Proliferation of HIV types frustrates hopes for AIDS vaccine or cure

by John Grauerholz, M.D.

One reason that the government is reluctant to acknowledge the full extent of HIV infection in the population is that it is becoming more and more obvious that the present level of biological science is inadequate to deal with this virus. This was the real "take home message" of the "Conference on Genetic Variation of Immunodeficiency Viruses" held on July 19 and 20 at the National Institutes of Health in Bethesda, Maryland. The conference was sponsored by the AIDS program of the National Institute of Allergy and Infectious Diseases and involved academic and governmental researchers from around the United States.

George Shaw of the University of Alabama in Birmingham described a study, subsequently published in the Aug. 4 issue of *Nature,* on variation of HIV or human immunodeficiency virus, the virus associated with the development of AIDS. Shaw and his colleagues, along with researchers at the University of Miami School of Medicine, examined molecular variation in the virus HIV-1 by isolating virus from two infected individuals at different points in time and examining the differences between the isolates. They then examined differences between changes which occurred in viruses grown in culture as opposed to viruses growing in living hosts.

At any given time, each individual was found to be carrying between 9 and 17 different, but related, variants of the AIDS virus. More interestingly, analysis of clones of virus from the same individual at different times showed progressive change, but they were still related to each other. On the other hand, clones grown in culture showed no significant change over time. As Shaw summarized the results "The data imply . . . that there is no such thing as an [AIDS virus] 'isolate.' You probably have enormous numbers of slightly different viruses in an individual."

Similar findings were described in HIV-infected infants in which new variants of the mother's virus arise in the child.

It is important to understand that these findings were not unpredicted, even before the identification of HIV as the so-called AIDS virus. The genetic material of HIV is composed of RNA, and it has been known for quite some time that there is a high rate of mutation in genetic sequences composed of RNA. This is because the enzymes which are responsible for replicating RNA are not as accurate as those which replicate DNA, the other chemical of which genetic material is composed. In the case of the retroviruses, such as HIV, the RNA of the virus is copied into DNA in the infected cells. This copying is done by an enzyme called reverse transcriptase, because it copies RNA into DNA instead of the usual procedure in which DNA is copied into RNA.

The reverse transcriptases of the retroviruses share the inaccuracy of the enzymes which replicate RNA. That is to say, they make errors—in fact, quite a few. And, according to Thomas Kunkel of the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina, "The HIV-1 reverse transcriptase is the least accurate of the enzymes we have examined." Kunkel's group found that the HIV-1 enzyme was roughly 10 times more inaccurate than other reverse transcriptases they studied.

Implications for the development of illness

What this means is that HIV is constantly generating genetically new variants with different immunological profiles and different biological activities. One implication of this is seen in work reported by Peter Nara of the Frederick (Maryland) Cancer Research Facility of the National Cancer Institute. As part of a project to develop an AIDS vaccine, Nara's group injected chimpanzees with HIV-1 and then isolated virus from the animals at two-week intervals. Virus isolated at two weeks was already resistant to neutralizing antibodies against the original virus, even though the animals hadn't yet mounted an antibody response to the virus.

Not only is this bad news as far as developing a vaccine against HIV is concerned, but it also undercuts one theory proposed to account for this variation. This theory, based on the Darwinian concept of natural selection, proposes that the emergence of new strains of HIV results from a selective pressure exerted by the body's immune response. Nara observes, however, that "Neutralizing antibodies don't seem to be the driving force for variant production in this species." Antibody resistant viruses can arise whether or not an antibody is even present.

That these variations have implications for the development of illness is shown by a number of other studies reported. Variations in the outer envelope of the virus significantly affect which cells, if any, a given virus will grow in. This was shown by studies in which viruses were constructed that were identical except for their outer envelopes. These viruses showed significant differences in the types of cells in which they would grow.

Another study examined two genetically distinct HIV-1s from the same AIDS patient. One form of the virus grew in monocytes, a white blood cell which circulates throughout the body, but not in brain cells. Another form grew in brain cells—known as glial cells—but not in monocytes. This confirms earlier reports that some forms of HIV appear to destroy the nervous system, whereas others destroy the T-cells of the immune system.

As illness develops, the viruses isolated from the patient become more effective at killing cultured cells. In other words, with the passage of time, the virus becomes more virulent. Since HIV establishes a lifetime infection, which the body appears unable to control, the virus has plenty of time to mutate to a more lethal form.

Moreover, disease may be produced by viruses which are incapable of growing outside the body. These forms, known as replication defective variants, are more virulent than forms capable of growing on their own. This phenomenon, too, has been well known for many years in other retroviruses, especially those responsible for causing immune system tumors in various animals. In this case, the virus you grow out of the patient may not even be the one causing his or her disease.

To top this off, it is now evident that a person can be infected by HIV for up to three and a half years before developing antibodies to the virus. Indeed, a number of children have developed AIDS without antibodies to HIV being present in their blood. In these patients, the presence of virus can be detected by a test known as the "polymerase chain reaction," or PCR, which is capable of detecting the gene product of the virus genetic material in the genetic material of an infected cell. This test is sensitive enough to detect 1 infected cell in 1 million.

The irony of all this is that, while the various AIDS viruses may have actually arisen as a side effect of molecular biological research, it is more and more evident that molecular biology is inadequate to deal with them, other than in the development of increasingly sophisticated tests for the presence of infection. Since the present policy is to reject the use of mass testing, even this progress is meaningless.

In a way, the various AIDS viruses could almost be viewed as the toxic waste of molecular biology. If so, then, just as with all previous forms of toxic waste, the solution lies not in abandoning technology, but in advancing to a higher technology which is capable of dealing with the problem. Instead, the present approach is to reject the capabilities we do have and invest in research which, by its own premises, is incapable of finding a prevention and cure for HIV infection.

Currency Rates