HTLV-I: To Test or Not to Test

As researchers identify more viruses and private companies develop new tests for them, who will decide how to keep the blood supply safe and when it is safe enough?

WITHIN THE NEXT MONTH OR TWO, the Food and Drug Administration is expected to license tests that can detect antibodies against human T-lymphotropic virus type I (HTLV-I), a relatively rare virus that sometimes causes cancer. Does this mean that blood banks in the United States should routinely screen for HTLV-I? In April, the American Red Cross said yes—as soon as the FDA issues licenses for the tests. This announcement, the events that precipitated it, and those that have followed are provoking intense scrutiny of the process by which such decisions are made.

There are at least two sides to the problem. One is the public health perspective that screening should be done to prevent disease and viral transmission. A second viewpoint is that each new screening procedure adds a finite cost to the price of blood and reduces the amount of blood available for transfusion or manufacture of blood products. To some extent, this argument can be reduced to a cost-benefit analysis.

The case for HTLV-I testing is far from being clear-cut. If it is possible to rid the blood supply of a cancer-causing virus, most researchers and health officials agree that it is prudent to do so. HTLV-I can cause a form of leukemia and a progressive neurological disease. Only 3 to 4% of infected people get sick from it, however, and those who do may take several decades to develop an illness—by which time they are likely to have died from something else.

HTLV-I is not a new virus. It has probably infected people in the United States for 50 to 100 years, although it was not identified until 1980. But the antibody tests to detect the virus are new, creating a situation in which blood-screening technology has developed faster than knowledge about the virus itself. No one knows how many people are infected with HTLV-I, whether the number is increasing or decreasing in the general population, or how dangerous the virus is in any particular individual.

A broader issue is whether blood banks will be expected to screen for every disease-causing, blood-borne virus for which a test is developed. Moreover, should blood banks combine such massive screening programs with more general techniques—many of which are still being designed—that could rid the blood of undetected viruses or those that might escape the screens? As one researcher put it, "Why are we doing all this? Is it really the best use of our medical resources?"

Some researchers see the decision to screen for HTLV-I as an indication that times have changed—not necessarily for the better. "In the good old days, decisions about blood testing were made on the basis of scientific data—by the FDA in consultation with the blood-banking community," says Joel Solomon of the FDA. "But with hepatitis and AIDS, other factors began to drive the system."

"We need a process. That's the lesson we have learned from HTLV-I."

In October 1986, Gerald Sandler of the American Red Cross in Washington, D.C., wrote an editorial in the *Journal of the American Medical Association* that outlined his views on the necessity of screening blood for HTLV-I. This set in motion a series of events that would inevitably lead to HTLV-I screening by all blood-banking organizations. "When the American Red Cross is in print in a widely read journal as advocating HTLV-I testing, the die is cast," says Jay Menitove of the American Association of Blood Banks (AABB) in Arlington, Virginia. As *Science* goes to press, AABB, the American Red Cross, and the Council of Community Blood Centers are preparing a joint statement that describes how HTLV-I testing will be implemented.

In an interview with *The New York Times* in April, Sandler said that the American Red Cross would screen blood for HTLV-I as soon as a licensed test was available. At that time, the FDA was still in the early stages of reviewing three license applications for an HTLV-I test. "Pressure was put on the FDA because a decision about testing appeared to have been made," says Solomon. Biotechnology stock analysts quickly estimated annual profits for the new tests—possibly $50 million for the first generation of assays, with most sales going to blood banks. Sandler's statements also stimulated the three companies whose license applications were under review—Abbott Laboratories in North Chicago, Illinois, the Du Pont Company in Wilmington, Delaware, and Cellular Products in Buffalo, New York—to find creative but still legal ways to promote their product prior to licensure.

Why did Sandler make his decision to test for HTLV-I so early? "This is part of taking our leadership role and responsibility seriously," he says. "HTLV-I is a retrovirus shown to be spread by blood, particularly blood transfusions. It is associated with serious disease in areas outside the United States, namely adult T cell leukemia in Japan and tropical spastic paraparesis in Caribbean countries." (The paraparesis, also known as HTLV-I–associated myelopathy or HAM, is a slowly progressive neurological disease that causes weakness in the legs and lower body.) Furthermore, says Sandler, a recent American Red Cross survey in which he participated indicated that 10 of nearly 40,000 blood donors were infected with HTLV-I—a prevalence rate of 0.025%.

The survey, published in *Science* (29 April, page 643), included people from eight different regions of the country. Six of seven infected people whose identities were known had risk factors that could be traced. These included intravenous drug abuse, sexual contact with a drug user, and sexual contact with someone from an area where HTLV-I is endemic.

Many researchers regard the study as valuable because of its scope, but it became somewhat controversial. Enzyme-linked immunoassays from Du Pont, Cellular Products, and, later, Abbott were used to test for antibodies against HTLV-I in the blood samples, but none of the companies strictly adhered to FDA regulations for using their unlicensed assays in a large-scale study. This meant that the FDA had not approved the study before it was started. Although no insurmountable problem resulted, the incident was yet another complication in an already unorthodox process.

Since then, all three companies have adjusted their antibody assay kits and achieved 97 to 100% sensitivity, says David Anderson of the FDA. Data from their specificity testing is still being submitted.

Where does that leave blood-banking organizations now? "The rationale for testing for HTLV-I as a disease-control measure is much less persuasive than it is for AIDS," says Thomas Zuck of Hoxworth Blood Center in Cincinnati, Ohio. "The rationale is more of a public health measure—to prevent the spread of the virus."

HTLV-I appears to be transmitted in the same ways as HIV, but it is less efficient and the virus replicates more slowly in an infected person. "In the six or seven families that we have studied, if you find a father that is antibody positive for HTLV-I, usually other family members are also positive," says Bernard Poiesz of the State University of New York Health Science Center in Syracuse. This is probably because the virus is spread in breast milk and through sexual contact. Like HIV-1, it is not known to be spread by casual contact. Approximately two-thirds of people transfused with blood containing HTLV-I probably become infected, although no cases of HTLV-I infection by this route have been documented in the United States. Poiesz, who now has 75 patients with HTLV-I diseases, emphasizes that prospective studies are needed to determine how often infected people develop disease and which diseases they get.

Poiesz argues forcefully that it is very important to prevent the spread of this virus. "Why would anyone not want to test for HTLV-I?" he asks. "This can be a lethal virus. But most people who are infected will not get sick. That's the good news."

This "good news" aspect of HTLV-I screening for an individual may create a testing and counseling nightmare for blood banks, however. More than half of the people in low-risk groups who initially test positive for HTLV-I are either found to be uninfected or are classified as "indeterminate," says Zuck. The virus occurs largely inside cells and many infected people do not make high levels of antibody. People with inconclusive antibody tests require two confirmatory tests, neither of which has been reviewed by the FDA for licensing. Furthermore, no regulations exist on what constitutes a positive confirmatory test.

Another complication is that the antibody tests about to be licensed by FDA do not discriminate between HTLV-I and HTLV-II, a closely related retrovirus that shares very similar proteins. "We can't even tell the patient what virus they are infected with," says Jonathan Kaplan of the Centers for Disease Control in Atlanta. (HTLV-II has been linked to hairy cell leukemia, but the number of cases is small and the evidence that it causes the disease is not very strong.) Also, how should doctors address questions from their HTLV-I–infected patients about sexual contact with others? "We are uncertain about what to tell them because we know so little about sexual transmission," says Kaplan.

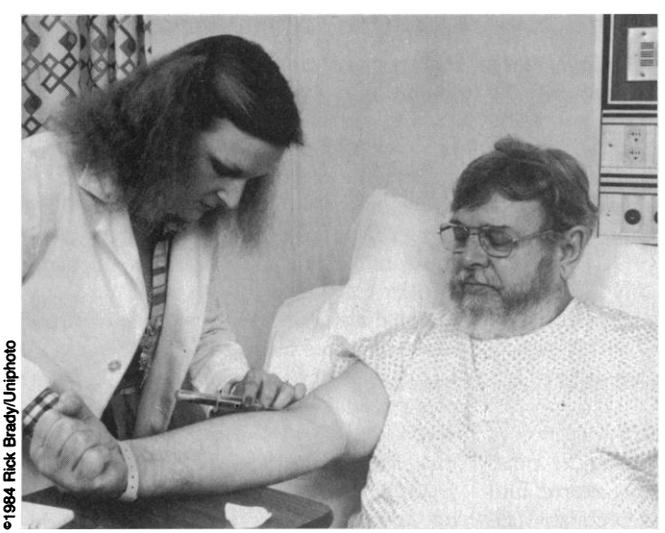
Will blood banks continue to add more and more tests to their blood screening procedures as more viruses are identified? Some researchers see HTLV-I screening as a harbinger of screens for other viruses—perhaps HIV-2, which appears to cause a milder immunodeficiency disease than HIV-1. An infinite number of virus-specific screens is not likely to result, says Sandler, because new methods for eliminating viruses from the blood are being developed.

Currently, researchers are exploring two general approaches to decontaminating blood, says Leonard Friedman of the American Red Cross Jerome H. Holland Laboratory in Rockville, Maryland. One is to inactivate viruses so they cannot reproduce and the other is to remove them from blood or blood products. Several strategies are tailored to specific components of blood. For instance, a combination of filtering and washing red blood cells might be used to remove viruses, says Friedman. Or perhaps platelets could be treated by adding chemicals that can be photoactivated with either white light or ultraviolet radiation to kill viruses, says Roger Dodd, also of the Red Cross Laboratory. As yet, however, most of these techniques are still being developed. Dodd and Friedman see them as being added to the present screening processes, not as substituting for them.

While no one will say that biotechnology companies are helping to create a demand for increased blood screening, it is clear that they stand to benefit financially if the demand exists. It is illegal for a company to advertise a diagnostic product before the FDA licenses it, but the industry walks a fine line. For example, Abbott sponsored a scientific meeting on HTLV-I testing earlier this year. More recently, Du Pont and *U.S. News and World Report* cosponsored a "workshop" on the subject for science reporters in Washington, D.C. Its stated purpose was to provide background information on the virus so as to avoid the kind of "confusion" that surrounded HIV testing. "This could be seen as indirect advertising," says an FDA official. "That is why the companies do things like this."

The cost of HTLV-I testing will probably be modest—perhaps a few dollars per unit of blood. This will not affect hospitals very much because blood and blood products are only about 0.5 to 0.6% of their total costs, says Solomon of the FDA. "But the cost is not trivial for blood centers," he says. For instance, Zuck estimates that direct costs for HTLV-I testing next year will be about $2.80 per unit of blood for his organization. "That does not include the confirmatory assays, the units discarded, the costs of counseling the donors, or those for tracing people who may receive blood later found to be infected with HTLV-I," he says.

No one is saying that HTLV-I screening should not be done. The emerging debate is not really whether blood banks should test for this particular virus, but how "safe" the blood supply should be and to what extent blood-banking organizations should go to ensure safety. As things stand today, no formal mechanism exists for making these decisions. "We need a process," says Menitove of AABB. "That's the lesson we have learned from HTLV-I." FDA will address the issue directly at a workshop to be held next year. ■ **DEBORAH M. BARNES**



Donated blood *is being subjected to more and more tests as researchers identify additional viruses that are carried in the blood.*