HTLV-I was 0.7% (Delaporte *et al.*, 1995). Risk factors for HTLV-I infection in Jamaican women attending sexually transmitted disease clinics included multiple sexual partnership, a current diagnosis of syphilis and the presence of other venereal diseases (Murphy *et al.*, 1989a). Further strong evidence for sexually transmitted infection comes from a

prospective study of 600 subjects over the age of 40 years tested during 1976–93; eight seroconverted, of whom five had an HTLV-I-seropositive spouse and two seroconverted after blood transfusions (Takezaki *et al.*, 1995). In Europe, HTLV-I-infected blood donors, who are usually female, are almost always from an endemic area or have had sexual intercourse with a person from an HTLV-I endemic area (The HTLV Europe Research Network, 1996; Taylor, 1996). Seroconversion in the female partner of a transplant recipient infected by blood transfusion has also been documented (Gout *et al.*, 1990).

(*c*) *Transmission by blood*

Infection by blood transfusion appears to be the most efficient mode of HTLV-I transmission, with a 15–60% risk of infection among recipients of a contaminated cellular blood product (Okochi *et al.*, 1984; Inaba *et al.*, 1989; Manns *et al.*, 1991; Sandler *et al.*, 1991; Manns *et al.*, 1992; Donegan *et al.*, 1994). Fresh frozen plasma, which is acellular, is not infectious. Platelets are more likely than red blood cells to transmit HTLV-I infection when transfused, probably because they are more heavily contaminated by T lymphocytes (Okochi *et al.*, 1984; Lairmore *et al.*, 1989; Manns *et al.*, 1991; Sandler *et al.*, 1991; Manns *et al.*, 1992). Infectivity decreases with increasing duration of storage at 4 °C, a temperature at which lymphocyte survival is reduced. In a study in Jamaica, immunosuppressive therapy at the time of transfusion was found to increase the risk of HTLV-I seroconversion (Manns *et al.*, 1992).

In highly endemic areas such as southern Japan and the West Indies, with a 0.5–5% HTLV-I seroprevalence among blood donors (Gessain *et al.*, 1984; Minamoto *et al.*, 1988), multi-transfused patients (Barbara, 1994) including renal transplant recipients (Linhares *et al.*, 1994) have high HTLV-I seroprevalence. Screening of blood donations has been implemented in Japan (Maeda *et al.*, 1984; Okochi *et al.*, 1984), French Guiana and the Caribbean islands of Martinique and Guadeloupe (Massari *et al.*, 1994; Pillonel *et al.*, 1994), the United States (Williams *et al.*, 1988; Lee *et al.*, 1991; Sandler *et al.*, 1991), Canada, France (Couroucé *et al.*, 1993; Massari *et al.*, 1994; Pillonel *et al.*, 1994) and Denmark (Bohn Christiansen *et al.*, 1995) and Netherlands during the last decade. The issues in relation to testing blood donors in other European countries have been discussed (Salker *et al.*, 1990; Brennan *et al.*, 1993; Soriano *et al.*, 1993; Taylor, 1996). In areas of low endemicity (0.002–0.02% among blood donors) such as metropolitan France and the United States, HTLV-I seropositivity among donors is associated mainly with birth in highly endemic regions (such as the West Indies) or with having sexual partners from endemic areas. In various African and South American countries, where HTLV-I seroprevalence in blood donors ranges from 0.2% to 1%, it has been suggested that compulsory HTLV-I screening of donors should be considered (Gutfraind *et al.*, 1994; Ferreira *et al.*, 1995).

Transmission of both HTLV-I and HTLV-II between intravenous drug users has been documented, with a higher rate for HTLV-II than for HTLV-I (Hall *et al.*, 1994; Schwebke *et al.*, 1994; Hall *et al.*, 1996).

1.3.2 *Animal models of HTLV-I transmission*

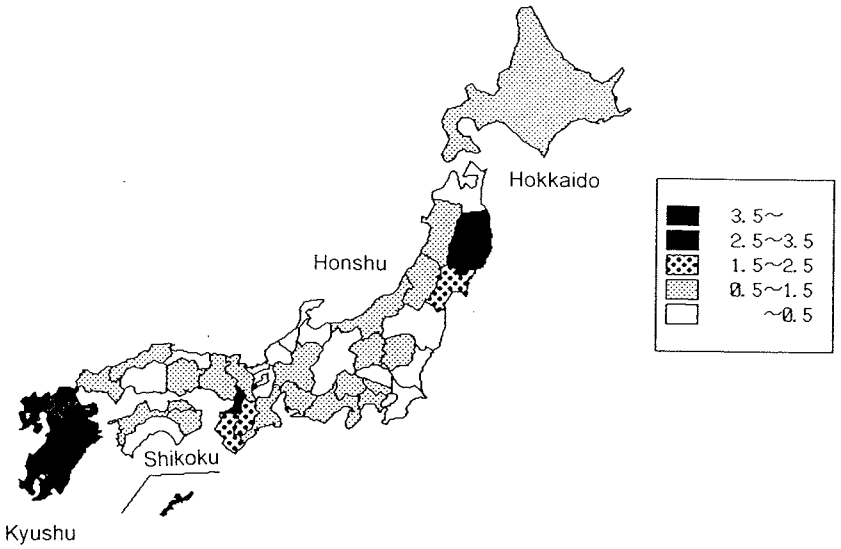
Experiments have demonstrated that HTLV-I can be transmitted to and infect several species of monkeys (Yamamoto *et al.*, 1984; Nakamura *et al.*, 1986), rabbits (Miyoshi *et al.*, 1985; Cockerell *et al.*, 1991) and rats (Ibrahim *et al.*, 1994) by either intravenous or intraperitoneal inoculation of autologous or heterologous HTLV-I-transformed cell lines. HTLV-I infection of rabbits or marmosets has been effected by intravenous or oral inoculation of HTLV-I-transformed and virus-producing cells (Kinoshita *et al.*, 1985a; Yamanouchi *et al.*, 1985; Uemura *et al.*, 1986; Iwahara *et al.*, 1990). Inoculation of rabbits with cell-free concentrated HTLV-I virions led to only a transient seroconversion, without detectable virus remaining after a few months (Miyoshi, 1994). Experimental transmission of HTLV-I by blood transfusion and from mother to offspring has also been observed in rabbits (Uemura *et al.*, 1986; Iwahara *et al.*, 1990); as little as 0.01 mL of infected blood (corresponding to 1.7×10^4 lymphocytes) was capable of transmitting the virus. Hori *et al.* (1995) have demonstrated intrauterine transmission of HTLV-I in rats, albeit at a low rate.

1.3.3 *Geographical distribution of HTLV-I*

HTLV-I is not a ubiquitous virus but is spread throughout the world with small clusters of hyperendemicity located within endemic areas (Levine *et al.*, 1988; Mueller, 1991; Blattner & Gallo, 1994). Information on seroprevalence has been based on surveys of highly variable size and quality and may not be reliable. Only in Japan have population-based studies been conducted. In endemic areas, the HTLV-I antibody prevalence in the adult population varies from 0.2% to 15% (see Figure 5). Based on strict diagnostic criteria using confirmatory assays (western blot; WHO, 1990; Gessain & Mathieux, 1995) and/or specific immunofluorescence (Gallo *et al.*, 1991), low HTLV-I seroprevalence refers to seropositivity in adults ranging from 0.2% to 2%, while higher rates in adults define highly endemic areas. The latter include the south-western islands of Japan, the Caribbean, South America, intertropical Africa, parts of the Middle East (Iran) and Melanesia.

In the Far East, the Japanese islands of Okinawa, Kyushu and Shikoku represent highly endemic areas, with an estimated one million HTLV-I carriers (Tajima *et al.*, 1982; Hino *et al.*, 1984; Ishida *et al.*, 1985; Hinuma, 1986; Tajima *et al.*, 1986, 1987; Kosaka *et al.*, 1989; Tajima & Hinuma, 1992; Morofuji-Hirata *et al.*, 1993; Tajima *et al.*, 1994; Brodine *et al.*, 1995). Most other parts of Japan have lower seroprevalence. The rest of the Far East region has a low level of HTLV-I endemicity, with sporadic cases reported in Taiwan (Wang *et al.*, 1988; Chen *et al.*, 1994), in some areas of India (Babu *et al.*, 1993; Singhal *et al.*, 1993), China (Pan *et al.*, 1991), Korea (Lee *et al.*, 1986), Nepal (Ishida *et al.*, 1992) and the Philippines (Ishida *et al.*, 1988). Few data are available relating to Siberia (Gessain *et al.*, 1996a) or Mongolia (Batsuuri *et al.*, 1993), but sporadic cases of HTLV-I infection in individuals living in the central part of Sakhalin island have been reported (Gurtsevitch *et al.*, 1995; Gessain *et al.*, 1996a). In spite of some reported cases of HTLV-I infection, circumpolar populations cannot be considered as endemically infected (Robert-Guroff *et al.*, 1985; Davidson *et al.*, 1990).

Figure 5. Estimated percentage of HTLV-I carriers among blood donors ≥ 40 years) in Japanese prefectures in 1983



From Maeda *et al.* (1984)

Africa is often considered to be the largest reservoir for HTLV-I infection. It has been estimated that 5–10 million individuals may be infected (Hunsmann *et al.*, 1984; Saxinger *et al.*, 1984; Verdier *et al.*, 1994), in most tropical countries including Benin, Burkina-Fasso, Equatorial Guinea, Ghana, Guinea, Guinea Bissau, Ivory Coast, Mali, Nigeria, Senegal and Tchad in west Africa (Biggar *et al.*, 1984; Hunsmann *et al.*, 1984; Saxinger *et al.*, 1984; de Thé *et al.*, 1985; de Thé & Gessain, 1986; Delaporte *et al.*, 1989a; Ouattara *et al.*, 1989; Verdier *et al.*, 1989; Dumas *et al.*, 1991; Biggar *et al.*, 1993; Dada *et al.*, 1993; Del Mistro *et al.*, 1994; Verdier *et al.*, 1994; Jeannel *et al.*, 1995) and Cameroon, Central African Republic, the Congo, Gabon and Zaire in central Africa (Hunsmann *et al.*, 1984; Saxinger *et al.*, 1984; Delaporte *et al.*, 1989b; Goubau *et al.*, 1990; Delaporte *et al.*, 1991; Schrijvers *et al.*, 1991; Goubau *et al.*, 1993a; Garin *et al.*, 1994; Mauclere *et al.*, 1994; Tuppin *et al.*, 1996). While most of these countries exhibit low HTLV-I seroprevalence overall, areas of high prevalence have been detected in southern Gabon (Delaporte *et al.*, 1989, 1991; Schrijvers *et al.*, 1991) and northern Zaire (Goubau *et al.*, 1990, 1993a; Garin *et al.*, 1994). In north Africa (El-Farrash *et al.*, 1988; Farouqi *et al.*, 1992), east and South Africa (Hunsmann *et al.*, 1984; Saxinger *et al.*, 1984; Bhigjee *et al.*, 1990, 1993; Verdier *et al.*, 1994) and Indian Ocean islands (Mahieux *et al.*, 1994), the level of endemicity seems very low, despite occasional clusters, such as in the Seychelles (Román *et al.*, 1987).

In the Americas, highly endemic areas include the Caribbean islands of Haiti, Jamaica, Martinique and Trinidad (Schaffar-Deshayes *et al.*, 1984; Clark *et al.*, 1985a; Miller *et al.*, 1986; Gibbs *et al.*, 1987; Riedel *et al.*, 1989; Blattner *et al.*, 1990; Fréry *et al.*, 1991; Maloney *et al.*, 1991; Murphy *et al.*, 1991; Ramirez *et al.*, 1991; Allain *et al.*, 1992; Manns *et al.*, 1992; Miller *et al.*, 1994) and limited areas of South America such as Tumaco in Colombia (Trujillo *et al.*, 1992) and the Noir-Marron territory in

French Guiana (Gessain *et al.*, 1984; Gérard *et al.*, 1995; Tuppin *et al.*, 1995). Low-level HTLV-I endemicity has been reported in large regions of Latin America (Ohtsu *et al.*, 1987; Maloney *et al.*, 1989; Cevallos *et al.*, 1990; Pombo de Oliveira *et al.*, 1990; Zamora *et al.*, 1990; Guerena-Burgueno *et al.*, 1992; Duenas-Barajas *et al.*, 1993). In the United States and Canada, prevalence is low except in Afro-Americans and in recent immigrants from endemic areas (Weinberg *et al.*, 1988; Williams *et al.*, 1988; Khabbaz *et al.*, 1990; Chadburn *et al.*, 1991; Eble *et al.*, 1993; Dekaban *et al.*, 1994; Harrington *et al.*, 1995).

There is no known HTLV-I endemic area in Europe; early reports from southern Italy (Manzari *et al.*, 1985) are disputed (de Stasio *et al.*, 1989; Chironna *et al.*, 1994) and most cases of HTLV-I infection have been in immigrants from the West Indies, Africa or the Middle East, or in persons who had sexual relationships with such immigrants (Cruickshank *et al.*, 1989; Wyld *et al.*, 1990; Taylor, 1996). However, sporadic cases of HTLV-I infection without evidence of a link with an endemic area have been reported in Greece (Dalekos *et al.*, 1995), Romania (Paun *et al.*, 1994), Georgia (Senjuta *et al.*, 1991), Sicily (Boeii *et al.*, 1995; Mansueto *et al.*, 1995) and the United Kingdom (Wyld *et al.*, 1990).

While in European countries the great majority of HTLV-seropositive blood donors are infected with HTLV-I (Taylor, 1996), in the United States (Lee *et al.*, 1991), 60–70% are infected with HTLV-II.

In the Middle East, the Mashhad region in northern Iran appears to be an important reservoir of HTLV-I infection (Achiron *et al.*, 1993; Nerurkar *et al.*, 1995), with seropositive emigrants from this region now living in Israel, the United States (Meytes *et al.*, 1990) and northern Italy (Achiron *et al.*, 1993). Furthermore, sporadic cases of HTLV-I infection have been reported in Iraq (Denic *et al.*, 1990) and Kuwait (Voevodin *et al.*, 1995).

In the Pacific region, isolated clusters of HTLV-I have been described, especially in two tribes of Papua New Guinea (Garruto *et al.*, 1990; Yanagihara *et al.*, 1990; Lal *et al.*, 1992c; Nerurkar *et al.*, 1992; Yanagihara, 1994) and in the Australian Aboriginal population (May *et al.*, 1988; Bastian *et al.*, 1993; Bolton *et al.*, 1994). Furthermore, HTLV-I is endemic in the Solomon Islands (Garruto *et al.*, 1990; Yanagihara *et al.*, 1991), but seems very rare in most other Pacific islands (Garruto *et al.*, 1990).

The origin of this puzzling geographical clustering is not well understood, but is probably linked to a founder effect in certain communities, with persistence due to a putatively high mother-to-child transmission of the virus under favourable environmental and cultural conditions (Tajima *et al.*, 1990a; Mueller, 1991; Kaplan & Khabbaz, 1993; Blattner & Gallo, 1994; Tajima *et al.*, 1994). Such clustering linked to the background of the population has been studied in French Guiana (Tuppin *et al.*, 1995): among 1873 pregnant women (the HTLV-I serological status could be established for 1716 of them), the HTLV-I seroprevalence rate differed significantly between ethnic groups: 5.7% for Noir-Marron (70/1302), 6.3% for Haitian (3/50) and 0% for Creole (0/126), Amerindians (0/166) and Hmong (0/64). Thus, the Noir-Marron, descendants of fugitive slaves of African origin, with limited contact with other groups, represent a major reservoir for

HTLV-I infection (Gessain *et al.*, 1984; Gérard *et al.*, 1995; Tuppin *et al.*, 1995). In Trinidad, among a sample of persons selected from a government register, 3.2% of 1025 persons of African descent were HTLV-I-seropositive compared with 0.2% among 487 persons of Asian descent, while the prevalence of HTLV-I infection was 11.4% among persons of African ancestry in a coastal village of Tobago (Blattner *et al.*, 1990).

1.3.4 *HTLV-I prevalence and demographic features of HTLV-I infection*

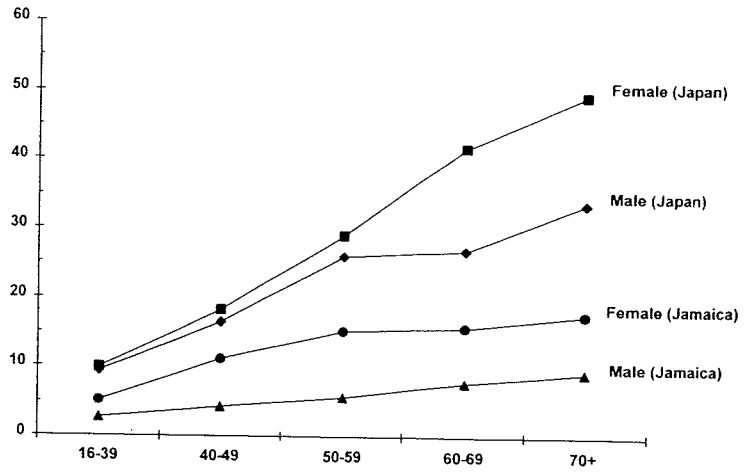
It has been estimated that worldwide between 15 and 20 million individuals are infected with HTLV-I, with 2–10% developing an HTLV-I-associated disease during their lifetime (de Thé & Bomford, 1993; Blattner & Gallo, 1994) (described in Sections 1.4 and 2.1). In highly endemic areas, and despite widely different socioeconomic and cultural environments, the HTLV-I seroprevalence is low and stable among children but increases gradually with age, most markedly in women over 50 years of age, but also in men (Tajima & Hinuma, 1984; Tajima *et al.*, 1987; Maloney *et al.*, 1991; Mueller, 1991; Murphy *et al.*, 1991; Blattner & Gallo, 1994). Several explanations for this significant age-dependent increase in HTLV-I seroprevalence in women have been proposed. First, it could be the result of an accumulation of sexual exposure with increasing age. However, for most sexually transmitted infections, transmission occurs mainly during the period when sexual activity is at its peak (Mueller, 1991). Second, the apparent age-dependence may be confounded by a cohort effect (Blattner *et al.*, 1986; Chavance *et al.*, 1989; Ueda *et al.*, 1989; Chavance & Fréry, 1993; Takezaki *et al.*, 1995), suggested in some but not all cross-sectional surveys in Japan. Finally, these infections in older persons might be due to reactivation of silent infection which becomes apparent on account of immuno-dysregulation that occurs with aging. However, several studies using PCR methods have failed to detect proviral DNA sequences in the PBMCs of HTLV-I-seronegative healthy individuals (Nakashima *et al.*, 1990). Thus, there is at present no consistent explanation for the excess prevalence among older people (Figure 6).

In Kumamoto (Japan), the annual age- and sex-specific HTLV-I carrier prevalence in blood donors below 50 years of age declined between 1986 to 1990 in both sexes, and it has been suggested that the HTLV-I carrier state of individuals below the age of 50 years will become negligible in southern Japan within the first half of the next century (Oguma, 1990; Oguma *et al.*, 1992, 1995).

1.3.5 *Epidemiology of tropical spastic paraparesis/HTLV-I-associated myelopathy*

The etiological link between HTLV-I and tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM) is based on: (1) observations of very high prevalence (up to 90%) of HTLV-I infection in patients with TSP, (2) the occurrence of TSP/HAM following transfusion with HTLV-I-contaminated blood and (3) the decreased incidence of TSP/HAM in transfusion recipients after the introduction of blood donor screening for HTLV-I in Japan (Gessain *et al.*, 1985; Osame *et al.*, 1986a,b; Gout *et al.*, 1990; Kaplan *et al.*, 1990).

Figure 6. Age- and sex-specific HTLV-I seroprevalence in Japan (Miyazaki cohort study) and Jamaica (applicants for food-handling licences)



From Mueller & Blattner (1996)

The association between HTLV-I and tropical spastic paraparesis (TSP) in the French West Indies (Martinique) was described in 1985 (Gessain *et al.*, 1985) and was soon confirmed in Jamaica (Rodgers-Johnson *et al.*, 1988) and in Colombia (Rodgers-Johnson *et al.*, 1985), and subsequently in Japan, where the same clinical entity was named HTLV-I-associated myelopathy (HAM) by Osame *et al.* (1986a). TSP/HAM is more frequent in women (sex ratio ranging from 1 : 1.5 in Japan 1 : 3.5 in Martinique) and is common in most HTLV-I endemic areas, but is very rare in children (Osame *et al.*, 1986a; Román *et al.*, 1987; Shibasaki *et al.*, 1989; Kaplan *et al.*, 1990; Kayembe *et al.*, 1990; Janssen *et al.*, 1991; Ramiandrisoa *et al.*, 1991; Gessain & Gout, 1992; Jeannel *et al.*, 1993), where it can be one of the major neurological diseases. Reliable estimates of TSP/HAM incidence and prevalence are available only for Japan, some Caribbean areas and rare clusters in Africa and South America (Gessain & Gout, 1992). Thus, the prevalence of TSP/HAM ranges from 8.6/100 000 inhabitants in Kyushu (Japan) (Shibasaki *et al.*, 1989; Kaplan *et al.*, 1990; Osame *et al.*, 1990) to 128/100 000 in Mahé (Seychelles) (Gessain & Gout, 1992). Estimates of the annual incidence range from 0.04/100 000 in Kyushu (Shibasaki *et al.*, 1989; Kaplan *et al.*, 1990) to 3/100 000 in Lisala (Zaire) (Kayembe *et al.*, 1990). The female predominance seems to be less marked in South America (Araújo *et al.*, 1993), where TSP/HAM affects all racial groups (Araújo *et al.*, 1993; Rodgers-Johnson, 1994; Domingues *et al.*, 1995).

The prevalence of TSP/HAM varies greatly across geographical areas despite similar levels of HTLV-I seropositivity (Román *et al.*, 1987; Kaplan *et al.*, 1990; Kayembe *et al.*, 1990; Trujillo *et al.*, 1992; Jeannel *et al.*, 1993). Thus, southern Japan and Martinique have similar seroprevalence of HTLV-I, but in Martinique, the prevalence of TSP/HAM among HTLV-I carriers (around 250 cases among 6000–10 000 HTLV-I carriers in a total population of 333 000) is estimated at 1.5–3%, while in Japan,

the prevalence of TSP/HAM in HTLV-I-infected persons is estimated to be only 0.08% (Kaplan *et al.*, 1990).

Within a particular geographical area, the prevalence of TSP/HAM can vary according to ethnic group. Thus in Inongo, Zaire (Jeannel *et al.*, 1993), among the five major ethnic groups, the Bolia exhibit the highest prevalence of HTLV-I (6.5%) without any detected TSP/HAM cases, while six TSP/HAM cases were found among the Ntomba, whose HTLV-I prevalence rate was only 2.2%. Such findings suggest that, besides HTLV-I infection, environmental and/or genetic cofactors play a part in the development of TSP/HAM.

People infected with HTLV-I through blood transfusion have a higher risk for developing TSP/HAM than people infected by other means (Gout *et al.*, 1990; Osame *et al.*, 1990). In Japan and Martinique, up to 20% of TSP/HAM patients had a blood transfusion in the five years preceding onset of the disease. In the first two years of screening of the blood supply in Japan for HTLV-I, started at the end of 1986, a 16% decrease in patients with TSP/HAM was reported (Osame *et al.*, 1990). Direct evidence for a causal relationship between HTLV-I and TSP/HAM was obtained when a seronegative cardiac graft recipient seroconverted 14 weeks after an HTLV-I-positive blood transfusion and, four weeks later, exhibited a severe disorder of the pyramidal tract identical to that seen in TSP/HAM. HTLV-I was isolated from mononuclear cell cultures from his peripheral blood and from his cerebrospinal fluid (Gout *et al.*, 1990).

In contrast, development of ATLL after HTLV-I infection by blood transfusion seems extremely rare, if it exists (Williams *et al.*, 1991).

1.3.6 *Natural history of HTLV-I primary infection*

Among the several dozen documented cases of HTLV-I seroconversion, no acute seroconversion illness has been reported. Following infection with HTLV-I by blood transfusion, viral IgG-specific antibodies are detectable within one to four months in most cases. In the first two months after infection, antibody to Gag protein predominates, with anti-p24 generally appearing before anti-p19. Antibody to recombinant gp21 is frequently the earliest Env reactivity detected, with anti-gp46 appearing later. Anti-Tax antibodies appear much later (Manns *et al.*, 1991, 1994). In the first three months, IgM are the most frequent isotypes, although IgG and IgA can also be detected. HTLV-I-specific antibody responses persist in all Ig isotypes during the next four to six months and remain for many years (Manns *et al.*, 1994).

1.3.7 *Molecular epidemiology of HTLV-I*

Based on sequence and/or RFLP analysis of more than 250 HTLV-I isolates originating from the main viral endemic areas, three major clades have emerged (Gessain *et al.*, 1996b). Between the three clades (HTLV-I_{Cosm} or HTLV-IA, HTLV-I_{Zaire} or HTLV-IB and HTLV-I_{Mel} or HTLV-IC (see Section 1.1.2), depending on the gene, the nucleotide changes range from 0.5 to 10%. DNA sequence analyses indicate that, within the three clades, there exist molecular subgroups clearly defined by several specific mutations, but these are not always consistent with phylogenetic analyses. For example, there is evi-

dence for two ancestral HTLV-I lineages in Japan (Mahieux *et al.*, 1995): the classical cosmopolitan genotype, that represents around 25% of the Japanese HTLV-I and is found mainly in the southern islands, and another related subgroup called the 'Japanese' group, that differs at the nucleotide level by around 1.6% in the LTR and is evenly distributed in the Japanese archipelago (Ureta-Vidal *et al.*, 1994). Similarly, within the central African clade (HTLV-I_{Zaire}), there are molecular subgroups defined by specific substitutions in either the Env or the LTR sequences.

1.3.8 *HTLV-II epidemiology*

In 1982, HTLV-II was isolated from a cell line derived from the splenic cells of a patient with a lymphoproliferative disease originally considered to be a 'T variant of hairy-cell leukaemia' (Kalyanaraman *et al.*, 1982).

While the modes of transmission of HTLV-II appear to be basically the same as those of HTLV-I, the global distribution of HTLV-II is very different. HTLV-II is highly endemic among some scattered Amerindian tribes including the Navajo and Pueblo in New Mexico, the Seminole in Florida, the Guaymi in Panama, the Cayapo (Kayapo) and Kraho in Brazil, the Wayu and Guahido in Colombia and the Tobas and Matacos in northern Argentina (Heneine *et al.*, 1991; Gabbai *et al.*, 1993; Black *et al.*, 1994b; Bouzas *et al.*, 1994) (reviewed in Hall *et al.*, 1994, 1996). In these populations, HTLV-II seroprevalence varies greatly but can reach 20% of the general adult population and up to 50% in women aged over 50 years, as in Cayapo groups living in Brazil (Black *et al.*, 1994b). HTLV-II also appears to be endemic in some pygmy tribes from Zaire and Cameroon (Goubau *et al.*, 1993b) (reviewed in Gessain *et al.*, 1995a; Gessain & de Thé, 1996), in contradiction to the earlier idea that HTLV-II was exclusively a 'New World virus' brought to the Americas by migrations of infected Mongoloid populations, who were the ancestors of the present-day Amerindians.

In aboriginal groups, mother-to-child transmission of HTLV-II through breast-feeding and sexual transmission appears to be important (Black *et al.*, 1994b). In the developed countries, HTLV-II is found almost exclusively in intravenous drug users and their sexual partners (Tedder *et al.*, 1984; Lee *et al.*, 1989; Zella *et al.*, 1990; Parry *et al.*, 1991; Khabbaz *et al.*, 1992; Al *et al.*, 1993; Coste *et al.*, 1993; Blomberg *et al.*, 1994; Vallejo & Garcia-Saiz, 1994; Henrard *et al.*, 1995); transmission occurs mainly through sharing contaminated needles (among intravenous drug users) (Lee *et al.*, 1989; Khabbaz *et al.*, 1992) and blood transfusion (Lee *et al.*, 1991).

1.4 Clinical description of non-neoplastic disorders

1.4.1 *HTLV-I infection*

(*a*) *Tropical spastic paraparesis/HTLV-I-associated myelopathy*

TSP/HAM is a progressive form of chronic spastic myelopathy associated with demyelination of the spinal cord motor neurons (Gessain *et al.*, 1985; Osame *et al.*, 1986a; Dalgleish *et al.*, 1988; Salazar-Grueso *et al.*, 1990; Cruickshank *et al.*, 1992; Araújo *et al.*, 1993; Domingues *et al.*, 1995; Harrington *et al.*, 1995). It usually has an

insidious onset but rare cases of more rapid onset have been described, particularly following blood transfusion. The main clinical manifestations are weakness and stiffness of the lower limbs, urinary bladder disturbances, paraesthesias, lumbar pain and impotence. Difficulty in walking develops several months after presentation (Cruickshank *et al.*, 1992; Rodgers-Johnson, 1994; St Clair Morgan, 1994). Cerebellar signs, cranial nerve palsies and convulsions are rare. Neurological examination reveals spasticity and/or hyperreflexia and muscle weakness in the lower extremities; half of the patients have mild sensory abnormalities. Objective clinical criteria for the diagnosis of TSP/HAM have been published by a WHO working group (WHO, 1989). [The diagnosis of TSP/HAM requires differentiation from multiple sclerosis, spinal cord compression, spinal canal stenosis and cervical spondylosis.]

The main immuno-virological features of TSP/HAM are: the presence of high titres of anti-HTLV-I antibodies in serum and cerebrospinal fluid (Dalgleish *et al.*, 1988); pleocytosis in the cerebrospinal fluid with intrathecal IgG synthesis with oligoclonal bands that react with HTLV-I (Gessain *et al.*, 1988); a high proviral load in the PBMCs (Yoshida *et al.*, 1989; Gessain *et al.*, 1990b); ex-vivo spontaneous lymphoid proliferation (Itoyama *et al.*, 1988); circulating activated T-cell subpopulations (Minato *et al.*, 1989; Shibayama *et al.*, 1992) and presence of cytotoxic T-cells which recognize epitopes of the products of the *tax* gene (Jacobson *et al.*, 1990). All of these features except those in the cerebrospinal fluid have been described in asymptomatic carriers.

A small number of circulating abnormal 'flower-like' lymphocytes similar to those of ATLL are present in about half of the patients (Dalgleish *et al.*, 1988; St Clair Morgan, 1994).

Magnetic resonance imaging may reveal abnormalities in the white matter of the brain and electrophysiology often demonstrates latency delays of visual, brain stem auditory and somatosensory evoked potentials with normal peripheral nerve conduction (St Clair Morgan, 1994).

Histological data are derived mainly from post-mortem examinations. The pathological changes affect the grey and white matter of the spinal cord, particularly the lateral columns; the brain is grossly normal and the leptomeninges are thickened (St Clair Morgan, 1994). The main features are marked demyelination and axonal destruction with an inflammatory mononuclear-cell infiltrate; astrocytic gliosis and meningeal thickening are common. By immunohistology, perivascular infiltrating mononuclear cells are T cells, mainly $CD4^+$ at early stages and $CD8^+$ in the later stages. Macrophages may also be found. HTLV-I has been detected in the nervous tissue by PCR with primers against *pol*, *env* and *pX* genes and by in-situ hybridization (Kira *et al.*, 1991, 1992a; Kira, 1994; Kuroda *et al.*, 1994; Sueyoshi *et al.*, 1994; Umehara *et al.*, 1994), but there is no direct evidence that HTLV-I infects neurons *in vivo* (St Clair Morgan, 1994) and it is uncertain which cell type (T lymphocytes, microglia or neural cells) is infected.

The clinical course of TSP/HAM is progressive. Oral corticosteroids may produce a transient beneficial effect, particularly when given in the early phases of the disease. Other drugs including azathioprine, danazol, intrathecal hydrocortisone and α-interferon

can provide temporary relief. In addition, symptomatic treatment with diazepam or dantrolene can be used to relieve spasticity (St Clair Morgan, 1994).

The pathogenesis of TSP/HAM is uncertain, but viral load, specific molecular viral strain, specific and non-specific immune response and human leukocyte antigen (HLA) variability have been considered as potential factors in disease development (Gessain & Gout, 1992; Bangham, 1993; Bangham *et al.*, 1996). Extensive sequence studies mainly of the LTR region and the *env* gene have failed to define any specific nucleotide changes linked to disease (Mahieux *et al.*, 1995). Although Tax-specific cytotoxic T-cells were first described in the PBMCs of TSP/HAM patients (Jacobson *et al.*, 1990), their prevalence and frequency have been reported to be the same in TSP/HAM cases and asymptomatic carriers (Parker *et al.*, 1994; Daenke *et al.*, 1996). Central nervous system (CNS) inflammation is characterized by perivascular infiltration of lymphocytes (mainly $CD8^+$), but HTLV-I is rarely detected in the CNS. It has therefore been suggested that the CNS damage may be a non-specific consequence of T-cells activated by HTLV-I leaving the circulation and causing bystander damage (Bangham *et al.*, 1996).

(*b*) *Uveitis*

Uveitis is an inflammatory condition of the uveal tract. The majority of cases of uveitis are idiopathic, but some are caused by bacterial or viral infections and some are associated with autoimmune diseases, such as in Behçet's syndrome. Idiopathic uveitis in Japan is more frequent in HTLV-I endemic areas, such as southern Kyushu, and the seroprevalence of HTLV-I in these patients is significantly higher (up to 38%) than in patients with uveitis of other known etiologies (Mochizuki *et al.*, 1992, 1994). Because the seroprevalence of HTLV-I is much higher in young patients, it has been suggested that early exposure to the virus, such as at birth, is important in the development of uveitis (Mochizuki *et al.*, 1994).

HTLV-I-associated uveitis affects younger adults, usually under 50 years of age, and can be uni- or bilateral. It has a subacute onset, presenting with blurred vision but with little or no decrease in visual acuity. The main physical sign of HTLV-I uveitis is vitreous opacity (Mochizuki *et al.*, 1994). The course is progressive in the absence of treatment with topical or systemic corticosteroids. Recurrence of uveitis is common but remission may last for years (Ohba *et al.*, 1994). Familial occurrence of HTLV-I uveitis has been described (Araki *et al.*, 1993), as well as its association with TSP/HAM and hyperthyroidism (Nakao *et al.*, 1994; Ohba *et al.*, 1994).

An association between HTLV-I-associated uveitis and Graves' disease has been reported, evoking speculation that thyroid hormones may modify the host response to the virus and/or activate viral replication (Mochizuki *et al.*, 1994).

Inflammatory cellular infiltrates with HTLV-I-infected cells are present in the ocular tissues. Infiltrating lymphocytes in the vitreous and aqueous humour contain integrated proviral *tax* gene (Mochizuki *et al.*, 1994; Sagawa *et al.*, 1995) and express mRNA for HTLV-I proteins (Sagawa *et al.*, 1995). These lymphocytes display an activated T-cell phenotype ($CD3^+$, $CD4^+$, $CD25^+$) and release a variety of cytokines (such as ILs and tumour necrosis factor (TNF) α), which may be responsible for the inflammation

(Sagawa *et al.*, 1995). Sequencing of the LTR region of HTLV-I has shown that uveitis is not associated with a specific viral strain (Ono *et al.*, 1994). Although the etiopathogenesis is unknown, the evidence available supports an autoimmune mechanism mediated by HTLV-I-activated T cells.

(*c*) *Other inflammatory disorders*

Patients with TSP/HAM additionally have inflammation in tissues other than the CNS, that is characterized by infiltration with activated T-lymphocytes and antibodies in the relevant body fluids. HTLV-I has been detected by molecular methods in these tissues, usually in lymphocytes, but epidemiological data linking HTLV-I with these conditions are weaker than for TSP/HAM. In particular, there is ascertainment bias, with most conditions initially described in patients with TSP/HAM. These inflammatory disorders have also been reported in HTLV-I infected persons without TSP/HAM.

(i) *Infective dermatitis*

Infective dermatitis, an exudative dermatitis affecting the scalp, ears, axillae and groin, characterized by the presence of non-pathogenic bacteria, has been almost exclusively reported in HTLV-I-seropositive Jamaican children (LaGrenade *et al.*, 1990), with an average age at onset of two years. These children require long-term antibiotic therapy. There is mild lymphocytosis in peripheral blood with an increase in $CD4^+$ cells and often polyclonal hypergammaglobulinaemia. Retrospective analysis has suggested that children with infective dermatitis may be at increased risk of later developing TSP/HAM or ATLL (Bunker *et al.*, 1990; Pagliuca *et al.*, 1990; Hanchard *et al.*, 1991; LaGrenade, 1994).

(ii) *Polymyositis*

Polymyositis is an inflammatory myopathy characterized by proximal muscle weakness and wasting, raised serum levels of muscle enzymes (serum lactate dehydrogenase, creatine kinase and aminotransferase) and distinct histological changes. The cause is largely unknown, although some cases are linked to autoimmune disease or infections with viruses such as Coxsackie B. In HTLV-I-endemic areas, the prevalence of HTLV-I antibodies in patients with polymyositis has been found to be substantially higher than in corresponding control groups (85% against 8%: St Clair Morgan *et al.*, 1989; 28% against 11.6%: Higuchi *et al.*, 1992) (reviewed in Dalakas, 1993). HTLV-I-positive polymyositis affects women more frequently than men, appears to be more common in Caribbean than in Japanese patients and seems to be associated with TSP/HAM (St Clair Morgan *et al.*, 1989; Smadja *et al.*, 1993; Sherman *et al.*, 1995). Both IgM and IgG HTLV-I antibodies are detected in most cases. Electromyography shows changes consistent with an inflammatory myopathy, such as short duration of polyphasic motor unit potentials (St Clair Morgan *et al.*, 1989; Sherman *et al.*, 1995).

Histological features are those of a myositis (Sherman *et al.*, 1995), with atrophy, necrosis, oedema, fibrosis and interstitial cellular infiltrates composed of macrophages and lymphocytes (mainly $CD8^+$ with some $CD4^+$). HTLV-I sequences have not been found in the muscle cells (Higuchi *et al.*, 1992; Sherman *et al.*, 1995).

(iii) *Alveolitis*

In the original description, asymptomatic alveolitis was found at bronchoalveolar lavage (BAL) in patients with TSP/HAM (Sugimoto *et al.*, 1987). Asymptomatic alveolitis may occur in HLTV-I carriers and in patients with HTLV-I-associated uveitis (Maruyama *et al.*, 1988; Sugimoto *et al.*, 1993). However, a few patients have a persistent cough and/or a variable degree of dyspnoea. The chest X-ray is usually normal, but localized or patchy reticular shadows, pleural thickening and/or lung fibrosis have been described. Antibodies to HTLV-I are detected in both serum and BAL fluid. BAL fluid may contain lymphocytes predominantly of the $CD4^+$ phenotype (Maruyama *et al.*, 1988) or have a normal distribution of $CD4^+$ and $CD8^+$ cells (Sugimoto *et al.*, 1993) and display an immune response to HTLV-I (Maruyama *et al.*, 1988). An increased number of activated T cells ($CD3^+$, $CD4^+$ or $CD8^+$) expressing HLA-DR determinants and CD25 have been found in the blood and BAL fluid from these patients (Mukae *et al.*, 1994). Patients with alveolitis associated with TSP/HAM have increased soluble IL-2 receptors in the BAL fluid (Sugimoto *et al.*, 1989). Patients with alveolitis associated with uveitis have increased viral load in both blood and BAL fluid (Sugimoto *et al.*, 1993).

(iv) *Arthritis (HTLV-I-associated arthropathy)*

HTLV-I-associated arthropathy is a chronic inflammatory oligoarthritis of large joints, which preferentially affects middle-aged or elderly female HTLV-I carriers (Nishioka *et al.*, 1989; Ijichi *et al.*, 1990; Nishioka *et al.*, 1993) and is often associated with TSP/HAM (Kitajima *et al.*, 1989). Antibodies to HTLV-I are detected in both the serum and synovial fluid. Most patients have IgG antibodies, but up to two thirds also have IgM antibodies, suggesting active replication of the virus in the synovial fluid. Rheumatoid factor and features of autoimmune disease are usually absent and X-rays of the affected joints show marginal erosions and narrowing of the joint spaces (Kitajima *et al.*, 1989). Arthroscopy reveals synovial proliferation, while mild changes in the cartilage and subchondrial bone are seen histologically, with mononuclear infiltrates composed of lymphocytes with multilobulated nuclei (Nishioka *et al.*, 1989, 1993). Immunostaining demonstrates HLA-DR expression by the synovial cells and by lymphocytes that are mainly $CD4^+$ and $CD8^+$ T-cells expressing retroviral proteins (Nishioka *et al.*, 1993). By PCR, HTLV-I proviral sequences have been detected in both lymphocytes and synovial cells purified by T-cell depletion (Kitajima *et al.*, 1991). Cultured synovial cells express mRNA for HTLV-I *tax/rex* as well as HTLV-I core and envelope proteins, as detected by immunostaining (Kitajima *et al.*, 1991; Nishioka *et al.*, 1993). In-vitro studies have also demonstrated that synovial cells are susceptible to infection by HTLV-I, proliferate vigorously and produce large amounts of granulocyte-macrophage colony-stimulating factor (Sakai *et al.*, 1993).

The importance of HTLV-I *tax* in the pathogenesis of this condition is supported by studies in which transgenic mice with the HTLV-I *pX* gene develop a similar polyarthritis (Iwakura *et al.*, 1991; Yamamoto *et al.*, 1993). Whether this is mediated by HTLV-I-infected lymphocytes secreting cytokines which stimulate the proliferation of synovial cells or by a direct stimulation of synovial cells by HTLV-I is unknown.

(v) *Thyroiditis*

An association between HTLV-I infection and Hashimoto's thyroiditis (inflammation of the thyroid gland with autoantibodies) has been reported from Japan (Kawai *et al.*, 1991, 1992; Smadja *et al.*, 1993; Mizokami *et al.*, 1995). The seroprevalence of HTLV-I in these patients was significantly higher than that in the corresponding general population (6.3% versus 2.2%) (Kawai *et al.*, 1992). This condition is often found in patients with TSP/HAM (Kawai *et al.*, 1991, 1992) and uveitis (Mizokami *et al.*, 1995).

(vi) *Sjögren's syndrome*

Sjögren's syndrome, a keratoconjunctivitis, with dryness of the eyes and mouth and hypertrophy and lymphocytic infiltration of the salivary glands, has been observed in HTLV-I carriers and in patients with HTLV-I-associated diseases (Merle *et al.*, 1994; Eguchi *et al.*, 1992; Plumelle *et al.*, 1993). As with other inflammatory diseases associated with HTLV-I, there is an increase in circulating activated cells ($CD3^+$, $CD25^+$, HLA-DR) that display spontaneous proliferation (Eguchi *et al.*, 1992). In some HTLV-I-seronegative patients with Sjögren's syndrome, HTLV-I *tax* but not *pol*, *gag* and *env* sequences have been detected in labial salivary glands (Mariette *et al.*, 1993, 1994; Sumida *et al.*, 1994).

Transgenic mice with the HTLV-I *tax* gene have been shown to develop a condition similar to Sjögren's syndrome. Lymphocytic infiltration of the salivary glands with the presence of *tax* in the epithelial cells has been demonstrated in these mice (Green *et al.*, 1989a).

(*d*) *Immune suppression*

T-cell subsets and CD4/CD8 ratios do not appear to be affected by HTLV-I infection (Matutes *et al.*, 1986; Welles *et al.*, 1994).

Evidence of mild immune suppression due to HTLV-I infection has been seen in studies of healthy carriers who had decreased delayed hypersensitivity to the purified protein derivative of tuberculin (Tachibana *et al.*, 1988) and marked suppression of T-cell control of B cells infected with Epstein–Barr virus (EBV) (Katsuki *et al.*, 1987). Indirect evidence of impaired cellular immunity has come from studies showing that HTLV-I carriers have a reduced ability to clear infection with *Strongyloides stercoralis* (Nakada *et al.*, 1987). *S. stercoralis* infection is associated with ATLL and, when present, is often severe (Nakada *et al.*, 1987; Dixon *et al.*, 1989; Phels *et al.*, 1991; Patey *et al.*, 1992; Plumelle *et al.*, 1993).

1.4.2 *HTLV-II infection*

HTLV-II has occasionally been associated with a myeloneuropathy resembling TSP/HAM with ataxia (Hjelle *et al.*, 1992; Murphy *et al.*, 1993; Harrington *et al.*, 1993; Murphy *et al.*, 1996). Few studies have attempted to investigate the association between HTLV-II and diseases in populations in which the infection is endemic.

1.4.3 *HTLV/HIV co-infection*

Co-infection with HIV and HTLV-I or HTLV-II is common among HIV-1-infected intravenous drug users and patients attending clinics for sexually transmitted diseases in areas where both viruses are endemic (Harper *et al.*, 1986; Wiley *et al.*, 1989; Manzari *et al.*, 1990; Khabaz *et al.*, 1992; Beilke *et al.*, 1994; Harrington *et al.*, 1995). Although the clinical consequences of the co-infection are largely unknown, it has been suggested that HTLV-I but not HTLV-II may accelerate the course of HIV-1 infection. Patients with HTLV-I and HIV-1 co-infection develop specific HIV-1-related disease manifestation at higher $CD4^+$ T-cell count than patients with HIV-1 infection only (Beilke *et al.*, 1994; Harrington *et al.*, 1995; Schechter *et al.*, 1994).

There have been some case reports of co-infected persons developing either associated haematological disease or inflammatory disease (Harper *et al.*, 1986).

1.5 Control and prevention

Prevention of HTLV-I and HTLV-II infection must be directed at the main modes of HTLV-I transmission: perinatal, especially postnatal though breast-feeding; parenteral, through blood transfusion or exposure to contaminated needles; and sexual, essentially male to female (Hino, 1990b; Sato & Okochi, 1990; Bentrem *et al.*, 1994).

Prevention of HTLV-I infection in neonates appears to be particularly important because of the association of ATLL with childhood infection. Maternal antibodies may protect infants during short-term (less than six months) exposure but, as this wanes, susceptibility to infection appears to increase (Takahashi *et al.*, 1991). An intervention programme to screen and counsel HTLV-I-seropositive mothers against breast-feeding began in Japan in the late 1980s and has been shown to prevent 90% of maternal infection of infants (Hino, 1990b). More recently, these recommendations have been changed to permit short-duration breast-feeding. Such a policy can be adopted only where safe and sustainable alternatives to breast-feeding are available.

Transmission of HTLV-I in cellular blood products is highly efficient, with a seroconversion rate of 63% (Bentrem *et al.*, 1994), and TSP/HAM and other inflammatory HTLV-I-linked diseases develop within a relatively short time following blood transfusion (Osame *et al.*, 1986b). Transfusion-related transmission can be prevented by systematic screening of blood donors for HTLV-I and HTLV-II antibodies, as is practised in several countries (see Section 1.3.1). Infection of a health worker with HTLV-I by puncture with a contaminated needle has been known to occur (Bentrem *et al.*, 1994), emphasizing the need for universal precautions in dealing with biological materials.

Use of condoms during sexual intercourse should be considered by couples when only one partner is infected with HTLV-I or HTLV-II.

Passive immunization has been shown to be effective in rabbits: hyperimmune IgG prepared from seropositive healthy persons given 24 h before transfusion with infected blood appeared to protect the recipient rabbit from infection (Takehara *et al.*, 1989; Kataoka *et al.*, 1990).

Although such policies may help to control the spread of HTLV-I and HTLV-II, the ideal intervention would be immunization with a preventive vaccine. Preclinical studies in animal models have suggested the feasibility of an HTLV-I vaccine. Various live recombinant pox virus vectors carrying the HTLV-I envelope protein have conferred protection against a cell-associated HTLV-I challenge in non-human primates (Shida *et al.*, 1987) and rabbits (Franchini *et al.*, 1995). Certain live recombinant envelope proteins alone have also conferred protection in non-human primates (Nakamura *et al.*, 1987). However, no trials of HTLV-I vaccines in humans have yet been undertaken.

2. Studies of Cancer in Humans

2.1 T-Cell malignancies

2.1.1 *HTLV-I-infection and adult T-cell leukaemia/lymphoma*

Adult T-cell leukaemia/lymphoma (ATLL) was described as a distinct clinicopathological entity by Uchiyama *et al.* (1977). Seroepidemiological surveys on lymphoid neoplasms and healthy populations in the early 1980s demonstrated that HTLV-I and ATLL were both clustered in south-western Japan and in Caribbean islands (Hinuma *et al.*, 1982; Blattner *et al.*, 1983). In the mid-1980s and early 1990s, a number of other HTLV-I endemic areas with evidence of ATLL were recognized, chiefly in central and west Africa, South America and the Middle East, and the disease was also found among immigrants from these countries to Europe and the United States (Catovsky *et al.*, 1982; Hahn *et al.*, 1984; Williams *et al.*, 1984; Delaporte *et al.*, 1989b; Denic *et al.*, 1990; Meytes *et al.*, 1990; Sidi *et al.*, 1990; Cabrera *et al.*, 1994; Matutes & Catovsky, 1994; Pombo de Oliveira *et al.*, 1995).

(*a*) *Clinical description*

ATLL is a mature (post-thymic) T-cell malignancy which may be considered within the leukaemia/lymphoma syndromes. The disease arises in peripheral lymphoid tissues, e.g., nodes or skin, but a leukaemic picture is frequent.

(i) *Distribution by subtype*

ATLL has been classified into four subtypes: acute type, lymphoma type, chronic type and smouldering type, according to the clinicopathological features (Shimoyama *et al.*, 1991). The distinguishing features of the various forms of ATLL are summarized in Table 1. Among 1400 cases of ATLL registered throughout Japan during 1990–1993, 914 cases (65%) were classified as the acute type (prototype of ATLL), 330 cases (24%) as the lymphoma type, 83 cases (6%) as the chronic type and 73 cases (5%) as the smouldering type (see Table 1) (T- and B-Cell Malignancy Study Group, 1996).

Table 1. Average age, sex ratio and clinical findings in patients with adult T-cell leukaemia/lymphoma by subtype in Japan (1990–93)

Subtype	No. of cases (%)	Age (± SE)	Sex ratio (male : female)	Skin lesion (%)[a]	Hypercalcaemia (%)[a,b]
Acute	914 (65.3)	58.2 ± 0.39	1.2	31.4 %	32.8
Lymphoma	330 (23.6)	59.4 ± 0.66	1.2	14.0%	15.4
Chronic	83 (5.9)	58.8 ± 1.41	0.9	31.8%	1.1[c]
Smouldering	73 (5.2)	58.5 ± 1.59	1.0	55.7%	0
Total	1400 (100)	58.6 ± 0.32	1.2	28.5%	25.0

From T- and B-Cell Malignancy Study Group (1996); SE, standard error

[a] Calculated by the Working Group

[b] Adjusted Ca^{++} value ≥ 5.5 mEq/L

[c] One case of chronic-type ATLL showed 5.8 mEq/L (unadjusted value, 5.4 mEq/L)

As the clinical spectrum of conditions now accepted as part of ATLL has extended, these conditions have become increasingly difficult to distinguish from other types of T-cell malignancy and sometimes diagnoses have depended on the identification of HTLV-I antibody or genomic material in the subjects, making the understanding of the relationship between this virus and these manifestations difficult to disentangle.

Ocular manifestations, particularly retinitis, resulting from intraocular infiltration by leukaemic cells, can precede or occur during the course of ATLL (Kohno *et al.*, 1993; Kumar *et al.*, 1994).

Acute adult T-cell leukaemia/lymphoma

This is the most frequent presentation of ATLL, corresponding to two thirds of the cases. The main clinical manifestations are organomegaly, high white blood cell count with lymphocytosis and often skin involvement. Lactate dehydrogenase levels are elevated and hypercalcaemia is frequent, although these two parameters are not essential diagnostic criteria of this clinical form. Other less frequent manifestations include CNS involvement, pleural effusions or ascites, lung infiltrates due either to opportunistic infections or to leukaemic infiltration of the lungs and, more rarely, primary involvement of the gastrointestinal tract (Hattori *et al.*, 1991; Nishimura *et al.*, 1994), the Waldeyer's ring (Ohguro *et al.*, 1993) or the cardiac valves (Gabarre *et al.*, 1993).

Lymphomatous adult T-cell leukaemia/lymphoma

This corresponds to the tissue-based ATLL with no evidence of peripheral blood involvement and no lymphocytosis at onset. Many cases develop to leukaemic status at terminal stage. Otherwise, the symptoms are identical to those of the acute (or prototype) form of ATLL, although hypercalcaemia is less common.

Chronic adult T-cell leukaemia/lymphoma

This form is characterized by persistent T-cell lymphocytosis ($> 4 \times 10^9$/L) with atypical cells, minor or no lymphoid organ or skin involvement and lack of systemic symptoms. The lactate dehydrogenase level may be elevated. In both smouldering and chronic ATLL, serum calcium levels are within the normal range.

Smouldering adult T-cell leukaemia/lymphoma

Smouldering ATLL, sometimes referred to as pre-ATLL or pre-leukaemic ATLL (Kinoshita *et al.*, 1985b), is characterized by skin lesions (which usually respond to topical corticosteroids), frequently lung infiltrates and an absence of systemic symptoms (Yamaguchi *et al.*, 1983; Takatsuki *et al.*, 1985; Shimoyama *et al.*, 1991). Patients may be asymptomatic, the disease being discovered during incidental examination. The white blood cell count is normal except for the presence of a few (< 4%) circulating abnormal lymphocytes. Abnormal lymphocytes are sometimes seen in healthy carriers of HTLV-I (Matutes *et al.*, 1986), but in smouldering ATLL, there is clonal integration of viral DNA, as demonstrated by Southern blot.

Smouldering ATLL can be considered to be an early stage of the acute and lymphoma types of ATLL. There does not seem to be a natural progression from the smouldering stage to acute ATLL within a period of months to years (Yamaguchi *et al.*, 1983; Cabrera *et al.*, 1994; Matutes & Catovsky, 1994; Pombo di Oliveira *et al.*, 1995).

Pre-leukaemic cases of ATLL with monoclonal proliferation of abnormal lymphocytes (see 'Histological characteristics' below) without clinical signs or symptoms were studied in south-western Japan (Ikeda *et al.*, 1990). The prevalence rate of pre-leukaemic ATLL among HTLV-I carriers over 30 years of age was estimated as 2% and the age distribution of pre-leukaemic cases, ranging from 30 to 77 years, was no different from that of overt cases of ATLL. The pre-leukaemic stage is presumed to be the clinical stage which precedes ATLL, but it remains possible that an HTLV-I carrier may develop symptoms of ATLL directly, without going through the pre-leukaemic stage. [The Working Group noted that the distinction between pre-ATLL and smouldering ATLL is not well defined.]

(ii) *Laboratory findings (Table 2)*

Hypercalcaemia is the most distinctive abnormality related to ATLL because it is extremely rare in other lymphoid neoplasms (Grossman *et al.*, 1981; Matutes & Catovsky, 1992; Yamaguchi, 1994). It is more frequent in the acute form with high white blood cell count and is rarely associated with osteolytic lesions. Hypercalcaemia is related to the release of cytokines (chiefly a parathyroid-hormone-related protein (PTH-rP), IL-1 and TNF-β) by the malignant cells, with serum levels of parathyroid hormone and vitamin D_3 remaining within the normal range. This cytokine-mediated mechanism is supported by the findings that the gene encoding PTH-rP is continuously transcribed in ATLL cells (Watanabe *et al.*, 1990), that the cells express a high level of PTH-rP mRNA and that, when cultured, they release PTH-rP into the medium (Honda *et al.*, 1988). Other biochemical abnormalities that are also found in other T-cell

malignancies are high levels of lactate dehydrogenase and β_2-microglobulin; the latter is released either by the tumour cells or secondary to cytokine secretion by non-malignant cells. Both parameters are related to a poor outcome and survival (Shimamoto *et al.*, 1990a; Tsuda *et al.*, 1992).

Table 2. Diagnostic criteria of clinical subtypes of adult T-cell leukaemia/lymphoma

Feature	Smouldering	Chronic	Lymphoma	Acute
Lymphocytosis[a]	$< 4 \times 10^9$/L	$> 4 \times 10^9$/L	$< 4 \times 10^9$/L	$> 4 \times 10^9$/L
Lactate dehydrogenase	Normal or < 1.5 the normal limit	< 2 the normal limit	Variable[b]	Variable[b]
Calcium	Normal	Normal	Variable[b]	Variable[b]
Skin	Involved	Variable[b]	Variable[b]	Variable[b]
Lung	Often involved	Variable[b]	Variable[b]	Variable[b]
Systemic involvement[c]	No	No or minor	Variable[b]	Variable[b]

Adapted from Shimoyama *et al.* (1991) and Cann & Chen (1996)

[a] With > 5% atypical 'flower' cells except in the lymphoma form

[b] Not considered for the classification of the ATLL subtype

[c] Enlargement of lymph nodes, spleen, liver, central nervous system, gastrointestinal tract or other organ involvement

(iii) *Histological characteristics*

The diagnosis of ATLL is based on clinicopathological features and a number of laboratory parameters, including peripheral blood cell morphology, histopathology, immunological markers and demonstration of the presence of HTLV-I by serology or molecular analysis. The blood picture in the leukaemic forms of ATLL is pleomorphic, the predominant cell being a medium-sized lymphocyte with a highly irregular, frequently polylobated nucleus, that is often called a 'flower' cell. Circulating immunoblasts may be present in small numbers but they usually predominate in the lymphoid tissues. This blood picture is usually, but not always, distinguishable from that seen in Sézary syndrome, in which the cells have a hyperchromatic cerebriform nucleus (Matutes & Catovsky, 1992). The bone marrow is usually not heavily involved but trephine biopsy may show proliferation of osteoclasts and bone reabsorption, features which relate to the hypercalcaemia.

Histological analysis is essential in the lymphoma form of ATLL. However, there is no unique histological pattern of lymphoid involvement in ATLL, which may be very similar to that of other peripheral T-cell lymphomas. The lymph nodes show effacement of the normal architecture by lymphoid cells of different size, varying from small to large (mixed-cell pattern) (Lennert *et al.*, 1985). Cases with unusual histology or even with a clinical picture resembling that of Hodgkin's disease have been described (Duggan *et al.*, 1988; Ohshima *et al.*, 1991a; Picard *et al.*, 1990). The histological pattern of skin infiltration is not specific either; dermal infiltration by pleomorphic cells is often observed, but in some cases epidermotropism and Pautrier's microabscesses are seen.

These may also occur in Sézary syndrome and mycosis fungoides (Matutes & Catovsky, 1992; Whittaker *et al.*, 1993; Arai *et al.*, 1994; Pombo de Oliveira *et al.*, 1995). Therefore, differentiating between Sézary syndrome or other T-cell lymphomas and ATLL can be difficult on the basis of histological results.

Immunological markers reveal that ATLL cells have a mature post-thymic T-cell phenotype. The most common phenotype of ATLL cells is $CD4^+$, $CD8^-$, but a few patients may have unusual phenotypes such as CD4 loss, CD8 expression or both. In the rare cases with $CD4^+$, $CD8^+$ T-cells, the disease appears to have a more aggressive course (Tamura *et al.*, 1985). The thymic markers TdT and CD1a are always absent. Tumour cells are often positive for CD2 and CD5 markers but usually negative for CD7 (Matutes & Catovsky, 1992). CD3 may be absent or only weakly expressed on the membrane (Tsuda & Takatsuki, 1984) but is, as a rule, expressed in the cytoplasm (Matutes & Catovsky, 1992). A characteristic, but not specific, feature of ATLL cells is the strong expression of the p55 α-chain of the IL-2 receptor, detected by the monoclonal antibody CD25 (Uchiyama *et al.*, 1985; Yodoi & Uchiyama, 1986; Matutes & Catovsky, 1992; Yamaguchi, 1994); other T-cell activation antigens, such as HLA-DR determinants and CD38, may also be expressed. In addition, soluble IL-2 receptors can be detected in the serum of these patients and the levels seem to relate to tumour burden (Yamaguchi *et al.*, 1989). It has been shown that the high numbers of IL-2 receptors in the membrane of ATLL cells result from the continuous transcription of the IL-2 receptor gene (Yodoi & Uchiyama, 1986). These observations suggest that IL-2 receptors play a key role in the etiopathogenesis or progression of the disease.

In spite of the $CD4^+$, $CD8^-$ phenotype, ATLL cells are not helper cells functionally but act as potent suppressors of B-cell differentiation (Yamada, 1983; Miedema *et al.*, 1984). It is uncertain whether this function is direct or is mediated by an indirect mechanism through a suppressor $CD8^+$ T-cell subset. One consequence may be that some patients have concomitant disease related to immune suppression.

(iv) *Genetic studies*

In ATLL, a range of chromosomal abnormalities occur but, unlike those seen in some lymphoid malignancies, such as Burkitt's lymphoma, they are not specific. Abnormalities may involve chromosomes 3, 7 and X, and/or affect 6q, 14q, 3q, 1q and 10p (Shimoyama *et al.*, 1987; Kamada *et al.*, 1990). They are often more complex and are more frequently found in the acute and lymphomatous forms than in smouldering or chronic ATLL, which suggests that they correlate with disease progression.

Familial ATLL has been documented in HTLV-I endemic regions (Kawano *et al.*, 1984; Miyamoto *et al.*, 1985; Matutes & Catovsky, 1994) and less frequently in countries with low HTLV-I seroprevalence such as the United Kingdom (Matutes *et al.*, 1995a). In some families, several cases of TSP/HAM and ATLL have been seen (Uozumi *et al.*, 1991; Plumelle *et al.*, 1993) and the coexistence of the two diseases in the same patient has been described (Cartier *et al.*, 1995; Harrington *et al.*, 1995). The fact that, in the familial clusters, patients did not always share the same household suggests that it was the genetic background rather than the environment which influenced the development of ATLL. Early exposure to HTLV-I, e.g., neonatal or during childhood, seems to be

important for the development of ATLL, as the disease occurs many years after the retroviral infection, in contrast to TSP/HAM, which may develop shortly after infection by HTLV-I.

(v) *Prognosis*

ATLL is an aggressive malignancy with poor prognosis and short median survival ranging from 5 to 13 months in all areas (Shimamoto *et al.*, 1990a,b; Lymphoma Study Group (1984–1987), 1991; Shih *et al.*, 1991; Plumelle *et al.*, 1993; Matutes & Catovsky, 1994; Yamaguchi, 1994). Patients respond poorly to chemotherapeutic schedules used successfully against other high-grade lymphomas (Shimamoto *et al.*, 1990b; Matutes & Catovsky, 1994; Mercieca *et al.*, 1994). Experimental approaches such as therapy with antibody against the IL-2 receptor anti-Tac have yielded only transient responses (Waldmann *et al.*, 1988, 1995). There have, however, been reports of good response to a combination of α-interferon and zidovudine (Gallo, 1995; Gill *et al.*, 1995; Hermine *et al.*, 1995). The mechanism of action of this therapy is unknown. Furthermore, the duration of the response remains to be evaluated.

Patients with the smouldering and chronic forms of ATLL usually have a stable or very slowly progressive course and, during this phase, clinical problems are easier to control than in the acute forms. Generally, such patients are not treated aggressively.

(vi) *Prevention of ATLL*

Prevention of ATLL and/or cancers associated with HTLV-I is difficult, as the secondary factors promoting the evolution from healthy carrier status to ATLL or neoplasia are unknown. Although spontaneous remission of ATLL has been reported (Shimamoto *et al.*, 1993), this appears to be extremely rare. Experimental work has shown that inhibitors of thioredoxin reductase, such as retinoic acid derivatives, are able to inhibit DNA synthesis and growth and replication of HTLV-I-infected cells and therefore have a potential role in the treatment of HTLV-I carriers (U-Taniguchi *et al.*, 1995).

(*b*) *Epidemiology*

Consideration of the epidemiological evidence concerning the relationship between HTLV-I and ATLL must be viewed in the light of the history of HTLV-I's discovery in ATLL-endemic parts of the world. Reports in the early 1980s from these regions (discussed above) found a very high prevalence (> 90%) of HTLV infection in ATLL patients, compared with much lower population prevalence in the area from which the cases came. A few patients with clinical features indistinguishable from those of ATLL have, however, been reported in whom HTLV-I infection cannot be demonstrated (Shimoyama *et al.*, 1986, 1987; Pombo de Oliveira *et al.*, 1995).

The concordance between HTLV-I positivity and ATLL was so high in the endemic areas that HTLV-I became widely accepted as the cause of ATLL, and the presence of HTLV-I infection was adopted as an additional diagnostic criterion for ATLL for lesions in which the clinical findings were ambiguous. This practice complicates assessment of the association between HTLV-I and ATLL.

When the clinical and laboratory features characteristic of ATLL are present, serological assays for HTLV-I antibodies almost always show a strongly reactive test. However, if the features are atypical, DNA analysis by Southern blot using probes specific to HTLV-I sequences may be needed to demonstrate the clonal integration of HTLV-I in the tumour cells. All cases of ATLL have proviral HTLV-I DNA integrated in a monoclonal fashion, according to Yoshida *et al.* (1984). Therefore, the absence of HTLV-I clonal integration may be construed as evidence against this diagnosis in a case. In addition, DNA analysis helps to distinguish cases of smouldering ATLL from healthy carriers.

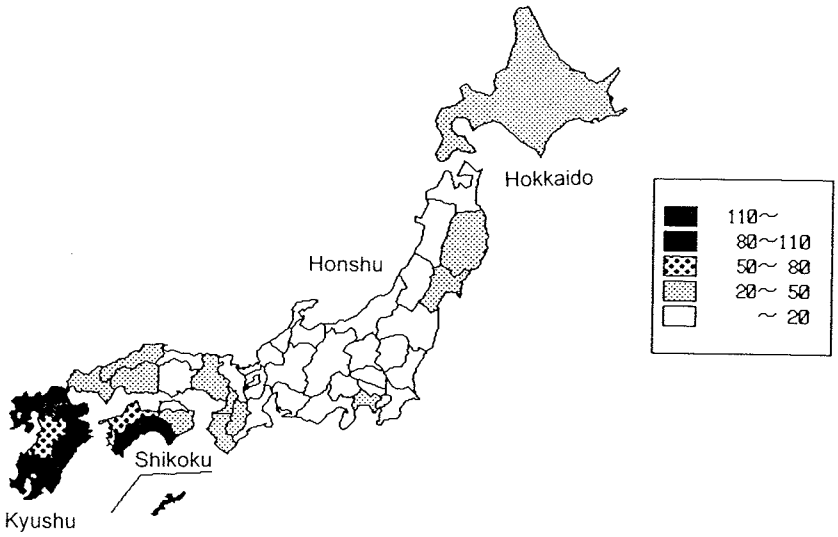
(i) *Geographical distribution*

Following the first report of ATLL cases from Japan by Uchiyama *et al.* (1977), 10 familial cases of ATLL were reported in the south-western part of Japan (Ichimaru *et al.*, 1979), where ATLL is highly endemic. A nationwide study, implemented in Japan soon after the original description, revealed that 50% of ATLL patients were registered in the southern Japanese island of Kyushu (see Figure 7). Only 25% were from major cities (Takatsuki *et al.*, 1977; Uchiyama *et al.*, 1977; Tajima *et al.*, 1990b; T- and B-cell Malignancy Study Group, 1988; Tajima, 1990; Tajima *et al.*, 1994), and 80% of these cases had been born in Kyushu. The sex ratio (male/female) is around 1.2 in Japan (T and B-cell Malignancy Study Group, 1996).

T-Cell leukaemia/lymphomas are not reported routinely as a separate diagnostic group in cancer incidence and mortality statistics. Their geographical distribution can, thus, be derived only from specific reports (or surveys) and the picture obtained is heavily influenced by the extent to which disease surveillance has been carried out in various areas. Studies in Brazil (Pombo de Oliveira *et al.*, 1990; Matutes *et al.*, 1994; Pombo de Oliveira *et al.*, 1995), in Gabon (Delaporte *et al.*, 1993) and in French Guiana (Gérard *et al.*, 1995) have demonstrated that the incidence of ATLL will continue to be greatly underestimated unless a specific search is carried out. This is mainly due to the acuteness and rapid evolution of the disease, so that many patients die before diagnosis can be made, as well as to confusion of ATLL with pathologically similar diseases, such as Sézary syndrome, mycosis fungoides and other types of T-cell non-Hodgkin's lymphoma (Gessain *et al.*, 1992b; Matutes & Catovsky, 1994; Pombo de Oliveira *et al.*, 1995). Furthermore, serological confirmatory tests for HTLV-I, such as western blot and/or molecular analyses, are not readily available in most countries. However, the geographical distribution of ATLL appears to be similar to that of HTLV-I, with rough correspondence of the relative prevalences of the conditions in different areas (see Section 1.3). ATLL has a high incidence in the south-western regions of the Japanese archipelago (Hinuma *et al.*, 1982; Clark *et al.*, 1985b; T- and B-cell Malignancy Study Group, 1985; Tajima & Cartier, 1995; T- and B-cell Malignancy Study Group, 1996). It is also prevalent in most other HTLV-I-endemic areas, including intertropical Africa, South and Central America and Iran (Clark *et al.*, 1988; Pombo de Oliveira *et al.*, 1990; Rio *et al.*, 1990; Gessain *et al.*, 1992a; Blank *et al.*, 1993; Delaporte *et al.*, 1993; Plumelle *et al.*, 1993; Pombo de Oliveira *et al.*, 1995). Furthermore, sporadic cases of ATLL have been described in Europe and the United States, mostly in immigrants

originating from regions of endemic HTLV-I infection (Rio *et al.*, 1990; Patey *et al.*, 1992; Matutes & Catovsky, 1994).

Figure 7. Estimated incidence rate of ATLL in persons (≥ 40 years) per 1 000 000 in Japanese prefectures during 1988–93



From the T- and B-cell Malignancy Study Group (1996)

Extensive reliable data concerning the occurrence of ATLL are available only for Japan and some Caribbean areas.

(ii) *Age- and sex-distribution of ATLL*

The average ages and sex ratios among ATLL cases are presented in Table 3. The average age of ATLL patients at diagnosis in Japan is 57 years (T- and B-cell Malignancy Study Group, 1988). The age pattern in Japan and the Caribbean is presented in Table 4 and Figure 8. No case of ATLL has been reported in children in Japan. In the Caribbean, South America and Africa, the mean age at ATLL onset is around 15 years younger, namely 40–45 years of age (Bartholomew *et al.*, 1985; Gibbs *et al.*, 1987; Gérard *et al.*, 1995; Pombo de Oliveira *et al.*, 1995). In addition, cases have been reported among children in Brazil (Pombo de Oliveira *et al.*, 1995). This suggests the presence of still unknown cofactors in the pathogenesis of this disease in areas of different environmental and cultural conditions or of a cohort effect on the proportion of HTLV-I carriers infected in early childhood (Manns, 1993).

In Japan, the estimated annual incidence of ATLL lies in the range 0.6–1.5 per 1000 HTLV-I carriers aged 40–59 years (Tajima & Kuroishi, 1985; Kondo *et al.*, 1989; Tokudome *et al.*, 1989). The rate appears to be similar in Jamaica (Murphy *et al.*, 1989b), but higher [6/1000] in the Noir-Marron population in French Guiana (Gérard *et al.*, 1995). The cumulative lifetime risk for ATLL among carriers has been estimated to lie in the range of 1–5% in both sexes in Japan and Jamaica (Kondo *et al.*, 1987, 1989;

Table 3. Average age, sex ratio and frequencies of abnormal clinical findings in patients with adult T-cell leukaemia/-lymphoma

	Japan[a] (1984–85)	Japan[b] (1992–93)	Taiwan[c] (1983–90)	USA[d] (until Dec. 1991)	Jamaica[e] (1982–85)	Trinidad[f] and Tobago (1982–83)	French Guiana[g] (1990–93)	Brazil[h] [1989–93]	UK[i] [1982–94]
Number of cases	181	712	27	102	52	12	19	53[k]	52
Average age (years)	56.9	58.9	48	~ 50	40	49.1	42.1	41	47
Age range (years)	24–90	25–87	28–71	7–75	20–70	22–84	21–71	2–65	19–77
Sex ratio (male versus female)	1.4	1.1	2.0	0.8	0.9	2.0	0.5	1.0	0.6
Skin lesions (%)	29.3	26.5	44	57	20	66.7	16	53	41
Hypercalcaemia (> 5.5 mEq/L)[j] (%)	17.1	23.6	37	72.5	48	58	53	34	51

Clinical findings on admission in Japanese cases in HTLV-I antibody positive cases

[a] T- and B-cell Malignancy Study Group (1988); [b] T- and B-cell Malignancy Study Group (1996); [c] Shih *et al.* (1992); [d] Levine *et al.* (1994); [e] Gibbs *et al.* (1987); [f] Bartholomew *et al.* (1985); [g] Gérard *et al.* (1995); [h] Pombo de Oliveira *et al.* (1995); [i] Matutes & Catovsky (1994); [j] In some of these series, calcium levels were measured on more than one occasion and this partially explains the variability of hypercalcaemia rates; [k] Five cases were HTLV-I negative by serology and PCR; there was 1 child and 52 adults.

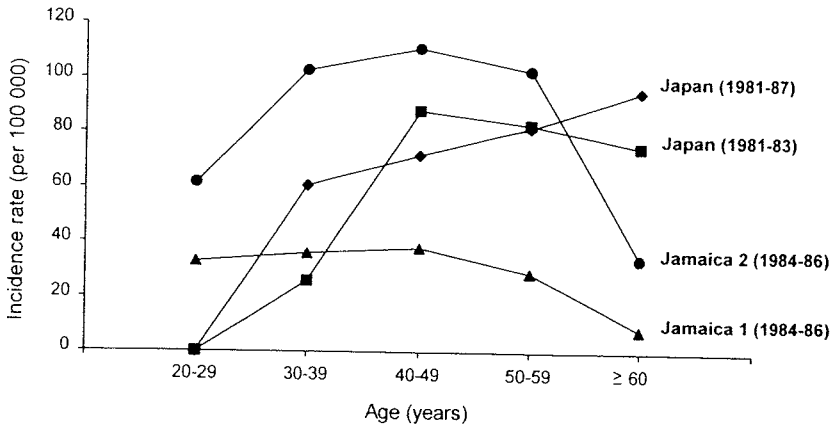
Table 4. Estimated incidence of adult T-cell leukaemia/lymphoma per 1000 HTLV-I carriers per year in adult T-cell leukaemia/lymphoma endemic areas of Japan and Jamaica

Age (years)	Japan (Uwajima): Kondo *et al.* (1989)			Japan (Saga): Tokudome *et al.* (1989)			Jamaica: Murphy *et al.* (1989b)			Jamaica: Murphy *et al.* (1989b)[a]		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
20–29	0	0	0	0	0	0	[0.31]	[0.34]	[0.33]	[0.45]	[0.76]	[0.62]
30–39	0.95	0.41	0.61	0.00	0.48	[0.26]	[0.47]	[0.31]	[0.36]	[0.94]	[1.10]	[1.03]
40–49	0.83	0.66	0.72	1.19	0.63	[0.88]	[0.64]	[0.28]	[0.38]	[1.12]	[1.10]	[1.11]
50–59	2.10	0.33	0.82	1.16	0.58	[0.83]	[0.61]	[0.18]	[0.29]	[1.26]	[0.83]	[1.03]
60	[1.45]	[0.68]	[0.95]	[0.96]	[0.63]	[0.75]	[0.11]	[0.07]	[0.08]	[0.31]	[0.38]	[0.34]
> 40	[1.50]	[0.58]	[0.89]	[1.06]	[0.61]	[0.93]	[0.34]	[0.15]	[0.21]	[0.80]	[0.71]	[0.75]
Cumulative rate												
(40–69)	[49.3]	[19.7]	[28.9]	[35.5]	[19.9]	[26.4]	[13.6]	[5.3]	[11.1]	[26.9]	[23.1]	[24.8]
(30–69)	[58.8]	[23.8]	[35.0]	[35.5]	[24.7]	[29.0]	[18.3]	[8.4]	[14.4]	[36.3]	[34.1]	[35.1]

[a] Calculated from HTLV-I carriers defined as people who might have been infected with HTLV-I as a newborn baby.
[ ] Calculated by the Working Group

Murphy *et al.*, 1989b; Tokudome *et al.*, 1989) (Table 4). The age distributions of ATLL incidence for men and women in Kyushu, Japan, are shown in Figure 9.

Figure 8. Estimated annual age-specific incidence rates (per 100 000) of adult T-cell leukaemia/lymphoma among HTLV-I carriers in Japan and Jamaica



Sources: Japan, 1981–1987: Kondo *et al.* (1989); Japan, 1981–83: Tokudome *et al.* (1989); Jamaica: Murphy *et al.* (1989b)
Jamaica 2: calculated from HTLV-I carriers defined as people who might have been infected with HTLV-I as a newborn baby

(iii) *Cohort studies*

Tokudome *et al.* (1991) followed 3991 HTLV-I-seropositive blood donors aged ≥ 40 years from four blood centres in Kyushu who had donated blood between 1984 and 1987. Positivity for HTLV-I was determined by a particle agglutination antibody assay confirmed by indirect immunofluorescence in two centres. Mortality was ascertained through to August 1989; the average length of follow-up was 2.7 years for a total of 4403 person-years for men and 5591 person-years for women. The crude mortality rates for ATLL (3 deaths in men and 2 in women) were 68.1 per 100 000 for men and 35.8 for women. There were two additional deaths from malignant B-cell lymphoma (one in each sex).

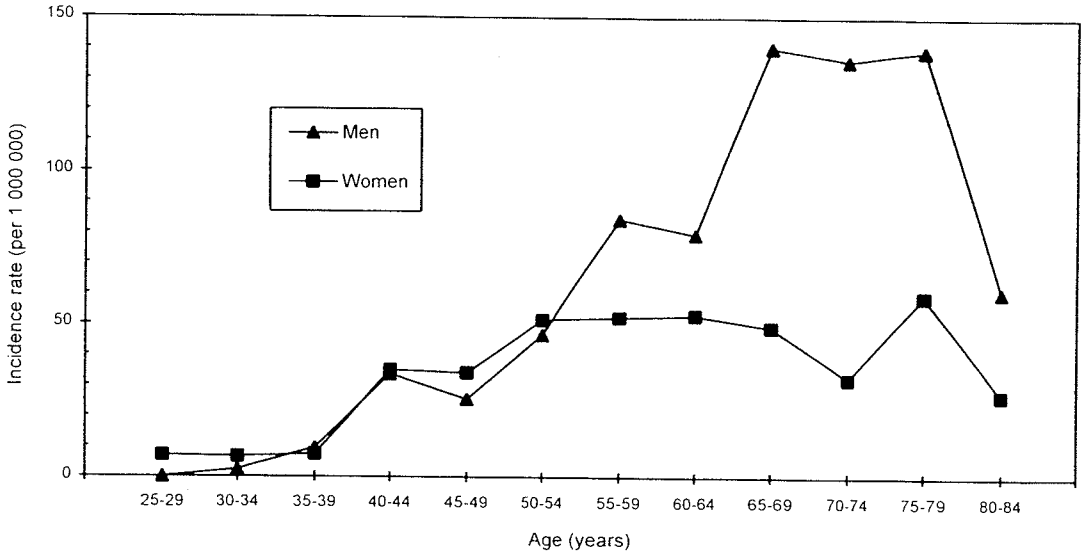
Iwata *et al.* (1994) followed a total of 1997 individuals aged ≥ 30 years from an HTLV-I-endemic community in Nagasaki Prefecture who were screened between 1984 and 1990. Of these, 503 (25.3%) were seropositive for HTLV-I by a particle agglutination antibody assay. The cohort was followed up to mid-1992, the average follow-up being 5.3 years for a total of 2581 person-years at risk. There were two deaths from ATLL (one in each sex). The crude mortality rate was 77 per 100 000 person-years. [No expected value was given but it must be very small.]

(iv) *Case–control studies on co-factors*

In ATLL-endemic areas, almost all ATLL cases diagnosed by clinicopathological features show seropositivity for HTLV-I (see Table 5). In areas of low ATLL incidence, a small proportion of cases lack HTLV-I antibody (T- and B-Cell Malignancy Group,

1985; Pombo de Oliveira, 1995), but the vast majority (> 90%) of cases are seropositive. The majority (> 60%) of all T-cell lymphomas in Jamaica and in Trinidad and Tobago are HTLV-I-seropositive versus less than 10% of other lymphoma cases (Manns *et al.*, 1993).

Figure 9. Estimated annual sex- and age-specific incidence rates (per 1 000 000) of adult T-cell leukaemia/lymphoma in Kyushu, Japan, 1992–93



From T- and B-cell Malignancy Study Group (1996)

Several case–control studies on ATLL have been conducted in Japan (T- and B-Cell Malignancy Study Group, 1985; Tokudome *et al.*, 1993). In one, 66 cases were compared with the same number of hospital controls without cancer selected by individual matching to each case for sex and age (within five years) (T- and B-Cell Malignancy Study Group, 1985). The investigators checked factors such as blood type (A, B, O), occupation, family history of cancer, habit of raising animals and habit of eating raw meat, but found no association of ATLL with any specific environmental risk factor. They found negative associations with hepatitis and blood transfusion. Tokudome *et al.* (1993) reported that the prevalence of smoking among 141 ATLL cases from northern Kyushu (Fukuoka and Saga) (65% of 75 men, 17% of 66 women) was significantly higher than that reported in the general population (53% and 4%, respectively). [The Working Group noted that smoking data from these cases may not be directly comparable to the general population rates, and that the inverse associations reported with hepatitis and transfusion history may be due to selection bias resulting from the use of hospitalized controls.]

To examine the importance of exposure to HTLV-I during early life (presumably from breast feeding), two groups have studied mothers of patients with ATLL and TSP/HAM. In both Jamaica (Wilks *et al.*, 1996) and Trinidad (Bartholomew *et al.*, 1994), 100% of mothers of ATLL patients were HTLV-I-infected compared with

Table 5. Proportion of anti-HTLV-I antibody-positive individuals in lymphoma cases and controls in Japan and Central/South America

	Japan (Kyushu)[a]	Japan (other districts)[a]	Brazil[b]	Jamaica[d]	Trinidad & Tobago[d]
	Positive/tested (%)	Positive/tested (%)	Positive/tested (%)	Positive/tested (%)	Positive/tested (%)
T-cell lymphoma	162/192 (84.4)	60/142 (42.3)	50/188 (26.5)	41/70 (58.6)	34/43 (79.1)
ATLL	130/130 (100.0)	49/54 (90.7)	48/53 (90.5)	–	45/48 (94)[e]
Other T-cell lymphoma	32/62 (51.6)	11/88 (12.5)	1/29 (3.4)	–	–
Cutaneous T-cell lymphoma	–	–	0/54 (0)	–	–
Non-T-cell lymphoma	12/49 (24.5)	4/117 (3.4)	–	1/24 (4.2)	1/25 (4.0)
Healthy adults	241/3026 (8.0)	95/12 090 (0.8)	697/93 087 (0.7)[c]	27/376 (7.2)	20/355 (5.6)

[a] T- and B-cell Malignancy Study Group (1985)
[b] Pombo de Oliveira *et al.* (1995) except when noted
[c] Matutes *et al.* (1994)
[d] Manns *et al.* (1993)
[e] Cleghorn *et al.* (1990)

27–30% of mothers of TSP/HAM patients. The results indicate that infection early in life may be very important for the development of ATLL but that some cases of TSP/HAM occur following transmission of the virus later in life.

Studies of the role of the HLA system in relation to HTLV-I-associated disease are presented in Section 4.2.

2.1.2 *HTLV-I infection and cutaneous T-cell lymphomas*

Cutaneous T-cell lymphoma is an uncommon malignancy, with an estimated incidence of 800–1000 new cases per year in the United States (Weinstock *et al.*, 1988). It represents a small proportion (2–5%) of malignant lymphomas. A three-fold increase in the incidence of cutaneous T-cell lymphoma has occurred over the last couple of decades, although some of this increase may be due to improved diagnosis. The incidence of cutaneous T-cell lymphomas rises sharply with age and the average age of a patient at diagnosis is 52 years; the majority of new cases are over 30 years old. Men are affected more frequently than women. In the United States, cutaneous T-cell lymphoma has been found to be more prevalent in blacks than in whites (Pancake *et al.*, 1995).

When ATLL presents predominantly with cutaneous manifestations, it is sometimes indistinguishable from cutaneous T-cell lymphoma on clinical and pathological grounds (Arai *et al.*, 1994). Both are mature T-cell malignancies of $CD4^+$, $CD8^-$ phenotype and affect the skin with a similar histological pattern of infiltration (Whittaker & Luzzatto, 1993; Whittaker *et al.*, 1993).

Over the past few years, a number of reports have indicated finding of HTLV-I and/or a related or partially deleted retrovirus in a subset of cutaneous T-cell lymphomas occurring in non-endemic areas (Hall *et al.*, 1991; Zucker-Franklin *et al.*, 1991; Srivastava *et al.*, 1992; Zucker-Franklin *et al.*, 1992; Pancake & Zucker-Franklin, 1993; Zucker-Franklin & Pancake, 1994; Manca *et al.*, 1994). However, HTLV-I-related sequences have not been found in other studies (Capésius *et al.*, 1991; Bazarbachi *et al.*, 1993, 1995; Matutes *et al.*, 1995b).

Even in the studies suggesting presence of the virus, the patients either lack antibodies to HTLV-I (Hall *et al.*, 1991; Zucker-Franklin *et al.*, 1991; Pancake & Zucker-Franklin, 1993) or show an indeterminate pattern of seroreactivity by the radioimmunoprecipitation assay (RIPA) and western blot, with weak p24 (Gag) reactivity but no anti-Tax or p19 (Gag) antibodies (Srivastava *et al.*, 1992). In one notable case, Picard *et al.* (1990) described one case first described as ATLL who was initially seronegative but produced antibodies several months after chemotherapy had begun; antibody studies were carried out with immunofluorescence techniques. In cases of cutaneous T-cell lymphoma positive for some part of HTLV-I (Gag, Pol or Env) by PCR, none contained a full-length proviral DNA; only one study has shown conservation of the pX region in cutaneous T-cell lymphoma, which is considered to be essential in the pathogenesis of ATLL (Manca *et al.*, 1994). Finally, with one possible exception (Hall *et al.*, 1994), no study has documented monoclonal or oligoclonal integration of HTLV-I in the neoplastic cells, another essential feature of HTLV-associated ATLL.

It is possible that, on occasion, endogenous retroviral sequences have been amplified accidentally using HTLV-I-specific PCR primers (Bangham *et al.*, 1988; Fujihara *et al.*, 1994). Another possibility is that some patients may have an incorrect diagnosis and are considered as having cutaneous T-cell lymphomas, when in fact they have a cutaneous form of ATLL with partial expression of the HTLV-I genome. It is therefore doubtful whether non-ATLL T-cell lymphomas are really associated with HTLV-I sequences.

2.1.3 *HTLV-II infection*

The role of HTLV-II in the pathogenesis of lymphoid neoplasms remains uncertain (Fouchard *et al.*, 1995). HTLV-II was first isolated from spleen cells of a patient with a T-cell malignancy diagnosed as a T-cell variant of hairy-cell leukaemia (Kalyanaraman *et al.*, 1982). In a subsequent case (Rosenblatt *et al.*, 1986), the patient was found to have two distinct neoplasms: a typical B-cell hairy-cell leukaemia in which HTLV-II was not detected and a $CD8^+$ T-cell disorder equivalent to large granular-lymphocyte leukaemia in which HTLV-II was oligoclonally integrated (Rosenblatt *et al.*, 1988a,b). As the T-cell variant form of hairy-cell leukaemia is not a recognized entity among lympho-proliferative disorders, the original patient may have had a condition other than hairy-cell leukaemia.

In 1987, two groups reported finding that patients with large granular-lymphocyte leukaemia had a high prevalence (7/27 and 6/12, respectively) of antibodies against HTLV-II (Pandolfi *et al.*, 1987; Starkebaum *et al.*, 1987). The antibody profile seemed incomplete in most instances, prompting speculation that the response might be due to a related retrovirus. This leukaemia is a rare, chronic T-cell lymphoproliferation with a $CD8^+$, $CD4^-$ phenotype. The patients often present with splenomegaly and have an indolent course lasting for years.

Loughran *et al.* (1994) reported that six out of 28 patients with large granular-lymphocyte leukaemia were serologically positive for HTLV-I or HTLV-II by ELISA, although some had indeterminate patterns in which the western blot reacted only with either Gag protein or recombinant Env p21. Of these, only one patient with large granular-lymphocyte leukaemia was reported to have HTLV-II sequences in the lymphocytes, detected by PCR (using Pol and/or pX region primers) (Loughran *et al.*, 1992). However, in other cases reported, clonal integration of the retrovirus in the lymphoma cells was not found by Martin *et al.* (1993) and not investigated by Loughran *et al.* (1992, 1994), even though the patients had HTLV-II infection. Furthermore, Heneine *et al.* (1994) screened 51 patients with large granular-lymphocyte leukaemia but found only one to have HTLV-II antibodies. An unusual case of HTLV-I-positive ATLL with a blood picture similar to that of large granular-lymphocyte leukaemia has been reported in Japan (Sakamoto *et al.*, 1994).

Therefore, it remains doubtful whether HTLV-II plays a pathogenic role in large granular-lymphocyte leukaemia; undetected retroviruses or variant virus might be responsible (as proposed by Loughran *et al.*, 1994) or an indirect and non-specific mechanism may be involved (as proposed by Martin *et al.*, 1993).

One patient with mycosis fungoides associated with HTLV-II has been described (Zucker-Franklin *et al.*, 1992).

2.2 Other malignancies

2.2.1 *HTLV-I*

(*a*) *Case reports and case series*

One approach to studying the risk of other malignancies in HTLV-I-infected persons is to look at multiple cancers in ATLL patients. Most reports of such cases come from populations in Japan, where HTLV-I infection is endemic.

Ono *et al.* (1989) reported that, of 43 consecutive patients with ATLL seen in northern Kyushu (Saga) between 1982 and 1987, five (all aged ≥ 70 years) had additional multiple cancers, including two persons with triple separate malignancies. This was significantly higher than the two multiple cancers seen in 36 similarly aged cases with other haematological malignancies during the same time period (not adjusted for age or sex). The other second primary cancers seen in the cases of ATLL were tumours of the colon, larynx, thyroid, stomach (three), liver and kidney. Similarly, Imamura *et al.* (1993) found that five of 15 ATLL cases seen at one institution between 1963 and 1985 had a second malignancy (of the thyroid, stomach, larynx, lip and lung); this was significantly higher than the 44 multiple primaries among 1156 patients with other haematological malignancies (not adjusted for age or sex).

There have been various case reports of second non-T-cell primary malignancies in cases of ATLL, including two cases of Kaposi's sarcoma (Greenberg *et al.*, 1990; Veyssier-Belot *et al.*, 1990), an EBV-positive B-cell lymphoma (Tobinai *et al.*, 1991), an acute monoblastic leukaemia (Tokioka *et al.*, 1992) and a cerebral small-cell lymphoma (Komori *et al.*, 1995). Shibata *et al.* (1995) described a Japanese HTLV-I carrier with a high prevalence (13%) of circulating abnormal lymphocytes and a long history of lymphadenopathy, having a tumour diagnosed as mantle-cell lymphoma with features of mucosa-associated lymphoid tissue lymphoma. EBV genome was not detectable in this B-cell tumour. In these case reports, no integrated HTLV-I provirus was found in the non-ATLL tumour. [The Working Group noted that in the reports of Ono *et al.* and Veyssier-Belot *et al.*, it is unclear whether the non-ATLL cases were tested for the presence of HTLV-I genome.]

A number of cases have been reported of HTLV-I detected by PCR in tumours other than ATLL. Since PCR will detect HTLV-I in infiltrating lymphocytes, the significance of such findings is open to question (Matsuzati *et al.*, 1990; Imajo *et al.*, 1993; Inoue *et al.*, 1994a).

Several reports dealing mainly with HTLV-I-endemic populations outside Japan describe chronic lymphocytic leukaemia in HTLV-I carriers. Blattner *et al.* (1983) reported that, of 14 cases of chronic lymphocytic leukaemia identified among a series of haematopoietic malignancies in Jamaica, four were HTLV-I-seropositive but were negative for HTLV-I provirus. Mann *et al.* (1987) reported experiments using tumour cells from two HTLV-I-seropositive Jamaicans with B-cell chronic lymphocytic

leukaemia. In these experiments, the cells were fused with a human B-lymphoblastoid cell line, and the secreted immunoglobulin was then characterized as to its antigen specificity for HTLV-I proteins. In one case, the antibodies reacted to the p24 Gag protein of HTLV-I, and in the other case, to the gp61 Env protein. The authors speculated that HTLV-I infection played an indirect role in the oncogenesis of antigen-committed B cells responding to the infection. [The Working Group noted that it was not clear whether the cases reported by Blattner *et al.* were of B-cell origin.]

Although there is a suggestion from case series of an excess of cancers other than ATLL among persons infected with HTLV-I, this is not supported by cohort studies (see below).

(*b*) *Cohort studies*

Tokudome *et al.* (1991) followed 3991 HTLV-I-seropositive blood donors aged ≥ 40 years from four communities in Kyushu who had donated blood between 1984 and 1987. Positivity for HTLV-I was determined by a particle agglutination antibody assay (see p. 297). Mortality was ascertained through to August 1989; the average length of follow-up was 2.7 years. Twenty-six deaths were reported in the cohort, four from malignancies (excluding those from ATLL and malignant lymphoma). Expected numbers were calculated on the basis of national age-specific rates. There was a significant deficit among HTLV-I carriers for deaths from other cancers: observed/expected, 0.32 (95% CI, 0.07–0.93) for men and 0.13 (95% CI, 0.00–0.71) for women. The authors noted that these findings are underestimates because of the healthy donor effect.

Iwata *et al.* (1994) followed up a total of 1997 individuals aged ≥ 30 years from an HTLV-I-endemic community in Nagasaki Prefecture for an average of 5.3 years (see p. 297). Population registries, death certificates and hospital records were used to identify a total of 120 deaths within the cohort; of these, 45 occurred among 503 HTLV-I carriers and included 10 non-ATLL malignancies. Based on proportionate mortality hazard, the risk for death from all other malignancies associated with HTLV-I infection was 1.2 (95% CI, 0.39–3.5) for men and 1.8 (0.61–5.2) for women.

(*c*) *Case–control studies*

In order to examine the association between HTLV-I infection and non-ATLL malignancies, Asou *et al.* (1986) identified 685 patients with malignancies other than ATLL (average age, 60 years) in 11 hospitals in central Kyushu (Kumamoto), Japan, between February and March 1985. Patients with an unknown history of blood transfusion were excluded. Seven patients had double malignancies. The comparison group included 22 726 healthy individuals who were part of a health survey by the Japanese Red Cross Health Service Center; all had lived in the Prefecture since early childhood. The two groups were compared for seroprevalence of HTLV-I as determined by ELISA, with adjustment for age and sex. The results were reported separately for cases according to whether or not they had a history of blood transfusion. The overall seroprevalence in the 394 non-transfused cases with other malignancies was 15.5% and for the 291 with a history of transfusion was 26.1%. The corresponding crude prevalence rate in the comparison population was 3.0%. The relative risk associated with HTLV-I

infection for malignancies other than ATLL was 2.2 ($p < 0.01$) among the non-transfused cases and 4.2 among the transfused cases ($p < 0.03$). [The Working Group noted that the controls were likely to be more healthy than the general population and were not stratified by transfusion history.]

A series of reports described an association of HTLV-I with hepatocellular carcinoma in Japan, which is commonly due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) (see IARC, 1994). Iida *et al.* (1988) evaluated the HTLV-I antibody status of 380 patients with various liver diseases including hepatocellular carcinoma in Kyushu (Kumamoto), Japan. HTLV-I seropositivity was determined by ELISA with western blot confirmation. For comparison, the overall seroprevalence rate in 62 000 blood donors from the area was 4.7%. The crude seroprevalence rate of 17.5% among the 40 cases of hepatocellular carcinoma was significantly higher than the comparison rates ($p < 0.001$); however, six of the seven seropositive cases had a history of transfusion. Among 93 cases of liver cirrhosis, a condition which almost always precedes the development of hepatocellular carcinoma, the HTLV-I seroprevalence of 10.8% was also significantly higher ($p < 0.01$), but 6 of the 10 seropositive cases had a history of transfusion. [The Working Group noted that it was unclear whether the higher HTLV-I infection rate in cases was due to disease-related transfusions or whether HTLV-I contributed to the occurrence of hepatocellular carcinoma. The data given are not sufficient to calculate age- and sex-adjusted estimates of relative risk.]

Kamihira *et al.* (1994) examined the prevalence of co-infection with HTLV-I and HCV and HBV in cases of liver disease including hepatocellular carcinoma in blood donors in Nagasaki. Cases included 181 cases of hepatocellular carcinoma seen at Nagasaki University Hospital and 228 cases of either chronic hepatitis or cirrhosis. Control data were obtained from 77 540 local blood donors. HTLV-I positivity was determined by particle agglutination assay and ELISA, with confirmation by western blot if necessary. [The Working Group noted that it was unclear whether positivity was based on either particle agglutination or ELISA or whether all sera were screened by both assays.] HBV status was detected by particle agglutination assays and HCV status by the first-generation ELISA. Among the control data, there was a significant association between HCV and HTLV-I infection (1.9% HCV-positive among 2907 HTLV-I seropositive versus 1.1% among 74 633 HTLV-I seronegative ($p = 0.04$)), but not between HBV and HTLV-I infections ($p = 0.70$). The mean age at hepatocellular carcinoma diagnosis among the 31 patients with HTLV-I antibody (61.5 years) was significantly lower than that of the 112 HTLV-I-seronegative cases (64.8 years; $p = 0.04$).

Okayama *et al.* (1995) examined the effect of HTLV-I co-infection on risk for HCV-positive hepatocellular carcinoma in comparison to HCV-positive chronic hepatitis. The cases included 43 sequentially seen hepatocellular carcinoma patients (33 men and 10 women) in southern Kyushu (Miyazaki), Japan, with a mean age of 62.4 years. The control group consisted of 127 biopsy-proven HCV-positive chronic hepatitis patients (86 men and 41 women) with a mean age of 51.7 years. All subjects were seropositive for HCV antibody and negative for HBV surface antigen. HTLV-I antibody status was determined by the particle agglutination assay, with confirmation by western blot. HCV

antibody status was determined by a second-generation ELISA. The HTLV-I seroprevalence among the cases of hepatocellular carcinoma was 30.2% and that among the chronic hepatitis controls was 9.5%. Among the 41 cases aged ≥ 50 years, 31.7% were HTLV-I carriers compared with 7.3% among the 82 HCV-positive chronic hepatitis patients of the same age ($p = 0.001$). With adjustment for broad age groups, the relative risk for HCV-positive hepatocellular carcinoma associated with co-infection with HTLV-I was 12.8 (95% CI, 3.3–52.3) among men; among women, there was no significant difference (relative risk, 1.3; 0.17–10.1). In this study, the prevalence of history of transfusion was similar among cases (42.9%) and chronic hepatitis controls (38.9%).

Several studies have examined the relationship between HTLV-I infection and human papillomavirus (HPV)-associated gynaecological malignancies (see IARC, 1995).

Miyazaki *et al.* (1991) examined the association of HTLV-I infection with gynaecological malignancies in patients from central Kyushu, Japan. Cases included 226 patients with gynaecological malignancies newly treated between April 1986 and July 1989, excluding those with a history of blood transfusion. The case group included 153 cervical cancer patients, 28 endometrial carcinoma patients, 37 ovarian carcinoma patients and 8 vaginal carcinoma patients. For comparison, the HTLV-I seroprevalence among 6701 healthy women seen at a mass health screening was used. HTLV-I status was determined by both immunofluorescence and ELISA assays. The relative risk for HTLV-I seroprevalence associated with cervical cancer among the 88 women aged ≤ 59 years was 2.9 ($p < 0.005$) and that for older cases was 1.7. Similarly, based on eight cases of vaginal carcinoma, the relative risk was 7.4 ($p < 0.001$). One of the latter cases also had smouldering ATLL. However, for the cases of endometrial and ovarian cancer, there was no association with HTLV-I (relative risks, 0.97 and 0.87, respectively). There was no significant association between HTLV-I status and stage of cervical cancer or the presence of regional node metastases in 59 patients who had primary radical surgery. However, HTLV-I status was predictive of recurrence among the cases of cervical and vaginal cancer combined ($p < 0.05$).

Strickler *et al.* (1995) evaluated the association between HTLV-I infection and the degree of cervical epithelial abnormalities. Cases for this case–control study were 49 outpatients with cervical intraepithelial neoplasia (CIN)-III or invasive carcinoma of the cervix sequentially seen at a colposcopy clinic in Jamaica between March 1992 and August 1993, from whom adequate tissue for analysis was available. Controls were 120 women diagnosed with benign, atypical squamous cells of unknown significance (ASCUS), CIN I or koilocytotic atypia. HTLV-I antibody status was determined by either a whole virus or recombinant gp21 ELISA with western blot confirmation. HPV DNA was detected by PCR, with typing for 11 sub-types (low, intermediate, high risk). As expected, there was a strong association with the detection of HPV DNA: 92.1% of cases were positive versus 25.7% in benign, 50% in ASCUS and 49.2% of the CIN I and koilocytotic atypia control subjects. HTLV-I seropositivity was greater among cases, who had more advanced stage (14.3%) than the controls (2.9%) (age-adjusted relative risk, 3.8; 95% CI, 1.03–14.2).

These case–control studies are summarized in Table 6. Overall, case–control studies of HTLV-I and risk of malignancies other than ATLL are few and may be influenced by selection bias (e.g., use of blood donors as controls). Significant positive associations were found for hepatocellular carcinoma and cancers of the female lower genital tract, which showed associations with HBV and HCV and with HPV, respectively. However, since these viruses are transmissible by similar routes to HTLV-I, the reported associations may be confounded.

2.2.2 *HTLV-II*

The majority of studies investigating an association between HTLV-I and malignancy have used assays which would also detect HTLV-II, and none has reported an association of HTLV-II with malignancy.

3. Studies of Cancer in Animals

During the study of natural retroviral infection in non-human primates, it became apparent that many African and Asian non-human primate species had serum antibodies that cross-reacted with HTLV-I antigens. Prevalence of serum antibodies found in these populations varied from < 10 to > 80% and generally increased with age. African green monkeys (*Cercopithecus aethiops*) and macaque species generally had the highest seroprevalence (Miyoshi *et al.*, 1983; Hayami *et al.*, 1984; Ishikawa *et al.*, 1987; Fultz, 1994). A virus isolated from lymphoid cell lines established from seropositive monkeys was shown by Southern blot analysis of genomic DNA, nucleotide sequence analysis and type-specific synthetic peptide epitopes to be 90–95% homologous to HTLV-I (Komuro *et al.*, 1984; Tsujimoto *et al.*, 1985; Watanabe *et al.*, 1985; Ishikawa *et al.*, 1987; Rudolph *et al.*, 1991) and was designated as simian T-cell lymphotropic virus type I (STLV-I).

3.1 HTLV-I in animal models

3.1.1 *Non-human primates*

Six cynomolgus (*Macaca fascicularis*) and two squirrel (*Saimiri sciureus*) monkeys were infected experimentally with HTLV-I by inoculation with autologous lymphoid cell lines immortalized by and producing HTLV-I. To produce the cell lines, monkey peripheral blood mononuclear cells were co-cultivated with lethally irradiated MT-2 cells producing HTLV-I. All the cell lines had monkey karyotypes, grew continuously and expressed IL-2 and virus-specific proteins of HTLV-I. Specific antibodies against HTLV-I and transformed HTLV-I-infected peripheral blood cells were found in the inoculated monkeys. No neoplastic lesion was detected up to two years after inoculation (Nakamura *et al.*, 1986).

Table 6. Case–control studies of the association of HTLV-I infection with malignancies other than adult T-cell leukaemia/lymphoma

Reference	Cancer site		Cases	HTLV-I+ (%)	Controls	HTLV-I+ (%)	Odds ratio	Comments
Asou *et al.* (1986)	All sites except ATLL		394	15.5	Healthy volunteers	3.0	2.2	Excludes cases with history of blood transfusion
	Liver only		33	15.2	Healthy volunteers	3.0	2.6	
Iida *et al.* (1988)	Liver		40	17.5	Local blood donors	4.7	NG	6/7 HTLV-I$^+$ cases had been transfused
Miyazaki *et al.* (1991)	Cervix	< 59 years	88	10.2	Healthy volunteers	[3.3]	2.9	
		> 60 years	65	16.9	Healthy volunteers	10.2	1.7	
	Ovary		37	2.7	Healthy volunteers		0.87	
	Vagina		8	50.0	Healthy volunteers		7.4	
	Endometrium		28	7.1	Healthy volunteers		0.97	
Kamihira *et al.* (1994)	Liver		181	20.4	Local blood donors	3.8	NG	HTLV-I seropositivity was associated with HCV seropositivity
Okayama *et al.* (1995)	Liver		43	30.2	HCV-positive chronic hepatitis	9.5	12.8 (males) 1.3 (females)	Transfusion prevalence similar in cases and controls
Strickler *et al.* (1995)	Cervix		49	14.3	Benign, ASCUS, koilocytotic atypia or CIN I	3.3	3.8	Cases had invasive carcinoma or CIN III

NG, not given; CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of unknown significance

3.1.2 *Other models*

Adult T-cell leukaemia-like disease was experimentally induced by injection of an HTLV-I-transformed rabbit T-cell line into syngenic rabbits. The cell line was obtained from peripheral blood of a two-month-old virus-infected (B/J × Chbb:HM) F1 rabbit. Fifty per cent of 13 intraperitoneally inoculated newborn rabbits died or were moribund within seven days. Four rabbits surviving for four weeks had detectable cellular cytotoxic activity against transformed cells, increased leukocyte counts and abnormal lymphocytes with convoluted or lobulated nuclei. Histologically, leukaemic infiltrates, probably direct cell-line progeny, were seen in the liver, lung, spleen and mesenteric lymph nodes. The same cell line and dosage killed two syngenic adult rabbits when given intravenously. Three adult virus carriers, 8–15 months of age, were resistant to similar doses (Seto *et al.*, 1988). [The Working Group noted the incomplete description of the lymphoid infiltrates and that this system was not sufficiently characterized to be accepted as a useful model.]

LTR-*tax* transgenic and HTLV-I infected severe combined immunodeficient (SCID) mouse models are discussed in Sections 4.3.2 and 4.3.4 respectively.

3.2 STLV-I in non-human primates

3.2.1 *STLV-I-associated lymphomas* (see also Table 7)

Malignant lymphoma is the most commonly occurring neoplasm in non-human primates and is found most frequently in Old World species (reviewed in Beniashvili, 1989).

Homma *et al.* (1984) detected serum antibodies to membrane antigens of HTLV-I-infected cells in 11 of 13 macaques (*Macaca cyclopis, M. mulatta, M. fascicularis*) with malignant lymphoma or lymphoproliferative disease. In contrast, these antibodies were found in only 7 of 95 healthy macaques of the same colony.

Voevodin *et al.* (1985) reported that, among Sukhumi lymphoma-prone baboons (*Papio hamadryas*), serum antibodies to HTLV-I antigens were found by the indirect immunofluorescence test in 57 of 58 lymphomatous baboons but in only 80 of 177 healthy baboons from the same 'lymphoma-prone' colony. The prevalence of HTLV-I antibodies in baboon populations considered to be 'lymphoma-free' was 5–8%. [The Working Group noted that interpretation of these data was complicated by the introduction of human leukaemic blood into the baboon colony. This blood was not evaluated for viral infection before use (Lapin, 1969). Herpesvirus papio (HVP) was also endemic in the colony.] Later it was shown that monoclonally integrated STLV-I proviral information of rhesus origin was present in the lymphomatous tissue of these baboons (Voevodin *et al.*, 1996).

Srivastava *et al.* (1986) detected antibodies reactive against HTLV-I by several assays, including western blot analysis, in three serum samples collected over a period of approximately four years from a 24-year-old female gorilla (*Gorilla gorilla graueri*) with non-Hodgkin's lymphoma. Morphologically, the neoplasm was diagnosed as a T-cell

Table 7. Lymphoid neoplasia in STLV-I-positive nonhuman primates

Genus, species	Country	No. of animals	Neoplasm	Proviral integration	Comments	Reference
Papio spp.	Georgia	57	Lymphoma	Monoclonal	Rhesus STLV-I$^+$	Voevodin *et al.* (1985, 1996)
Papio spp.	USA	27	Lymphoma (11 with leukaemia)	ND	–	Hubbard *et al.* (1993)
Papio spp.	USA	1	Leukaemia/lymphoma	ND	–	McCarthy *et al.* (1990)
Cercopithecus aethiops	USA	1	Lymphoproliferative disease	Monoclonal	SIV$^+$/STLV-I$^+$	Traina-Dorge *et al.* (1992)
Cercopithecus aethiops	Japan	6	Leukaemia (1) Pre-leukaemic (5)	Monoclonal	STLV-I$^+$	Tsujimoto *et al.* (1987)
Cercopithecus aethiops	Japan	1	Lymphoma	Monoclonal	–	Sakakibara *et al.* (1986)
Cercopithecus aethiops	USA	1	Lymphoma	ND	–	Jayo *et al.* (1990)
Cercocebus atys	USA	3	Lymphocytosis (1) Leukaemia (1) Lymphoma (1)	ND	SIV_{SMM}^+/STLV-I$^+$	McClure *et al.* (1992)
Macaca cyclops *Macaca mulatta* *Macaca fascicularis*	USA	3 5 3	Lymphoproliferative disease	ND	–	Homma *et al.* (1984)
Gorilla gorilla graueri	USA	1	Lymphoma	Monoclonal	–	Srivastava *et al.* (1986)

ND, not detected

histiocytic lymphoma. [The Working Group noted the lack of immunochemical information to confirm the T-cell origin of the neoplasm.] Southern blot analysis of DNA from *Bam*HI-digested neoplastic tissue using a complete HTLV-I genome probe yielded one 10-kb fragment and a 1.05-kb internal fragment common to all HTLV-I isolates. This confirmed that the gorilla was infected with HTLV-I or a closely related virus. The gorilla was also seropositive for cytomegalovirus, Epstein–Barr-like virus and Yaba virus.

Sakakibara *et al.* (1986) reported lymphoma and leukaemia in a wild-caught female green monkey (*Cercopithecus aethiops*) that was very similar to human ATLL. Neoplastic lymphocyte antigens reacted specifically with antibodies to HTLV-I and were $CD2^+$ ($Leu\ 2a^+$), $CD3^-$ ($Leu3a^-$) and negative for surface immunoglobulin.

Spontaneous malignant lymphomas, including 12 cases with leukaemia and lymphoma, were reported in 28 baboons and one African green monkey. All the lymphoma cases were seropositive for HTLV-I antigen, while the prevalence in the 3200-member baboon colony was about 40%. The disease in these monkeys had many similarities to ATLL in humans, including skin involvement, adult onset, generalized lymphadenopathy, hepatosplenomegaly, anaemia, leukaemia, hypercalcaemia, pulmonary involvement and similar histological and immunocytochemical features. Immunohistochemically, 24 of the lymphomas were of T-cell origin, two of B-cell lineage, two could not be identified as B- or T-cell origin and one was not evaluated (Jayo *et al.*, 1990; McCarthy *et al.*, 1990; Hubbard *et al.*, 1993).

McClure *et al.* (1992) found T-cell leukaemia, lymphocytosis and lymphoma, respectively, in three 10–23 year-old sooty mangabeys (*Cercocebus atys*) naturally infected with SIV_{SMM} and STLV-I. Another dual infection of SIV and STLV-I together with a lymphoproliferative disease was observed in an African green monkey (Traina-Dorge *et al.*, 1992).

3.2.2 *Pathological and molecular aspects*

Ishikawa *et al.* (1987) established 11 cell lines of virus-producing lymphoid cells in the presence of IL-2 from five species of STLV-I antibody-positive non-human primates. The cell lines expressed T-cell activation markers and either $CD3^+$ or $CD2^+$, expressed viral antigens that reacted with sera from human ATLL patients and monoclonal antibodies against p19 and p24 of HTLV-I core protein, and produced virus particles with RNA-dependent DNA polymerase activity. DNA from these cell lines contained proviral sequences similar to HTLV-I but with different restriction patterns.

Peripheral blood lymphocyte chromosomal DNA taken from 31 wild-caught captive STLV-I-seropositive African green monkeys was evaluated for proviral integration of STLV-I. One of these monkeys was overtly leukaemic and five were pre-leukaemic. Preleukaemia was diagnosed by finding abnormal lymphocytes in the peripheral blood. The monoclonal integration sites of the proviral genome in these six monkeys indicated proliferation of STLV-I-infected cells. Restriction patterns with *Pst*I and *Sst*I were the same as those for prior isolates from African green monkeys, except that three animals had deletions of one *Pst*I site, suggesting that the virus could be defective in these cases.

Lymphocytes from seropositive monkeys without leukaemic changes did not contain provirus detectable by Southern blot and were polyclonal. The development of ATLL-like disease with monoclonal integration of STLV-I proviral genome indicated that STLV-I has similar leukaemogenicity to HTLV-I (Tsujimoto *et al.*, 1987). [The Working Group noted that the pre-leukaemic diagnosis in five animals was tentative, as abnormal lymphocytes were found in STLV-I-seronegative monkeys, and it is difficult to correlate the occurrence of abnormal lymphocytes with seropositivity.]

Lymphoproliferative disease was diagnosed in an African green monkey with monoclonally integrated STLV-I. STLV-related sequences were identified by Southern blot analysis of DNA extracted from hyperplastic lymphoid tissue. This animal was also infected with SIV and was immunodeficient, as suggested by wasting, cryptosporidial intestinal infection and relatively low levels of $CD4^+$ and high levels of $CD8^+$ lymphocytes (Traina-Dorge *et al.*, 1992). [The Working Group noted that the immunodeficiency diagnosis was questionable.]

Moné *et al.* (1992) established a cell line from a non-Hodgkin's lymphoma of a baboon and detected monoclonally integrated STLV-I proviral DNA, using Southern blot assay and HTLV-I PCR.

An STLV-I rhesus strain (*M. mulatta*) has been characterized in lymphomas from Sukhumi baboons (*Papio hamadryas*). Thirty-seven STLV-I isolates were investigated by PCR which discriminated rhesus-type and baboon-type STLV-I strains. The PCR results were confirmed by DNA sequence data. Partial nucleotide sequences of both STLV-I isolates from lymphomatous baboons were 97–100% homologous to known rhesus STLV-I and 85% homologous to conventional baboon STLV-I. This macaque-to-baboon inter-species transfer of STLV-I may have initiated the outbreak and increased the incidence of lymphoma among Sukhumi baboon colonies (Voevodin *et al.*, 1996).

3.3 Bovine leukaemia virus in sheep and cattle

Bovine leukaemia virus (BLV), HTLV-I, HTLV-II and STLV constitute a unique subgroup within the retrovirus family, characterized by a distinct genetic content, genomic organization and strategy for gene expression (Cann & Chen, 1990; Gallo & Wong-Staal, 1990; Burny *et al.*, 1994; Kettmann *et al.*, 1994). Although BLV is not as closely related to HTLV-I as are the STLVs, much more is known about its pathogenicity and transmission. Therefore the carcinogenicity of BLV is considered here. BLV infection has been eradicated from western European cattle. No evidence of human infection has been documented.

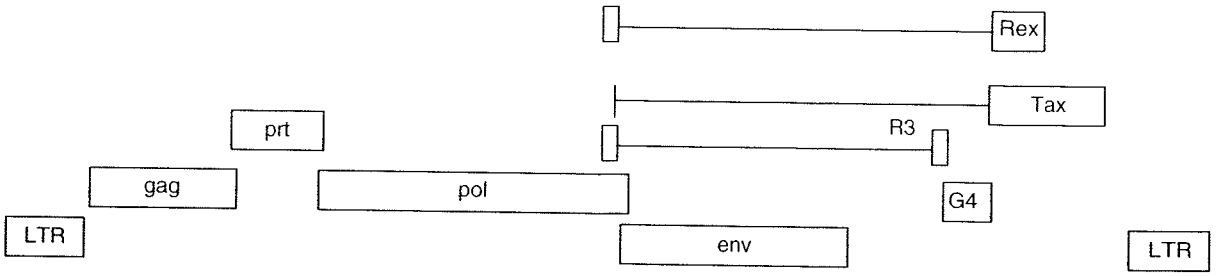
BLV is a transactivating retrovirus recognized as the etiological agent of enzootic bovine leukosis (reviewed in Burny *et al.*, 1994; Kettmann *et al.*, 1994; Schwartz & Lévy, 1994). Presence of the virus has been reported in cattle, sheep, water-buffaloes and capybaras (a South American rodent, *Hydrochoerus hydrochaeris*). Experimental induction of tumours by BLV has been carried out in cattle, sheep and goats (Kettmann *et al.*, 1984), but it is not known if tumours can be induced in water-buffaloes and capybaras.

Replication of these viruses is regulated at the transcriptional and post-transcriptional levels by their own regulatory proteins, notably Tax and Rex. Infection is followed by a long latent period, and only a small proportion of infected individuals develop the terminal neoplastic disease. BLV virions are difficult to identify in neoplastic tissue, but can be found in normal or neoplastic lymphoid cells from BLV-infected cattle or sheep (Jensen *et al.*, 1991; Powers & Radke, 1992). Apart from the difference in host range, a notable difference between BLV and HTLV is that infection by BLV is associated with malignancy of B cells, whereas HTLV affects T cells (Paul *et al.*, 1977).

BLV provirus comprises 8714 bp, making up the following genes (Figure 10):

- *gag*, representing the genetic information for the matrix (p15), capsid (p24) and nucleic acid-binding (p12) proteins;
- *prt*, encoding the viral protease, p14;
- *pol*, the gene for reverse transcriptase and integrase (852 amino acids);
- *env*, the gene for gp51 (268 amino acids) and gp30 (214 amino acids), the external and transmembrane glycoproteins respectively;
- *tax*, the genetic element coding for a transactivator protein, p34 Tax;
- *rex*, the sequence coding for the Rex protein (p18), a molecule involved in the export of genomic RNA from the nucleus;
- R3 and G4, two open reading frames coding for protein products of 44 amino acids and 105 amino acids, respectively, that upregulate BLV expression in the infected host.

Figure 10. Genomic organization of BLV provirus[a]



[a]From Schwarz & Lévy (1994)

Transmission of BLV occurs mainly via transfer of infected lymphocytes by contaminated needles, syringes, etc. Transmission can also occur via milk and *in utero* (Schwartz & Lévy, 1994). Infection can be experimentally transmitted to sheep, goats, pigs, rabbits, monkeys and buffalos (Kettmann *et al.*, 1984; 1994). Tattooing, dehorning, rectal palpation and vaccination procedures can be involved in the transmission of BLV via contaminated blood (Foil & Issel, 1991). Once established, infection is lifelong. The viral load of the inoculum, the time since infection, the efficiency of virus propagation and clonal expansion of BLV-infected cells are key factors determining the number of infected cells at any given time and the probability of neoplastic transformation.

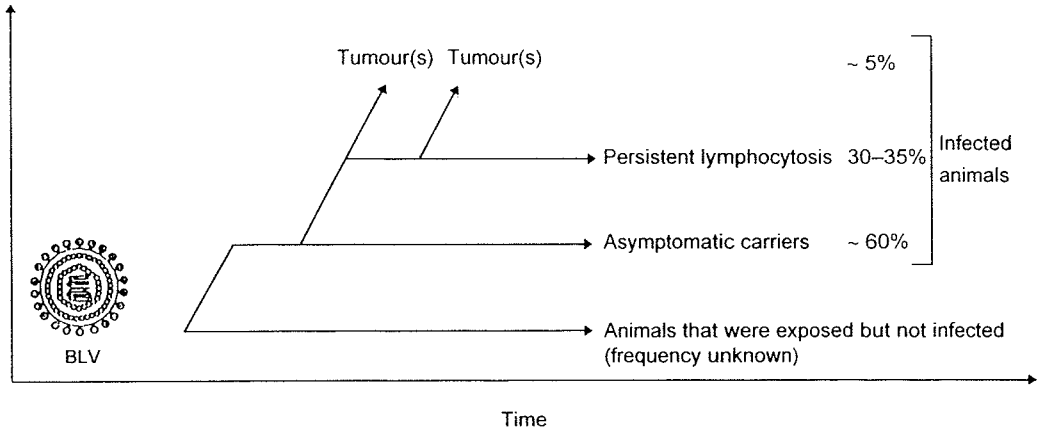
Experimental transmission via biting insects (Foil & Issel, 1991) or intradermal inoculation of BLV proviral DNA into sheep (Willems *et al.*, 1992b; 1993) has been reported.

The presence of BLV within a host is detected by agar-gel immunodiffusion and ELISA. PCR is not useful because viral propagation is slow and the immunogenicity of the virus is high. Seropositivity is detected by gp51 ELISA within two to three weeks after infection (see Kettmann *et al.*, 1994).

3.3.1 *Disorders induced by BLV*

BLV is associated with enzootic bovine leukosis (EBL) (also called bovine leukaemia, bovine lymphoma, bovine lymphosarcoma, bovine malignant lymphoma), which is the most common neoplastic disease of cattle. In terms of the long-term progression of BLV infection, cattle fall into three major groups (see Figure 11). The first and largest of these groups includes those animals (about 60%) that develop a persistent infection and humoral immune response but are normal in every other respect. The second group, representing 30–35% of all BLV-infected cattle, develop persistent lymphocytosis, a disorder that results from polyclonal expansion of the B-lymphocyte population (Kettmann *et al.*, 1980a,b). The third, and much smaller, group (about 5% of infected animals), includes animals that develop leukaemia/lymphosarcoma.

Figure 11. BLV-induced pathogenesis in cattle



From Kettmann *et al.* (1994)

BLV is the etiological agent of not only bovine leukosis but also ovine leukosis. Although less than 5% of BLV-infected cattle go on to develop tumours, all experimentally infected sheep progress to and die in the tumour phase of the disease and after shorter latency periods than cattle (Djilali *et al.*, 1987; Djilali & Parodi, 1989; Gatei *et al.*, 1989).

(*a*) *Cattle*

Three types of EBL are clinically recognized (International Committee on Bovine Leukosis, 1968):

Calf multicentric type: This is characterized by rapidly growing generalized lymph node enlargement with bone marrow involvement. Lymphocytes infiltrate various internal organs, particularly late in the disease.

Adult multicentric type: There is usually lymph node enlargement which may be either symmetrical or asymmetrical. Any tissue in the body may be infiltrated by neoplastic cells and clinical signs depend on the organs or organ systems involved.

Skin leukosis: The first sign may be an urticaria-like change in the skin, especially on the neck, back, rump and thighs. Lymph nodes may be enlarged and the skin lesions may become covered with a thick scab. There may be complete healing of skin lesions and lymph node regression. However, the disease may take a fatal course with typical lymph node involvement and neoplastic-cell infiltration of organs.

(*b*) *Sheep*

The haematological disorders associated with BLV infection are less well defined in sheep. BLV-infected sheep do not develop a persistent lymphocytosis lasting for years, as is seen in cattle. Some infected animals develop lymphosarcoma with no previous haematological disorder (Djilali & Parodi, 1989; Ohshima *et al.*, 1991b). Lymphoid leukaemia and localized lymphosarcoma frequently occur together (Gatei *et al.*, 1989; Ohshima *et al.*, 1991a; Murakami *et al.*, 1994a).

3.3.2 *Pathological and molecular aspects*

(*a*) *Cattle*

BLV persists in peripheral B-lymphocytes (Paul *et al.*, 1977) and the proportion of B-lymphocytes in the peripheral blood of BLV-positive animals increases before any potential increase in the number of circulating lymphocytes (Fossum *et al.*, 1988). Persistent lymphocytosis, when it develops (Figure 11), is a polyclonal expansion of the B-cell population, including BLV-infected and BLV-uninfected cells (Kenyon & Piper, 1977). The ratio of infected to uninfected cells is roughly 1 : 3 to 1 : 4 (Kettmann *et al.*, 1980a). Animals are considered to be in persistent lymphocytosis when successive total lymphocyte counts significantly exceed normal values (International Committee on Bovine Leukosis, 1968).

Studies of the heritability of susceptibility to persistent lymphocytosis led to the conclusion that persistent lymphocytosis is familial (Abt *et al.*, 1970; Lewin & Bernoco, 1986; Lewin *et al.*, 1988). BLV-infected B-cells from cows with persistent lymphocytosis expressed high levels of major histocompatibility complex (MHC) class II, surface IgM and CD5 antigen. Cells expressing CD11b and CD11c, normally expressed by cells of the myeloid lineage were also found. $CD5^+$ cells from BLV-positive cattle, whether with persistent lymphocytosis or not, are activated, cycling cells that respond to IL-2 (Matheise *et al.*, 1992).

In persistent lymphocytosis, proviral DNA is integrated at many genomic sites in BLV-positive circulating leukocytes. In lymphosarcoma, in contrast, proviral DNA is integrated at only one or a few sites. Tumours result from a mono- or oligoclonal proliferation of cells. Integration sites, however, are not conserved from one animal to another. For example, DNAs from 25 independent hamster × bovine somatic-cell hybrids were analysed by Southern blot with probes made of unique cell DNA fragments adjacent to single-copy proviruses from three different bovine tumours. It appeared that these cellular sequences, and thus the respective proviruses, belonged to three different chromosomes in the three tumours examined (Grégoire *et al.*, 1984). No rearrangement of cellular DNA sequences flanking a BLV provirus was found in 28 other BLV-induced tumours (Kettmann *et al.*, 1983). It can be concluded that tumour cells can accommodate proviral DNA sequences at many sites in the genome.

Histological classification of BLV-induced lymphomas was carried out using the National Cancer Institute Working Formulation (Vernau *et al.*, 1992). The distribution of cell types varied much more than in humans. Most of the bovine lymphomas (1067/1198; 89%) were high-grade tumours. The diffuse large-cell type and its cleaved variant comprised 66% of the lymphomas. Follicular tumours were extremely rare (4/1198; 0.3%), in marked contrast to human non-Hodgkin's lymphomas, of which at least 34% are follicular.

Seventeen BLV-induced bovine lymphoid tumours were determined to be of B-cell lineage, based on their immunoglobulin gene rearrangements (Heeney & Valli, 1990). Immunohistochemical studies of bovine lymphosarcomas using a pan-T monoclonal antibody revealed that they all lacked detectable-T cells. Although one tumour failed to react with monoclonal antibodies directed against either T- or B-cell determinants, all others were positive for various B-cell markers. The most frequent phenotype was Ia^+, cytoplasmic IgM^+ or surface IgM^+, with occasional concurrent appearance of the IgG isotype. Cells positive for terminal deoxynucleotidyl transferase (TdT^+) occurred sporadically. It follows that BLV-induced tumours are composed of relatively mature B-cells.

(*b*) *Sheep*

BLV infection in sheep causes increases in circulating B-lymphocytes. Tumours have been described as polymorphic centroblastic lymphosarcoma (Parodi *et al.*, 1982; Parodi, 1987), in which more than 95% of the cells were positive for surface immunoglobulins and MHC class II (Murakami *et al.*, 1994a,b). In one study, coexpression of CD5 and B-cell markers occurred in half of the cases (Dimmock *et al.*, 1990).

Tumours in sheep are monoclonal or oligoclonal expansions of cells carrying proviral information. Most of the tumours tested contained one BLV provirus per genome. In contrast, peripheral blood lymphocytes from aleukaemic sheep and sheep with early lymphocytosis are characterized by polyclonally integrated provirus. Appearance of a clonal subpopulation among cells with polyclonally integrated provirus indicates the onset of leukaemia (Rovnak *et al.*, 1993). Tumours from different sheep harbour the provirus at different sites, suggesting that the mechanisms for tumour initiation are independent of the integration site.

(*c*) *Mechanistic studies*

The mode of cell transformation by BLV remains conjectural. BLV Tax protein probably plays a central role, as it is a major determinant of the replication potential of the virus. The same is true of the protein products of the viral genes R3 and/or G4 (Willems *et al.*, 1994) and of the YXXL motifs of the transmembrane glycoprotein (Willems *et al.*, 1995). Bovine Tax protein complements activated human *ras* p21 in transforming Fischer rat embryo fibroblasts (Willems *et al.*, 1990) and the Tax/*ras* p21 cooperative effect is not hampered by a mutation that abrogates the transactivating activity of Tax protein (Willems *et al.*, 1990; 1992c). It is thus clear that transactivation by Tax and transformation by Tax in collaboration with *ras* p21 are separable functions of the Tax molecule. No data yet demonstrate whether the induction of leukaemia/-lymphoma is affected by cellular oncogenes in cattle, sheep or goats.

Alterations of the *p53* tumour-suppressor gene have been examined in cattle and sheep. No *p53* mutation was found in 10 BLV-induced sheep tumours. In cattle, 5 out of 10 tumours harboured *p53* mutations, whereas only one of seven samples from animals in persistent lymphocytosis showed an alteration of the *p53* gene. It appears that *p53* genomic alterations are not frequently involved in BLV-induced leukaemogenesis in sheep (Dequiedt *et al.*, 1995).

3.3.3 *Vaccination trials*

Protection against retrovirus infection has been achieved in sheep by vaccination with recombinant vaccinia viruses expressing the BLV Env protein (Ohishi *et al.*, 1991; Portetelle *et al.*, 1991). Sheep protected against infection showed a CD4 response to Env peptide 51-70 (Gatei *et al.*, 1993) and a high neutralizing antibody titre (Portetelle *et al.*, 1991). Vaccinated sheep which become infected after challenge with the virus maintain a low viral load for several years without signs of disease.

4. Other Data Relevant to an Evaluation of Carcinogenesis and its Mechanisms

4.1 General observations on retroviral oncogenesis

Oncogenic retroviruses are naturally occurring infections of a large number of vertebrate hosts ranging from fish to humans. Retroviruses cause many types of neoplasm, including leukaemias, lymphomas, mammary and other carcinomas, and sarcomas (Weiss *et al.*, 1985; Levy, 1992–1995).

There are several distinct mechanisms by which animal retroviruses may elicit neoplasms under experimental and natural conditions. An indirect oncogenic effect occurs when neither the malignant cell nor its precursors are infected by the retrovirus. An immunodeficiency virus may permit the appearance of neoplasms as opportunistic events in the same sense as opportunistic infections occur in immunodeficient animals and humans. A directly oncogenic retrovirus inserts its provirus into a cell destined to

become malignant. Such viruses may either cause cancer after a long incubation period, or do so acutely.

The majority of nonhuman retroviruses which are directly oncogenic are C-type viruses with 'simple' genomes containing the long terminal repeats (LTR) and *gag*, *pol* and *env* genes. Such viruses do not carry transforming genes but in the tumour cells, the DNA provirus is integrated adjacent to specific cellular proto-oncogenes. These cellular genes become overexpressed through *cis*-acting promoter or enhancer functions of the LTR. Oncogenesis usually depends on a period of high virus replication. The ectopic activation of the proto-oncogene by the LTR is the crucial viral step in oncogenesis. The viruses found in the tumour cells may be either replication competent or defective variants.

Acutely transforming retroviruses carry viral oncogenes originally derived from cellular oncogenes and which are not required for viral replication. These transduced oncogenes can induce the growth of tumours with a short latency (days in contrast to months or years). Acutely transforming retroviruses are usually replication-defective, as the oncogene is substituted for viral gene sequences in the genome. Their replication relies on replication-competent 'helper' viruses which provide the missing viral proteins. Despite an excess of helper virus, acutely transforming retroviruses are seldom transmitted from one host to another.

The human T-cell leukaemia viruses, together with the related STLV of primates and bovine leukosis virus, differ from both the acutely transforming, oncogene-transducing viruses and the slowly oncogenic, replication-competent viruses in having 'complex' genomes bearing regulatory genes, such as *tax* (Section 1.1.1), required for efficient viral replication. The *tax* gene encodes a protein which also activates the expression of cellular genes (transactivation) and this effect is related to the immortalizing properties of these viruses. The transactivating effect of *tax* probably plays an important role in HTLV-I oncogenesis (Section 4.3.2). While the *tax* genes of both HTLV-I and HTLV-II exert an immortalizing effect on human T-lymphocytes *in vitro* (Section 4.3.2), only HTLV-I has been strongly linked with malignancy on the basis of epidemiological evidence (Section 2). In contrast to the *cis*-acting, slowly transforming retroviruses, the HTLV-I provirus integrates at many different chromosomal sites in ATLL cells in different patients (Yoshida *et al.*, 1984). It therefore appears that the site of integration of the viral genome is not crucial for its oncogenic effect. However, the possibility that certain sites of proviral insertion predispose to malignant transformation as a multistep process requires further investigation.

4.2 Host factors

4.2.1 *The role of the HLA system in HTLV-I infection*

HTLV-I infection can result in no disease, leukaemia or one of a range of inflammatory conditions, but particular genotypes of the virus do not appear to be associated with these different manifestations (Bangham *et al.*, 1996). It is likely that host factors strongly influence the outcome of HTLV-I infection; the HLA system is a major

candidate for such a host factor, because of its association with many diseases, including inflammatory and infectious diseases. The high degree of polymorphism of the HLA system necessitates large sample and control sizes in studies designed to test for a possible HLA association with disease. To date, large enough samples have not been tested to allow a firm conclusion to be drawn about possible association between HLA and HTLV-I infection, or to estimate the strength of an association (relative risk of disease) with confidence. However, there are strong suggestions that genetic factors, including HLA, influence the outcome of HTLV-I infection. Specifically, genetic factors might influence either the proviral load and/or the development of HTLV-I associated disease.

Most of the work examining HLA genotypes in relation to HTLV-I infection has been carried out in the island of Kyushu in southern Japan, where the seroprevalence of HTLV-I exceeds 10%. Furukawa *et al.* (1992) showed that clonal proliferation of HTLV-I-infected T cells (as shown by clonal integration of HTLV-I provirus), which is associated with a high proviral load, is commoner in TSP/HAM patients and their first-degree relatives than in unrelated healthy HTLV-I-seropositive individuals. Usuku *et al.* (1988) examined the HLA types of 27 patients with TSP/HAM, 12 patients with ATLL and healthy asymptomatic controls. They found a predominance of certain haplotypes. In ATLL patients, the haplotype A26Bw62Cw3DR5 appeared to occur in excess, but no statistical correction for multiple comparisons was applied. Sonoda *et al.* (1992) extended these observations, and again found an apparent excess of certain A25 haplotypes in ATLL patients. However, because of the way in which the study was designed, a complete statistical analysis was not made, and so these interesting observations await confirmation.

4.2.2 *Immune surveillance and escape*

(*a*) *Antibodies*

It seems unlikely that antibodies are effective in limiting viral replication in established human HTLV-I infections, because the viral load increases mainly by division of infected proviral-DNA-containing cells (Wattel *et al.*, 1995). However, it appears that the antibody titre reflects the HTLV-I proviral load (Shinzato *et al.*, 1993; Ishihara *et al.*, 1994; Miyata *et al.*, 1995).

(*b*) *T-cells*

The cytotoxic T-lymphocyte (CTL) is the most important antigen-specific element of the immune system for controlling most established viral infections. Kannagi *et al.* (1983, 1984) detected a CTL response specific to HTLV-I in patients with a diagnosis of ATLL. Notably, they reported that the CTL response was detectable only in those patients in whom the ATLL was in remission, and disappeared when the patients relapsed.

It is now clear that there is a very powerful, chronically activated CTL response to HTLV-I in the majority of both TSP/HAM patients (Jacobson *et al.*, 1990; Parker *et al.*, 1992, 1994; Daenke *et al.*, 1996) and healthy carriers of the virus (Parker *et al.*, 1992,

1994; Daenke *et al.*, 1996). The great majority of these CTLs are specific to the Tax protein of HTLV-I. There is evidence that the Tax-specific CTLs select antigenic variants of the Tax protein (Niewiesk *et al.*, 1995) that escape recognition by the patient's own CTLs. The selection process appears to be more efficient in healthy carriers (Niewiesk *et al.*, 1994).

The above evidence suggests that Tax-specific CTLs play a significant part in limiting viral replication, but the precise role of CTLs in protection against HTLV-I-associated diseases, or in the pathogenesis of these conditions, is not yet clear. There appears to be little difference, if any, between healthy HTLV-I carriers and TSP/HAM patients with respect to the chronic activation state, the abundance in peripheral blood, the antigen specificity or the epitope specificity of these CTL.

The observations by Kannagi *et al.* (1983, 1984) suggested that the development of ATLL might be associated with inefficient immune surveillance by CTLs. This would probably be a result of the low expression of the Tax protein by leukaemic cells.

As observed in other viral infections and malignancies, natural killer (NK) cells may also play a part in surveillance of HTLV-I infection and ATLL (see Section 4.3.3).

4.2.3 *Host genetic factors required during the transition to ATLL*

Host genetic factors are thought to be required for the transition from HTLV-I-infection of a cell to ATLL. Chromosomal abnormalities have been described in ATLL, but no specific pattern has been identified. This topic is discussed more extensively in Section 2.1.1.

At the molecular level, mutations in three tumour-suppressor genes, *p53*, *p16* and *p15*, have been identified in ATLL samples and/or HTLV-I-transformed human T-cell lines.

p53 missense mutations have been observed in 17–40% of fresh ATLL samples (Sugito *et al.*, 1991; Sakashita *et al.*, 1992; Yamato *et al.*, 1993) as well as in some HTLV-I-transformed T-cell lines. The aberrant expression of p53 protein, in the presence or absence of p53 missense mutations, has also been noted in a proportion of both fresh ATLL samples and HTLV-I-transformed T-cell lines (Sugito *et al.*, 1991; Reid *et al.*, 1993; Yamamoto *et al.*, 1993). While one report noted a correlation between Tax expression and p53 expression in HTLV-I transformed T-cell lines which lacked p53 mutations, another study did not observe any difference in p53 gene expression, methylation, and chromatin structure between HTLV-I transformed and mitogen-activated human T-cells (Lübbert *et al.*, 1989). In HTLV-I-transformed T-cells, p53 is also functionally impaired, despite an increased expression of the cell-cycle control protein $p21^{waf1/cip1}$ (Cereseto *et al.*, 1996). Thus, p53 mutation and aberrant expression may occur in less than half of ATLL cases and could conceivably play a role in tumour progression. Tax has also been demonstrated to impair $p16^{INK}$ function (Suzuki *et al.*, 1996). Homozygous deletions of the p15 (MTS2) and/or p16 (CDKN2/MTSI) tumour-suppressor genes have been reported in 10/37 (27%) ATLL patients and individual cases suggest a possible association of deletions in the genes and leukaemia progression (Hatta

et al., 1995). Deletion, mutation or aberrant expression of tumour-suppressor genes may thus play a role in the pathogenesis of ATLL.

4.3 Viral factors

4.3.1 *Proviral load and clonal integration of HTLV-I infection*

The epidemiological evidence summarized in Section 2 links HTLV-I with the emergence of ATLL in a small proportion of HTLV-I-infected individuals after a delay of several decades.

The proportion of peripheral blood mononuclear cells (PBMCs) that carry an HTLV-I provirus — the proviral load — is usually between 10 and 100 times higher in patients with HTLV-I associated inflammatory diseases such as TSP/HAM than in healthy carriers of the virus (Yoshida *et al.*, 1989; Kira *et al.*, 1991; Gessain *et al.*, 1990a,b; Kira *et al.*, 1992a,b; Kubota *et al.*, 1993; Mita *et al.*, 1993; Sugimoto *et al.*, 1993), although the ranges overlap. Typically about 10% of peripheral blood lymphocytes are provirus-positive in TSP/HAM patients, and < 1% in healthy carriers of the virus. However, the fact that TSP/HAM and ATLL appear to occur independently suggests that a high HTLV-I proviral load does not necessarily predispose to ATLL. The proviral load in ATLL is largely dependent on the number of leukaemic cells and may be very high. However, no viral genes are expressed in ATLL cells (see below). In BLV infection (Section 3.3), a high virus load early after infection is associated with an elevated risk for development of leukaemia. It will be interesting to determine whether the same is true in HTLV-I infection.

HTLV-I-infected human T-cells show clonal expansion, even in asymptomatic individuals (Furukawa *et al.*, 1992; Wattel *et al.*, 1995). It has been suggested that after infection of human T-cells by HTLV-I and following a few rounds of reverse transcription, a clonal expansion of the infected cells predominates (Wattel *et al.*, 1996). Experiments using inverse or linker-mediated PCR have indeed indicated that HTLV-I proviral copy numbers increase predominantly via mitosis rather than via reverse transcription (Cavrois *et al.*, 1996). These findings may explain the remarkable stability of the HTLV-I genome and the high proviral load present in many HTLV-I infected individuals (Wattel *et al.*, 1995, 1996). The only viral mRNA to be reproducibly detected in PBMCs of HTLV-I-infected people is the mRNA encoding Tax/Rex/p21/Rex (Koralnik *et al.*, 1992b). This could explain the predominance of chronically activated Tax-specific CTLs in these individuals (see Section 4.2.2). In HTLV-I-infected PBMCs, the level of Tax mRNA expression per infected cell is the same in asymptomatic carriers and in TSP/HAM patients, but low or absent in uncultured ATLL samples (Franchini *et al.*, 1984; Furukawa *et al.*, 1995).

Thus, although HTLV-I-infected individuals carry HTLV-I provirus in a significant proportion of clonally expanded T-cell populations, the occurrence of ATLL is comparatively rare (Chen *et al.*, 1995).

4.3.2 *The role of Tax in cellular transformation/immortalization*

Following the discovery of the Tax protein of HTLV-I (Seiki *et al.*, 1983), intense efforts have been made to demonstrate its oncogenic properties *in vitro* and in animal models. These, as well as the possible role of other viral components in the development of ATLL, are reviewed in this section.

(*a*) *Transforming/immortalizing properties of HTLV-I Tax* in vitro

(i) *Immortalizing effects on T-cells in vitro*

In vitro, HTLV-I, as well as its close relative HTLV-II, can clearly cause human T-cells to proliferate continuously (immortalization) and, with time, acquire IL-2 independence (transformation). Co-cultivation of mitomycin-treated or lethally irradiated HTLV-I or HTLV-II producer cell lines with human peripheral blood or cord blood lymphocytes results in the immortalization of mainly $CD4^+$ and, occasionally, $CD8^+$ T-lymphocytes (Miyoshi *et al.*, 1981; Yamamoto *et al.*, 1982; Chen *et al.*, 1983; Popovic *et al.*, 1983). Several lines of evidence suggest that the viral transactivator Tax, encoded by two exons flanking the envelope gene (see Section 1.1.6), is involved in this process. Tax has immortalizing/transforming properties *in vitro:* when transduced into primary human T-cells from adult or cord blood by a retroviral vector (Akagi & Shimotohno, 1993) or a recombinant herpesvirus saimiri (Grassmann *et al.*, 1989, 1992), it is capable of altering their growth properties. Transduction of *tax* into peripheral blood T-cells by a retroviral vector leads to enhancement of the proliferation caused by IL-2 and anti-CD3 antibody (Akagi & Shimotohno, 1993). These *tax*-transduced T-cells are still dependent on IL-2, but do not require periodic restimulation with antigen and feeder cells (Akagi & Shimotohno, 1993). Transduction of cord blood cells with *tax* using a herpesvirus saimiri vector resulted in permanently growing, but still IL-2-dependent, T-cell lines (Grassmann *et al.*, 1989, 1992).

The ability of Tax to immortalize primary human T-cells may be linked to its ability to induce the expression of cellular genes which are normally involved in the early response to mitogenic and antigenic stimuli (Kelly *et al.*, 1992) as well as to a long list of cytokines and cytokine receptors (see below). However, it is possible that other viral and cellular factors contribute to the efficient immortalization of human T-cells by HTLV-I *in vitro*: whereas *tax*-transduced T-cells remain IL-2-dependent, T-cells infected in bulk culture by co-cultivation with HTLV-I producer cell lines lose their IL-2-dependence after extended passage *in vitro*. If co-cultivation is carried out with limiting numbers of HTLV-I producer cells, the resulting transformed T-cell lines can be shown to maintain their dependence on IL-2 for a longer time, and other lymphokines, such as IL-4 and IL-7, can substitute for IL-2 to some extent (Persaud *et al.*, 1995). The constitutive activation of the JAK3 and STAT kinases in HTLV-I infected T-cells could be a crucial step during the acquisition of IL-2 independence: the JAK/STAT pathway is normally required for the downstream signalling triggered by the β- and γ-chain of the IL-2 receptor and by other cytokine receptors (Migone *et al.*, 1995), suggesting that its constitutive activation would lead to IL-2 independence.

Four infectious molecular clones of HTLV-I have recently been reported (Nicot *et al.*, 1993; Kimata *et al.*, 1994; Derse *et al.*, 1995; Zhao *et al.*, 1995), some of which produce HTLV-I capable of stimulating PBMCs. However, only one of these (Zhao *et al.*, 1995) has been used successfully *in vitro* to transform (to IL-2 independence) human peripheral blood T-cells. It is also possible to achieve transformation of human PBMCs *in vitro* with a molecular clone of HTLV-II (Green *et al.*, 1995).

(ii) *Transforming effect of Tax on fibroblast cultures* in vitro

Transfection of *tax* into RAT-1 or NIH 3T3 fibroblasts results in colony formation in soft agar and morphological changes (transformation), and the *tax*-transfected RAT-1 cells are tumorigenic in nude mice (Tanaka *et al.*, 1990). This ability to transform rat fibroblasts is dependent on the CREB/ATF pathway of Tax action (see Section 1.1.6), but does not require interaction of Tax with nuclear factor-κB (NF-κB) (see Section 4.3.3) (Smith & Greene, 1991), a pathway which is predominantly activated by Tax in T-cells. Continuous expression of *tax* is required to maintain the transformed phenotype of RAT-1 fibroblasts (Yamaoka *et al.*, 1992). Fusion of *tax*-transformed rat fibroblasts with normal human fibroblasts results in suppression of the transformed phenotype even in the presence of continued *tax* expression, suggesting the existence of a dominant inhibitory human factor acting downstream of *tax* (Inoue *et al.*, 1994b). Tax has also been shown to immortalize and, in combination with the activated Ha-ras protein, to transform primary rat embryo fibroblasts (Pozzatti *et al.*, 1990). Some naturally occurring sequence variants of Tax which are capable of activating the NF-κB or CREB/ATF pathways and of transforming rat fibroblast cell lines lack the ability to cooperate with *ras* in this manner (Matsumoto *et al.*, 1994).

(*b*) *Tumorigenic properties of* tax *in transgenic mice*

Several groups have generated transgenic mice carrying different parts of the HTLV-I genome. Transgenic mice with the *tax* gene under the control of the HTLV-I LTR (Nerenberg *et al.*, 1987) developed thymic atrophy and mesenchymal tumours (Hinrichs *et al.*, 1987; Nerenberg *et al.*, 1987), proliferation of ductal epithelial cells of the salivary glands (Green *et al.*, 1989b), muscle degeneration (Nerenberg & Wiley, 1989) and adrenal medullary tumours characterized by proliferation of undifferentiated spindle cells (Green *et al.*, 1992). Thymic atrophy was also consistently observed in other lines of mice transgenic for *tax* under the control of the SV40 promoter, the Ig enhancer and the mouse mammary tumour virus (MMTV) LTR (Furuta *et al.*, 1989).

Environmental variables may contribute to tumour formation in LTR-*tax* transgenic mice, as the development of tumours can be delayed by feeding a low-folate diet (Bills *et al.*, 1992). No lymphomas or leukaemias have been seen in LTR-*tax* transgenic mice, which may be related to the fact that the LTR-*tax* transgene was most strongly expressed in muscle, bone and cartilage, brain, pituitary, skin and salivary glands, but less so in lymphoid tissue (Bieberich *et al.*, 1993). However, the use of a Thy-1 promoter to target the *tax* expression to the thymus of transgenic mice also resulted in the formation of fibroblastic tumours accompanied by infiltration of other cell types, as in the case of the LTR-*tax* transgenic mice, but did not lead to lymphoma formation. Nor was any

expansion or phenotypic alteration of circulating lymphocytes or lymphocytes of the thymus or spleen seen in these animals (Nerenberg *et al.*, 1991).

In contrast, transgenic mice carrying the complete pX region (i.e., the genomic region containing open reading frames I, II, III and IV; see Section 1.1.6 and Figure 4) under the control of the granzyme B promoter, targeting the transgene expression to mature T-cells and NK cells, develop large granular lymphocytic leukaemia and solid tumours composed of NK-large granular lymphocytic (LGL)-like cells, which expressed FcγR, Thy 1.2, CD 44 and lacked rearranged T-cell receptor β and γ genes, and neutrophils (Grossman *et al.*, 1995). While the phenotype of these NK-LGL-like cells is clearly different from that of ATLL cells, this experiment supports the transforming potential of Tax in lymphoid cells *in vivo*. The marked neutrophil infiltration of tumours in these animals has also been noted in neurofibromas of LTR-*tax* transgenic mice and may be related to the activation of granulocyte-macrophage colony-stimulating factor expression by Tax (Green *et al.*, 1989b). LTR-*tax* transgenic mice can also exhibit marked splenomegaly and lymphadenopathy, due to a striking increase in the percentage of B-cells in these organs. This expansion of the B-lymphocyte population may also be related to cytokines secreted from *tax*-expressing fibroblastoid tumour cells, which were shown to stimulate B-cell proliferation and IgM production (Peebles *et al.*, 1995). Transforming growth factor β1 (TGF-β1) is overexpressed in several tissues from LTR-*tax* transgenic mice and stimulates the growth of cell lines derived from neurofibromas of these animals, and it has therefore been suggested that this cytokine might be involved in the development of these tumours (Kim *et al.*, 1991). Mammary carcinomas observed in *tax*-transgenic rats also expressed several cytokines, including the granulocyte chemoattractants *Gro* and *MIP-2*, but not TGF-β1 (Yamada *et al.*, 1995). Similarly, the increased bone turnover and skeletal abnormalities of LTR-*tax* transgenic mice may be related to Tax-induced local expression of cytokines (Ruddle *et al.*, 1993). Thus, in addition to a directly transforming effect of Tax are demonstrated by these in-vivo experiments, more indirect mechanisms, involving a variety of cytokines, contribute to tumour formation and may underlie other pathological effects seen in these animals.

The lymphomas described above differ from ATLL in lacking CD4 expression. Lymphomas of a $CD4^+$ phenotype were observed in 70% of bitransgenic mice carrying an LTR-c-*myc* and an Ig promoter/enhancer-*tax* construct. In addition to $CD4^+$, $CD3^+$, $CD8^-$ lymphomas, these animals develop brain tumours of neuronal lineage at very high frequency (Benvenisty *et al.*, 1992). However, the relative contributions of overexpressed c-*myc* and *tax* to tumour development in this model remain unclear.

Transgenic mice carrying the *env* and pX region of HTLV-I [i.e., with the potential to encode the envelope proteins, Tax, Rex, $p21^{rexIII}$, $p12^{I}$, $p30^{II}$, $p13^{II}$; see Section 1.1] under the control of the HTLV-I LTR develop an inflammatory arthropathy resembling human rheumatoid arthritis, in addition to the thymic atrophy, mesenchymal tumours and adenocarcinomas reported in LTR-*tax* transgenic mice (Iwakura *et al.*, 1991, 1994). In addition to increased c-*fos* and c-*jun* expression in the tumours and normal skin and muscle of these animals (Iwakura *et al.*, 1994), a variety of inflammatory cytokines, including IL-1α, IL-1β, IL-6, TNF-α, TGF-β1, interferon-γ and IL-2, as well as MHC genes, are over-

expressed in transgenic joints (Iwakura *et al.*, 1995). This widespread activation of components of the immune system is probably related to the expression of the transgenic construct in many organs, including brain, salivary gland, spleen, thymus, skin, muscle and mammary gland (Iwakura *et al.*, 1994, 1995).

Taken together, the evidence emerging from studies with these different lines of HTLV-I transgenic mice suggests that *tax* has a relatively weak oncogenic effect *in vivo* which is apparent only in transgenic animals with high levels of *tax* expression. Lymphoid cells are not particularly sensitive to the transforming effect of Tax and T-cell malignancies have been found only when a strong, non-HTLV-I-derived, promoter was used, or after simultaneous expression of *tax* and c-*myc*. Some aspects of the pathology induced by *tax in vivo* may be related to the aberrant expression of a variety of lymphokines, resulting in marked neutrophil infiltration of mesenchymal tumours and increased bone turnover.

4.3.3 *Pathways of Tax-mediated transactivation of cellular genes*

The transforming properties of the Tax protein, demonstrated in transgenic mice, transduced T-cells and transfected fibroblasts (see above) are the result of its ability to induce the expression of a wide variety of cellular genes in addition to the HTLV-I LTR (see Table 8). Tax negatively regulates the expression of β-polymerase, a cellular DNA repair enzyme (Jeang *et al.*, 1990), and the tumour-suppressor genes *p53* (Uittenbogaard *et al.*, 1995) and $p16^{INK4A}$ and represses the tumour-suppressor role (Suzuki *et al.*, 1996).

Transcriptional activation by Tax of these various cellular and viral genes requires the presence of specific target sequences in the promoter DNA. Three different such target sequences, the cyclic AMP-responsive element (CRE), the NF-κB binding site and the serum response element (SRE), are known to mediate the Tax-induced transactivation of most of the cellular genes listed above. Additional, so far unidentified, pathways probably account for the activation of a few other Tax-responsive genes.

Modified CREs are present in the HTLV-I LTR within three 21-bp repeat elements, at least two of which are required for Tax-induced transactivation (Fujisawa *et al.*, 1986; Shimotohno *et al.*, 1986). CRE binds members of the bZIP family of cellular transcription factors which include CRE binding protein (CREB) (Zhao & Giam, 1992; Suzuki *et al.*, 1993), CRE modulator (CREM) (Foulkes *et al.*, 1991), activating transcription factor (ATF) (Hai *et al.*, 1989), Tax-responsive element binding protein (TREB) (Yoshimura *et al.*, 1989) and HEB (21-bp binding proteins) (Béraud *et al.*, 1991). Tax activates transcription from the HTLV-I LTR as well as the CRE-containing promoters of the *c-fos*, *c-egr* and nerve growth factor genes by binding to one or several of these transcription factors and enhancing their interaction with the target DNA (Zhao & Giam, 1992) or altering their DNA-binding specificity (Paca-Uccaralertkun *et al.*, 1994). Tax achieves this by binding to the basic domain of bZIP transcription factors (Baranger *et al.*, 1995; Perini *et al.*, 1995), thus enhancing their dimerization (Wagner & Green, 1993) and stabilizing a complex consisting of DNA, bZIP and Tax (Wagner & Green, 1993; Baranger *et al.*, 1995). As part of this process, Tax also alters the relative affinity

Table 8. Tax-activated cellular genes[a]

Interleukin (IL)-related genes	
IL-2Rα	Inoue *et al.* (1986)
IL-1	Sawada *et al.* (1992)
IL-2	Siekevitz *et al.* (1987)
IL-3	Wolin *et al.* (1993)
IL-6	Yamashita *et al.* (1994)
IL-8	Mori *et al.* (1995)
'Housekeeping' genes	
Vimentin	Lilienbaum *et al.* (1990)
MHC class I	Sawada *et al.* (1990)
Growth-factors/hormone genes	
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Miyatake *et al.* (1988)
Nerve growth factor (NGF)	Green (1991)
Transforming growth factor β1 (TGF-β1)	Kim *et al.* (1990)
Tumour necrosis factor α (TNF-α)	Dhib-Jalbut *et al.* (1994)
Tumour necrosis factor β (TNF- β)	Paul *et al.* (1993)
Parathyroid-hormone-related protein	Watanabe *et al.* (1990)
Proenkephalin	Joshi & Dave (1992)
Early response cellular genes	Alexandre *et al.* (1991); Kelly *et al.* (1992)
Cellular oncogenes	
c-*egr*	Fujii *et al.* (1991)
c-*fos*	Fujii *et al.* (1988)
c-*jun*	Fujii *et al.* (1991)
c-*myc*	Duyao *et al.* (1992)
c-*rel*	Li *et al.* (1993)
c-*sis*	Pantazis *et al.* (1987)
Viral promoters	
HTLV long terminal repeat	Sodroski *et al.* (1984); Felber *et al.* (1985)
HIV long terminal repeat	Jeang *et al.* (1988b)
Cytomegalovirus IE enhancer	Moch *et al.* (1992)
SV40 promoter	Fujisawa *et al.* (1988)

[a]Referencing is not exhaustive

of a bZIP protein for different DNA binding sites, thus modifying DNA binding site selection (Perini *et al.*, 1995). This explains the ability of Tax to transactivate a wide range of promoters containing recognition sites for members of the bZIP family. There are, however, subtle differences between the activation of the CRE-related sequences in the HTLV-I LTR and that of cellular CREs: in the case of the viral LTR, Tax binds to unphosphorylated CREB, increases its association with the 21 bp repeats and thus promotes interaction with CREB, an essential component of the transcription factor complex (Chrivia *et al.*, 1993; Kwok *et al.*, 1996). In contrast, Tax does not bind directly to CREB associated with a cellular CRE (Kwok *et al.*, 1996), and phosphorylation of CREB, which is required for its normal activation of cellular CRE-containing promoters

and interaction with CREB (Chrivia *et al.*, 1993), is also necessary for the activation of these cellular promoters by Tax. Rather, by also binding to CREB, Tax promotes its interaction with phosphorylated CREB associated with a cellular CRE (Kwok *et al.*, 1996). Thus, for activation of the viral LTR, Tax is able to bypass a normal control mechanism of this pathway, whereas this control step is still operative in the case of Tax-activated cellular genes.

In a related manner, Tax binds to all members of the NF-κB family of transcription factors to activate transcription (Suzuki *et al.*, 1994). The NF-κB binding site is present in several genes known to be activated by Tax, such as those encoding IL-2Rα, GM-CSF, TNF-β and the HIV LTR. In addition to binding to NF-κB in the nucleus, Tax also interacts with the NF-κB pathway at an earlier, cytoplasmic stage, in a completely different manner. Tax complexes with two proteins, I-κBα and I-κBγ, that are inhibitors of NF-κB. I-κB proteins normally bind to members of the NF-κB family in the cytoplasm and prevent their entry into the nucleus. Following stimulation of cells, I-κB proteins are phosphorylated and the NF-κB/I-κB complex dissociates, allowing the free NF-κB to enter the nucleus. Tax has been shown to bind to I-κBα and I-κBγ and it causes dissociation of NF-κB/I-κB complexes, thus increasing the turnover of NF-κB and its import into the nucleus (Hirai *et al.*, 1994; Suzuki *et al.*, 1995). As in the case of members of the CREB/ATF family, binding of Tax thus mimics the effect of phosphorylation and thus interferes with physiological control mechanisms of these different pathways.

The third target sequence known to be involved in Tax-mediated activation of cellular genes is the SRE. An SRE is found in the promoters of early response genes known to be activated by Tax (Kelly *et al.*, 1992) and interacts with the transcription factor SRF. Tax binds to SRF, including unphosphorylated SRF, and the SRF/Tax complex activates transcription (Fujii *et al.*, 1992).

An additional Tax-responsive sequence, TRE-2, is present in the HTLV-I LTR. TRE-2 alone is not sufficient to mediate a Tax response, but can do so in the presence of one single 21-bp element (Marriott *et al.*, 1990). A 36-kDa zinc finger protein, termed TIF-1 or THP and related to the GLI family of proteins, interacts with TRE-2 (Marriott *et al.*, 1990; Tanimura *et al.*, 1993). Thus, cooperative binding of a CREB/ATF protein (binding to CRE in the 21-bp element) and THP may be required for Tax-mediated activation of this target sequence.

Thus, the pleiotropic effect of Tax on at least three different enhancer sequences is explained by its ability to interact with a variety of different transcription factors or inhibitors. Binding of Tax to these proteins may substitute for modifications such as phosphorylation or dimerization which normally occur in these proteins as a result of intracellular signalling. Different regions in Tax are required for the activation of individual pathways and mutants with specificity for individual pathways have been designed (Smith & Greene, 1990, 1991). There is also evidence that extracellular Tax, released from infected cells, may induce NF-κB-site-containing promoters, such as the IL-2Rα or TNF-β promoter, and thus induce the activation of uninfected cells (Lindholm

et al., 1992; Marriott *et al.*, 1992). However, a role of extracellular Tax in the pathogenesis of ATLL, over and above that of Tax produced within infected cells, is uncertain.

In addition to its role in cellular activation, Tax may be involved in increasing the likelihood of DNA damage in infected cells, possibly by increasing DNA instability (Saggioro *et al.*, 1994) and/or through its inhibitory effect on the expression of the repair enzyme, β-polymerase (Jeang *et al.*, 1990).

4.3.4 *Differences between HTLV-I-transformed T-cells and ATLL cells*

Although the experiments summarized above indicate that *tax* has some transforming potential *in vitro,* as well as *in vivo*, it is clear that HTLV-I-transformed T-cell lines, or T-cells transduced with *tax*, are not representative of ATLL.

Whereas HTLV-I-transformed T-cell lines (either cell lines obtained by co-cultivation of irradiated HTLV-I producer cell lines with fresh human primary T-cells, or non-ATLL cells grown from HTLV-I infected individuals) express viral mRNAs *in vitro*, cell lines originating from ATLL do not (Maeda *et al.*, 1985; Imada *et al.*, 1995). Early experiments suggested that ATLL cells *in vivo* also do not express HTLV-I mRNAs (Franchini *et al.*, 1984). While some expression of viral mRNA in fresh ATLL samples has been seen using RT-PCR (Berneman *et al.*, 1992a; Koralnik *et al.*, 1992b), it is unclear whether this occurred in ATLL cells or other HTLV-I infected T-cells. In-situ hybridization suggested some expression of *tax* mRNA in ATLL cells (Setoyama *et al.*, 1994). However, ATLL-derived cell lines which engraft in SCID mice show no, or reduced, expression of viral mRNAs (Imada *et al.*, 1995).

Leukaemic cells from ATLL patients do not usually grow in the presence of IL-2 (Maeda *et al.*, 1985), but occasionally ATLL cells have been found to respond to IL-2, and grow as permanently IL-2-dependent cell lines, suggesting that at some stage during their development ATLL cells require IL-2 to proliferate (Maeda *et al.*, 1985, 1987).

Primary cultures of ATLL cells, as well as ATLL-derived cell lines, can grow in SCID mice to form tumours with the same phenotypic profile and HTLV-I integration patterns as the ATLL samples from which they were established (Feuer *et al.*, 1993; Kondo *et al.*, 1993; Imada *et al.*, 1995). While uncultured HTLV-I-infected T-cells from a few asymptomatic individuals and those from about one third of TSP/HAM patients will persist in SCID mice, they do not form tumours (Feuer *et al.*, 1993). In contrast to ATLL cells or cell lines, HTLV-I-transformed T-cell lines not derived from ATLL cells will only grow in SCID mice which have been pretreated with antibodies to asialo GM1 (Ishihara *et al.*, 1992; Feuer *et al.*, 1995) to reduce NK cell activity. However, this distinction may not be absolute: untreated animals can be successfully engrafted using increased numbers of an HTLV-I-transformed, non-leukaemic cell line (Ohsugi *et al.*, 1994), while blocking of NK function with monoclonal antibody TM-β1 or the β-chain of the murine IL-2 receptor may enhance the rate of engraftment of fresh ATLL cells. However, taken together, these reports suggest that ATLL cells have a higher tumorigenic potential *in vivo* than HTLV-I-transformed T-cell lines because of their ability to evade NK-mediated cell lysis (Feuer *et al.*, 1995).

Thus, infection of T-cells with HTLV-I may provide some proliferative advantage and oligoclonal expansion, probably related to the pleiotropic activating properties of *tax*. NK-cell activity as well as CTL activity (see Section 4.2.3) may play an important role in limiting the expansion of HTLV-I-infected T-cells at this stage, and progression to ATLL requires a number of additional events. Whereas HTLV-I producer T-cell lines express high levels of the adhesion molecules LFA-1, LFA-3 and ICAM-1, ATLL-derived cell lines show reduced expression of these surface markers (Fukudome *et al.*, 1992). As these molecules play an important role in the recognition of tumour cells by the immune system, it is conceivable that their reduced expression on ATLL cells may facilitate their escape from immunosurveillance. At present, there is no convincing evidence that variation in viral sequences (see Section 4.2.3) will allow the emergence of more 'leukaemogenic' clones of HTLV-I-infected cells.

4.3.5 *The role of other viral and host cell proteins in lymphocyte stimulation and leukaemogenesis*

Apart from Tax, the HTLV-I envelope protein and the recently described $p12^{I}$ protein have been investigated with regard to their potential roles in T-cell stimulation and/or leukaemogenesis. Purified HTLV-I viruses have been reported to stimulate human T-cells via the HTLV-I envelope protein and a CD2/LFA-3-dependent pathway (Gazzolo & Duc Dodon, 1987; Duc Dodon *et al.*, 1989), but the interpretation of this phenomenon remains controversial. Recombinant HTLV-I envelope protein, expressed in a vaccinia virus vector (Cassé *et al.*, 1994) does not induce T-cell proliferation. Whereas a $(YXXL/I)_2$ signalling motif in the cytoplasmic domain of the BLV envelope protein mediates activation of B-lymphocytes *in vitro* (Beaufils *et al.*, 1993), and is required for efficient replication *in vivo* (Willems *et al.*, 1995), the cytoplasmic domain of the HTLV-I envelope has only a truncated (YXXL) motif which appears functionally inactive (Beaufils *et al.*, 1993).

Several adhesion molecules, such as LFA-3, ICAM-1, LFA-1, and the cell surface markers CD28, CD69 and CD5 show increased expression on the surface of HTLV-I-infected (Fukudome *et al.*, 1992; Imai *et al.* 1993) or *tax*-transfected (Chlichlia *et al.*, 1995; Tanaka *et al.*, 1995) cells. Antibodies to CD2 and LFA-3 inhibit the mitogenic activity of HTLV-I-infected T-cell lines (Kimata *et al.*, 1993) and the spontaneous proliferation of PBMCs from HTLV-I-infected asymptomatic carriers or TSP/HAM patients (Höllsberg *et al.*, 1992; Wucherpfennig *et al.*, 1992), suggesting that these molecules contribute to the process of proliferation.

Contrary to this conclusion, results obtained with both the SCID model (see above) and the rabbit model suggest that the potential of HTLV-I-infected cell lines to stimulate lymphocyte proliferation *in vitro* does not necessarily correlate with their leukaemogenic potential *in vivo*. An experiment reported by Leno *et al.* (1995) suggests that the leukaemogenic potential of an HTLV-I-infected T-cell line could be linked to its ability to induce apoptosis, which was demonstrated in thymic cells *in vivo* and peripheral blood T-cells *in vitro,* rather than its ability to induce T-cell stimulation, and that this phenotype is due to a cellular, rather than viral, factor. However, in another report (Seto

& Kumagai, 1993), the leukaemogenic potential of individual cell lines in (B/J × Chbb:HM) F1 rabbits did correlate with their ability to induce leukocytosis *in vivo* in the parental Chbb:HM rabbit strain and this phenotype seemed to be linked to the surface expression of a cellular 65 kDa glycoprotein, the precise role of which remains to be established. While these experiments may help to identify cellular factors promoting the growth of HTLV-I-transformed cell lines in rabbits, they do not necessarily reflect events occurring in human ATLL.

The Tax protein itself has been shown to induce apoptosis in Jurkat cells (Chlichlia *et al.*, 1995), in particular when Tax-expressing Jurkat cells were stimulated via the T-cell receptor. *Tax*-transfected RAT-1 cells are also prone to apoptosis via a BCL-2-dependent pathway when cultured in the absence of serum (Yamada *et al.*, 1994). In RAT-1 cells, *tax* induces apoptosis less efficiently than the cellular oncogenes c-*myc* and c-*fos* and through a different pathway (Fujita & Shiku, 1995). The ability of Tax to induce apoptosis is probably related to its pleiotropic effect on cellular promoters (see above), and reflects an increased susceptibility of activated cells to undergo apoptosis in the absence of essential stimuli. These experiments may not explain the observations reported by Leno *et al.* (1995).

The $p12^{I}$ protein of HTLV-I (Koralnik *et al.* 1992b, 1993) has been shown to cooperate with the E5 protein of bovine papilloma virus in the transformation of C127 mouse cells (Franchini *et al.* 1993) and may thus have oncogenic properties. $p12^{I}$ and E5 share some structural similarity: both proteins localize to the cellular endomembranes and interact with another very hydrophobic protein, the 16 kDa subunit of H+ vacuolar ATPase (Schlegel *et al.*, 1986; Goldstein *et al.*, 1991; Franchini *et al.*, 1993). Both E5 and $p12^{I}$ interact with distinct growth factor receptors. E5 activates the platelet-derived growth factor receptor (Petti *et al.*, 1991; Goldstein *et al.*, 1994) and $p12^{I}$ specifically interacts with the β and γ, but not the α chains of the IL-2R (Mulloy *et al.*, 1994). Possibly, binding of $p12^{I}$ to the IL-2R chains could alter the receptor signalling by inducing their cytoplasmic juxtaposition, an event thought to be crucial in kinase activation and IL-2 signalling (Nelson *et al.*, 1994). In this regard, it is noteworthy that constitutive activation of STAT and JAK3 kinases has been demonstrated in HTLV-I-transformed T-cells (see Section 4.3.2). In fact, constitutive activation of the IL-2R signalling pathway is correlated with IL-2 independence (Migone *et al.*, 1995). The DNA sequence of the HTLV-I $p12^{I}$ gene from 21 HTLV-I positive individuals (7 healthy carriers, 8 TSP/HAM and 6 ATLL) has been found to be highly conserved (Franchini, 1995).

However, the precise role of $p12^{I}$ in T-cells is not yet understood. $p12^{I}$ is not required for the transformation of cord blood lymphocytes *in vitro* (Ratner *et al.*, 1985) and is dispensable for *tax*, *rex* or envelope expression *in vitro* (Roithmann *et al.*, 1994).

In proviral DNA extracted from ATLL, the genes encoding $p13^{II}$ and $p30^{II}$ appear to be subject to frequent mutations leading to premature translational termination codons, suggesting that these proteins might not be essential in maintaining disease (Berneman *et al.*, 1992b; Chou *et al.*, 1995).

4.3.6 *Differences between HTLV-I and HTLV-II*

As discussed in section 2.1, HTLV-I is associated with human leukaemia whereas HTLV-II is not. Section 1.1.7 summarized the differences in genomic structure between HTLV-I and HTLV-II.

It is unlikely that there is a functional homologue of HTLV-I $p12^{I}$ in HTLV-II, but deletions in the region between the HTLV-II *env* gene and the second *tax* exon, which would eliminate expression of any potential homologue of HTLV-I $p12^{I}$, $p13^{II}$ or $p30^{II}$, have no effect on virus production, envelope function or transforming potential *in vitro* (Green *et al.*, 1995). The effect of disrupting the G4 and R3 reading frames of BLV, located in a similar region of the BLV genome but of only limited similarity to HTLV-I $p12^{I}$, $p13^{II}$ or $p30^{II}$ (Alexandersen *et al.*, 1993), is discussed in Sections 1.1.7 and 3.3. In conclusion, it is not clear whether any of the small accessory proteins found only in HTLV-I, e.g., $p21^{I}$, is responsible for the leukaemogenic properties of HTLV-I in humans, and the precise roles of HTLV-I $p12^{I}$, $p13^{II}$ and $p30^{II}$ during in-vivo leukaemogenesis remain to be established.

It is also conceivable that as yet unidentified minor differences in the in-vitro transforming potential between HTLV-I and HTLV-II might translate into a weak oncogenic effect *in vivo* (for example, a long latency period for leukaemia development) for HTLV-I but not for HTLV-II.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Human T-lymphotropic viruses (HTLV-I and HTLV-II), the only known human *oncornavirinae*, have distinct genetic and structural features. Both HTLV-I and HTLV-II are complex retroviruses. Their genomes encode structural core and envelope proteins, regulatory proteins (Tax and Rex) and several additional proteins which may play an important role in the pathogenesis of the HTLV-I-associated diseases. Several related viruses (known as simian T-lymphotropic viruses; STLVs) have been identified in African and Asian non-human primates, and such primates appear to have been the original sources of the human retroviruses.

Serological detection of specific reactivity to Gag and Env HTLV-I or HTLV-II antigens, confirmed if necessary by western blot, is indicative of current infection. HTLV-I and HTLV-II infection can also be confirmed by amplification of viral sequences by polymerase chain reaction (PCR) from peripheral blood mononuclear cells. Three major clades of HTLV-I with distinct geographical distribution have been distinguished by PCR and sequencing or by restriction fragment length polymorphism. A higher prevalence among women, particularly over the age of 50 years, has been observed in highly endemic areas.

Three modes of transmission have been described for HTLV-I and HTLV-II: mother-to-child transmission, mainly due to breast-feeding beyond six months, sexual trans-

mission predominantly from men to women and transmission by transfusion of cellular blood products and through intravenous drug use.

HTLV-I prevalence varies widely worldwide, with high levels in diverse geographic areas: i.e., southwest Japan, the Caribbean basin, parts of South America, Central and West Africa and parts of Melanesia. Clusters of especially high endemicity occur within these areas. HTLV-I remains endemic among emigrants from these areas.

It is estimated that worldwide between 15 and 20 million individuals are infected by HTLV-I.

Independent of the background of HTLV-I seroprevalence, geographical and ethnic differences in the prevalence of tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM; a major HTLV-I-associated disease) have been reported. This is a chronic spastic myelopathy that preferentially affects middle-aged women. TSP/HAM may develop shortly after transfusion-acquired HTLV-I infection. Other inflammatory conditions associated with HTLV-I are uveitis, infective dermatitis, polymyositis, alveolitis, arthritis, thyroiditis and Sjögren's syndrome. Various combinations of these conditions may co-exist in the same patient and are often found in patients with TSP/HAM. HTLV-I-infected individuals may have impairment of the immune system, and some have reduced ability to clear *Strongyloides stercoralis*.

HTLV-II is endemic in several African pygmy and Amerindian populations and is epidemic among intravenous drug users in the Americas and parts of Europe. HTLV-II has not been clearly associated with any non-neoplastic human disease.

Control and prevention of HTLV-I and HTLV-II infection depend on reduced transmission by the three major routes: perinatal, sexual and parenteral. Perinatal transmission has been greatly reduced in Japan by avoidance of prolonged breast-feeding. Passive and active immunization is effective in animal models but no preventive vaccine is available for humans. A number of countries have introduced universal screening of blood donors to prevent transmission of HTLV-I and HTLV-II and in Japan a decline in the incidence of post-transfusion TSP/HAM has been demonstrated.

5.2 Human carcinogenicity data

Adult T-cell leukaemia/lymphoma (ATLL) occurs almost exclusively in areas where HTLV-I is endemic, such as Japan, the Caribbean and West Africa. Cases of ATLL described in Europe and the United States have mostly been in immigrants from HTLV-I endemic regions or their offspring. Evidence of HTLV-I infection was originally found in at least 90% of patients with ATLL in endemic regions. Subsequently, HTLV-I has become part of the diagnostic criteria for ATLL. In ATLL, the virus is clonally integrated into the tumour cells. ATLL develops in 2–5% of HTLV-I -infected individuals. Infection early in life appears to be important for the development of ATLL. No environmental cofactor promoting the progression to ATLL has so far been identified.

HTLV-I has been associated with non-ATLL cutaneous T-cell malignancies by a few investigators, but most studies have not found an association. Difficulties in distinguishing cutaneous T-cell lymphomas from ATLL may have contributed to these incon-

sistent findings. Some investigators have detected HTLV-I genome sequences in HTLV-I and HTLV-II-seronegative patients with cutaneous T-cell lymphomas, but this has not been confirmed by others.

HTLV-II antibody has been reported in a few patients with large granular lymphocyte leukaemia, but prevalence surveys and a lack of clonal integration of the virus have not supported an association.

Several case–control studies have found an association between HTLV-I seroprevalence and tumours of the vagina, cervix and liver, but confounding effects and bias could not be excluded.

5.3 Animal carcinogenicity data

In the few studies on HTLV-I infection of animals, no neoplastic disease was demonstrated.

While neoplastic disease has not been induced experimentally in non-human primates by infection with STLV-I, there is strong evidence that 'natural' infection with STLV-I is associated with lymphoid neoplasia in non-human primates. The following evidence supports this hypothesis: lymphoma is the most common malignancy in Old World non-human primates; STLV-I is endemic in Old World non-human primates; the disease in monkeys is very similar to ATLL; STLV-I is very similar biologically, morphologically, physicochemically and molecularly to HTLV-I; and STLV-I has the ability to activate and immortalize lymphocytes in culture. Monoclonally integrated provirus has been identified in all neoplastic tissues from STLV-I-infected non-human primates that have been evaluated.

Bovine leukaemia virus, which belongs to the same family as HTLV-I, is a good model for the study of lymphomas induced by viruses with *tax* and *rex* genes. This virus induces lymphomas in approximately 5% of infected cattle and in all experimentally infected sheep. Unlike HTLV-I-associated lymphomas in humans, all tumours are of B-cell origin.

5.4 Molecular mechanisms of leukaemogenesis

HTLV-I, as well as HTLV-II, is capable of immortalizing human and rabbit T-cells *in vitro*. Transfection of HTLV-I *tax* alone immortalizes and transforms primary human T-cells and transforms cells of fibroblastoid lineage. In transgenic models, HTLV-I *tax* under the control of HTLV-I long terminal repeat induces tumours of mesenchymal origin, whereas lymphomas have so far only been obtained by using a granzyme B promoter to control *tax* expression, or by producing mice transgenic for both c-*myc* and *tax*. Tax activates the expression of several cellular genes which are themselves involved in the control of cell proliferation. Tax achieves this pleiotropic effect by interfering with at least three different classes of transcription factors, at either nuclear or cytoplasmic levels. However, HTLV-I transformed cell lines, although capable of inducing lymphomas in severe combined immunodeficient mice (SCID) under certain conditions, are different from ATLL cells, for the development of which subsequent cellular changes are

required. In keeping with this scenario, clonally expanded HTLV-I-infected T-cell populations can persist *in vivo* for long periods of time without progression to leukaemia. While *tax* is expressed in non-neoplastic T-cell populations, its expression is lost in ATLL cells.

Observations made in *tax*-transgenic mice suggest that cytokines secreted by *tax*-expressing cells are responsible for some aspects of the pathologies observed in these animals; whether this applies to the pathogenesis of ATLL in humans is uncertain. The expression of *tax* during the early stages of leukaemogenesis may interfere with mechanisms of DNA repair by reducing the expression of β-polymerase and *p53*, and increasing chromosomal instability.

HTLV-I and HTLV-II have similar transforming properties *in vitro*. HTLV-I is associated with leukaemia, whereas HTLV-II is not. HTLV-I and HTLV-II differ in some of their small accessory proteins. The role of some of these HTLV-I encoded viral proteins, in particular the small accessory protein p12[I], during the early stages of leukaemogenesis is still uncertain, but in-vitro experiments suggest a possible involvement. There is no indisputable evidence that these accessory proteins are expressed in ATLL cells.

Cellular alterations required during the transition from an HTLV-I-infected T-cell to a malignant ATLL cell are largely undefined, but constitutive activation of signal transduction pathways may play a role. Mutations in several tumour-suppressor genes occur in some ATLL samples and HTLV-I-transformed cell lines and may play a role during tumour progression.

Cytotoxic T-cell (CTL) immunity is directed mainly against the Tax protein and there is evidence that CTLs play a role in killing HTLV-I expressing T-cells, but not ATLL cells as these do not express *tax*. The role of natural killer cells in human HTLV-I infection remains to be established, although such cells limit the growth of HTLV-I transformed human cells in immunodeficient mice. Studies in Japan suggest an association of certain human leukocyte antigen (HLA) haplotypes with TSP/HAM and ATLL. Different genotypes of HTLV-I do not appear to be associated with different diseases.

5.5 Evaluation[I]

There is *sufficient evidence* in humans for the carcinogenicity of HTLV-I.

There is *inadequate evidence* in humans for the carcinogenicity of HTLV-II.

Overall evaluation

HTLV-I is *carcinogenic to humans (Group 1)*.

HTLV-II is *not classifiable as to its carcinogenicity to humans (Group 3)*.

[I]For definition of the italicized terms, see Preamble, pp. 22–25.

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