Can AIDS be stopped?

by Dr. Myron Essex

Dr. Essex is chairman of the Department of Cancer Biology at the Harvard School of Public Health. He delivered the following speech at a forum on Oct. 3, at the Harvard School of Public Health.

Across the hall from our laboratory is a yellow poster announcing this forum, with the title, "Can AIDS Be Stopped?" On the announcement someone has scribbled a column headed "yes" and another headed "no." The "yes" column had five votes and the "no" column had two. By process of elimination, that means that we must have had six abstentions. This unsolicited and unscientific poll does, however, come close to my own sentiments on the issue, that of a very tough road ahead, but one that requires cautious optimism.

I'd like to make a few points about the disease and about HTLV-III/LAV, the virus that causes it.

Upwards of a million Americans, perhaps half a million to a million Europeans, and 10 million Africans are now infected with this virus. As far as we know, all of the infected individuals will continue to be infectious to others and will carry the virus for life. At least a third will develop AIDS or an AIDS-related disease within five years. Perhaps half, two-thirds, or more will eventually develop AIDS or a related disease. We just don't know.

There is no cure for AIDS. Experimental therapy has been so disappointing that clinicians are already directing much of their attention to the possibility of treating virus-infected carriers before they have AIDS.

The greatest risk for expansion of the pool of infected people now is for promiscuous heterosexuals. The virus can be transmitted from male to female and from female to male. Up to 50% of the female prostitutes in New York and major metropolitan areas in Western Europe are already infected, as are 4% of the U.S. military recruits that visit VD clinics in West Germany and more than 1% of the healthy military recruits in Fort Bragg, N.C.

In Africa the ratio of infection in males and females is 1 to 1, not 8 or 10 to 1 as it is here. Ten million people in the AIDS Belt of Africa are already infected and there the virus is spreading primarily by heterosexual intercourse. We must expect that young sexually active males and females will become infected in this country at greatly increasing rates. We can only hope that the rates will not increase as rapidly as they did for some of the other risk groups.

We suspect that the AIDS virus was newly introduced to the human population only 15-20 years ago. It apparently originated in Central Africa, and was probably introduced to people from African Green monkeys, where a related virus infects a large fraction of the healthy animals. If we assume that this was indeed the source of the human virus, it suggests why the infection is so devastating for the human population. Unlike the monkeys, we have not yet had sufficient time for the evolutionary selection of adequate immune resistance mechanisms in our species.

For every AIDS patient, there are 50 or 100 people who are virus carriers and capable of transmitting the virus to others. If anything, they appear more likely to transmit the virus than AIDS patients. This suggests how irrational it is to worry about transmission from AIDS patients in the workplace, home, or community. Even if you refuse to accept the very extensive evidence that the virus cannot be transmitted by casual contact, how would you possibly avoid casual exposure to the 40 or 50 healthy carriers that don't even know they are infected?

Not like other viruses

Although distantly related to other human retroviruses, the AIDS virus is distinctly different. It has three new genes whose protein products are just now being identified and whose function in disease development remains unknown.

The most important gene of the virus from the standpoint of diagnosis or prevention is the one designated *env*, for envelope. It is the most effective antigen to use in blood-bank screening and the protein that will be absolutely necessary for vaccine development. It is the most effective inducer of antibodies, but unfortunately it is very hard to purify with virus particles used for test preparations. One can opt to retain as much of this antigen as possible, to maximize our chances that adequate amounts are present in blood-bank screening tests. But the price we pay is a very large number of false positives, because the process of concentrating the virus must be so delicate that it fails to exclude contaminating cell proteins that give non-specific reactions.

The opposite approach is to try to prepare a more highly purified virus, to minimize the large number of false positives. But the price we then pay is to retain only those parts

of the virus in the antigen preparation that are less efficient for detecting antibodies in people. This is an antibody test, so we then have an unacceptable number of false negatives. By false negatives, we mean blood units that test negative but contain infectious virus.

The blood supply is not safe!

The statement has been made that our blood supply is now safe. Supposedly the currently existing blood screening tests are 99.8% specific. I believe that both of these statements are grossly inaccurate and at best misleading.

Why do I say this? Let me cite one example. In a representative screen of about 107,000 blood units conducted between April and September of this year, 719, or 0.67%, tested positive. When the same test was repeated three times, only 218 tested positive all three times. Are 0.67% of our blood units contaminated, or only 0.22%? Do we have three false positives that surface in the screening system for every true positive? Or were some of the 500 putative false positives true positives that would then be scored as false negatives if we only use the 0.22% figure?

We can predict that 5–10 years from now, we will have at least 4–5 million Americans infected and several hundred thousand with AIDS. We must act fast enough so that we won't have 20 to 40 million Americans infected and several million with AIDS.

The 218 that tested positive in triplicate were then tested by immunoblotting or Western blotting, the so-called gold standard. Thirty-five of the 218, or 16%, were judged positive or confirmed. Thus, of the 719 that were judged ELISA positive on the first try, only 35, or 5%, were ultimately confirmed by Western blotting. With figures such as these, it is hard to take comfort in the recently released statement, "the AIDS blood test was about 99.8% accurate."

Are our first screen ELISA tests giving 95% false positives or was the so-called gold standard Western blot giving us an unacceptable number of false negatives? We don't know! From how many of the 719, 218, or 35 could the virus actually be isolated and proven to be present? We just don't know! Those studies have not been done.

And what about the 99.3% that test negative on even the first screen? Would any yield virus by cultivation and actually be false negatives by even the most crude assay? *Yes!* In a study done recently with sexually active homosexual males that tested antibody-negative, about 5% yielded infectious virus by cultivation. Similar results have been obtained in a very limited number of spouses of infected men.

So our blood supply is not safe!

On the optimistic side, we do have all the basic information we need to make better tests. In the second generation of tests, where the virus antigens will be made by genetic engineering, we will almost certainly do much better. But we don't yet know how to screen out the small number of infected units that contain virus but no antibodies by any test, and, until we do, our blood supply will not be entirely safe.

What about a vaccine? The molecule that must be used for a vaccine antigen has been identified and characterized. Every nucleotide and amino acid is known and the antigen can be made in large amounts in bacteria or yeast using gene-splicing techniques. Neutralizing antibodies that might be protective *in vitro* are found in low titers in both healthy carriers and in AIDS patients. Obviously they did not prevent the disease in the AIDS patients. Is this a case where the antibody observed was too little too late and a cause for great pessimism? Hopefully not! Perhaps it will be a case where a little will be enough if present *before* virus infection. There is a precedent for such optimism with other retroviruses, such as the cat leukemia virus, which represents the only retrovirus vaccine currently in clinical use.

But major problems of both a theoretical and a practical nature remain. The virus genome and the important envelope gene itself undergo mutation 100-fold faster than a virus such as influenza, which as you know, changes its antigenic structure every few years. Will the AIDS virus present in the population change the structure of its important surface antigens every few weeks or months? We certainly hope not. On the positive side, we know that essentially all people who become infected have antibodies to a common epitope of the virus surface protein. What we don't know, and must find out, is whether those antibodies react with a portion of the molecule that is necessary to initiate the biological process of infection *in vivo*.

Even if we get this far, however, we face the tremendous task of reducing the results from the research lab to clinical practice. I've already mentioned how difficult this has been for the blood-bank screening tests. For a vaccine, it will be far tougher, but still theoretically possible.

So what we need most at this point is a more aggressive policy on the part of government to increase the pace of research. And we need the type of financial commitment and inducement that will activate a larger proportion of our brightest scientists, many of whom are not now involved, but should be. We frequently hear the statement that the AIDS epidemic is the most frightening medical problem of modern times. Unfortunately we can predict that 5-10 years from now we will have at least 4-5 million Americans infected and several hundred thousand with AIDS. What we must do is act fast enough so that we won't have 20 to 40 million Americans infected and several million with AIDS.