Editorials

HTLV-II Infection in the Western United States

RETROVIRUSES are the first known transmissible oncogenic agents. Peyton Rous recognized the first oncornavirus at the turn of the 20th century, when he identified a filterable agent that caused transmissible sarcomas in chickens.[1] The discovery of human T-cell leukemia or lymphoma virus type I (HTLV-I) represented the culmination of a prolonged and frustrating effort to identify a human counterpart to oncogenic retroviruses of birds and rodents. This retrovirus was first isolated from a patient with a cutaneous T-cell lymphoma.[2]

Human T-lymphotropic virus type I has properties that render it distinct from either of the two previously described RNA tumor virus groups. Like the chronic RNA tumor viruses, HTLV-I induces a clonal malignant neoplasm (adult T-cell leukemia or lymphoma) after prolonged latency. Like the acute RNA tumor viruses, HTLV-I unilaterally transforms cells in vitro to a malignant phenotype. These novel properties of HTLV-I can be ascribed, in part, to a weakly oncogenic replicative gene known as *tax*.[3] A simian version of HTLV-I, known as STLV-I, is widespread in Old World primates.[4]

By the mid-1980s, it was appreciated that HTLV-I was also responsible for a chronic, debilitating paralytic illness known as tropical spastic paraparesis or HTLV-I-associated myelopathy (TSP/HAM).[5,6] The collective risk of adult T-cell leukemia or lymphoma or TSP/HAM in HTLV-I-seropositive patients is low but not negligible. Depending on the age at which HTLV-I is contracted, the risk of either a fatal malignant disorder or progressive neurologic disease developing is about 2% to 6%.[3]

The endemism of HTLV-I is highly focal. High seroprevalence is found in southwestern Japan, in regions populated by the descendants of west African slaves (the Caribbean, Brazil, the southeastern United States), in sub-Saharan Africa, and in Iranian Jews.

In late 1988, the United States Food and Drug Administration (FDA) approved an enzyme-linked immunosorbent assay to screen blood donors and others for HTLV-I antibodies.[7] Screening was instituted immediately by all US blood banks. Western blot confirmatory assays were developed, although none are yet FDA-approved.[8,9] A wealth of seropositive blood donors was soon identified. Epidemiologic correlates to HTLV-I seroprevalence were discovered. Injection-drug users, certain ethnic minorities, and transfusion recipients (but not homosexual men) were found to have an increased risk for HTLV-I.

There was already a fly in the ointment. Workers were noticing two distinct and specific Western blot banding patterns among donors considered to be HTLV-I-seropositive.[8] One pattern, similar to that seen in known HTLV-I-seropositive persons in Japan and the Caribbean, predominated in the eastern United States. Another pattern was predominant in the West. Some investigators considered that this pattern could be due to HTLV-II, a relative of HTLV-I. At first this seemed unlikely. As of 1989, only 7 persons were known to be infected with HTLV-II.

Using the polymerase chain reaction, researchers showed that HTLV-II was not rare and obscure, but was in fact the predominant retrovirus in "HTLV-I"-seropositive users of injection drugs.[10] This surprising finding was confirmed in subsequent studies of western US blood donors.[11] Most seropositive western blood donors were found to be infected with HTLV-II. By contrast, seropositive blood donors from the eastern states are usually infected with HTLV-I.[11,12] Most HTLV-I-seropositive donors had a link to a known area of endemic HTLV-I infection, such as Japan.

What, then, was the source of the western focus of HTLV-II? This remains unknown. The virus comes in two distinct variants, known as HTLV-IIa and -IIb.[13] These two viruses differ by 3% to 4% at the nucleotide sequence level, translating to a difference of but 1.5% to 2% at the protein level. Although the difference is small, the HTLV-IIa and -IIb viruses represent highly discrete and distinctive forms of HTLV-II. There are no intermediate forms. Both forms of HTLV-II can be identified among contemporary injection-drug users.[13] The source of HTLV-II must thus encompass both forms if western HTLV-II endemism is indeed to be ascribed to a single source.

Of those groups with no identifiable parenteral risk for HTLV infection, New World Indians have the highest HTLV-II prevalence.[14-16] The highest HTLV-II prevalences by far occur in certain remote Indian tribes.[16] New World Indian groups appear to be host to both HTLV-IIa and HTLV-IIb.[17] Blood donation is common among members of some of these tribes. Such donations, made before blood banks instituted HTLV-I antibody screening, have resulted in the transmission of HTLV-II.[3] Although some unexplained African foci of HTLV-II exist, it appears that HTLV-II is essentially a New World counterpart to HTLV-I. That concept is strengthened considerably by the recent discovery that New World monkeys are host to an HTLV-II-like simian virus known as STLV-II.[18]

The findings of the study by Hanne Thiede, DVM, MPH, and colleagues reported elsewhere in this issue of the journal, offer additional support for the concept of an old, widespread, and entrenched HTLV-II endemic focus in injection-drug users.[19] Other studies have shown that HTLV-II-infected persons have been present among urban injection-drug users since at least the mid-1970s.[20] With seroprevalences that dwarf those of the human immunodeficiency virus (HIV) and that increase with age, the King County study suggests that HTLV-II is endemic and mature in Washington State injection-drug users. If anything, the authors may have underestimated the prevalence of HTLV-II in their study population. Many HTLV-II-infected subjects have HTLV-II antibodies that go undetected in the HTLV-I enzyme-linked immunosorbent assay.[21,22] Furthermore, Thiede and co-workers insisted on

the demonstration of antibodies to HTLV-I gp 46 or gp 63 in their confirmatory definition of seropositivity. Such antibodies are often absent in subjects with HTLV-II infection (unpublished data, 1992).

The largest remaining question concerns the clinical import of HTLV-II infection. This is a difficult question, in part because the known worldwide burden of HTLV-II infection is small compared with that of HTLV-I. Many populations with high HTLV-II prevalence are small and geographically remote.[16] Others, such as injection-drug users, are unstable and prone to other serious health problems such as HIV infection. It has proved difficult to show definitively that HTLV-II is responsible for human disease. The first HTLV-II organisms identified were derived from patients with atypical T-cell malignant disorders with some features of hairy cell leukemia.[23,24] Other isolated organisms have been derived from patients with large granular lymphoma or mycosis fungoides.[25,26] Epidemiologic investigation has failed to demonstrate any increased rate of lymphoid malignancy in populations with high HTLV-II prevalence or to identify increased HTLV-II prevalence in patients with lymphoid malignancy.[14] A number of patients with TSP/HAM-like neurologic disease have been identified among those with HTLV-II infection, however.[27-32] Despite this suggested association between HTLV-II and TSP/HAM, neurologic disease is apparently a rare consequence of infection with HTLV-II.

The identification of any new population with high HTLV-II prevalence is welcomed by researchers interested in possible pathogenic effects of this virus. Perhaps the substantial group of HTLV-II-infected subjects in King County will be large enough—and stable enough—to contribute to a definitive longitudinal study that will show that HTLV-II does or does not cause disease.

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What Columbus's Voyages Wrought

RECENT EVENTS surrounding the celebration of America's quincentenary have forced historians on both sides of the Atlantic to reexamine the ideologic foundations of earlier views of the highly touted and now politically incorrect "discovery" of the "New World." Instead, politicians and intellectuals have adopted a perspective recently articulated by, among others, Mexico's renowned scholar Miguel Leon-Portilla. To characterize the first contact and subsequent colonial process, Leon-Portilla employed the Spanish word *encuentro* ("encounter") to convey the meanings of collision, conflict, and opposition, but also approach, convergence, and linkage between the various cultures representing the Old and New