AIDS: Where are we today?

Dr. John Grauerholz reviews where science stands on the nature of the virus, treatment, and testing.

The Fifth International Conference on AIDS has now passed into history and it is useful to look at where science now stands in light of what this magazine, and some of our co-thinkers on the AIDS issue, predicted over three and four years ago.

What kind of virus?

On the issue of the virus itself, it was evident from the time the virus was first identified that it was related to the so-called slow viruses, such as the Visna virus of sheep rather than the RNA tumor viruses. In 1983, Dr. John Seale of Britain had already predicted, on epidemiologic grounds, that the epidemic was most likely caused by a blood-borne, slow virus of the Visna type. The first description of the virus, by François Barre-Sinoussi of the Pasteur Institute, was of a retrovirus of the lentivirus (slow virus) family. The virus was given the descriptive name LAV (Lymphadenopathy Associated Virus).

Subsequently Dr. Robert Gallo, of the National Cancer Institute, grew out the same virus from a sample he acquired from the Pasteur Institute and christened it Human T-Cell Leukemia Virus-III (HTLV-III), thus classifying it as the third of three human RNA tumor viruses he had discovered. The distinction was important because it indicated that the primary cell affected by the virus was the T4 or CD-4 lymphocyte. When it became evident that the action of the virus more resembled the slow viruses than the tumor viruses, Gallo renamed it Human T-Cell Lymphotrophic Virus-III (HTLV-III).

This terminology served to do two things. One, it upheld Gallo's claim that the virus was similar to his leukemia viruses and second, it obscured the relation to its actual closest relatives, the Visna viruses. This was especially so since the Visna virus affected cells known as monocytes whereas HTLV-III infected T-4 lymphocytes, which the Visna viruses did not. Since the Visna virus was known to be spread by respiratory aerosols, whereas the official position was that HTLV-III (or LAV) was spread by needles and sex, this distinction was important.

When Gallo, among others, discovered that HTLV-III/LAV, now known as HIV (Human Immunodeficiency Virus—another misnomer) infected monocytes just like Visna, and produced primary brain and lung disease, just like Visna, the fallback position was that infection took place via attachment to the CD-4 receptor molecule, which is particularly abundant on CD-4 lymphocytes, hence their name, but is also present on some monocytes, though in much lower concentration.

When it was shown that cells bearing this receptor are present in the very superficial layers of the skin and the lining of the mouth and are capable of being infected by HIV, it was still adamantly insisted that infection could only occur by sexual contact—just as Gallo had insisted, in 1985, that high titers (levels) of free virus could be found in semen, even though no one has demonstrated any level of free virus in semen to date.

Later, it was discovered that a previously known retrovirus of cattle, Bovine Visna Virus, also infected lymphocytes and produced a clinical illness like AIDS in cattle, as well as affecting the nervous system, as HIV is known to do today. This virus, now called Bovine Immunodeficiency Virus (BIV) had earlier been seen to be capable of infecting and growing in human cells in the laboratory and was known to be a contaminant of the serum used to grow viruses and tissue cultures since the 1950s.

It is now established that HIV is capable of infecting cells which do not carry the CD-4 surface receptor. This includes not only immune system cells, such as the lymphocytes and macrophages, but connective tissue cells known as fibroblasts which make up much of the so-called supporting tissues of the body, as well as the surface cells of the mouth, gums, and intestines. In addition, infections have been produced in a number of different cell types in culture. This ability to infect non CD-4 carrying cells occurs as one of the many genetic variations of the virus and, in the laboratory, the ability to infect new types of cells, known as host variation, can occur in one passage.

This means that all that is necessary to produce a virus with the ability to infect a new and different cell type is to place it in culture with the new cell type and then harvest the first generation of new viruses which are produced. In addition it is now known that progression to disease is accom-

panied by the development of higher levels of more virulent strains of the virus, capable of infecting more different cells.

In spite of all this mutation, in spite of the demonstrated ability of the virus to infect many different cell types, in spite of documented cases in which sex, needle injection, transfusion, or mother-to-child transmission could be absolutely excluded, one biologic constant has remained. HIV, or HTLV-III (leukemia or lymphotrophic, take your choice, they're both wrong) or LAV or ARV (AIDS Associated Retrovirus, which was discovered by Jay Levy of San Francisco who must not have as good a press agent as the others) is only spread by sexual intercourse, dirty needles, blood transfusions, and by an infected mother to her child.

Now if we return to the Visna virus of sheep we find an agent which produces two primary diseases, a chronic degenerative disease of the nervous system and a chronic lung infection. If we look at HIV, we see a virus which produces similar diseases in humans, AIDS dementia and a number of degenerative processes in the nervous system, and a primary lung infection known as Chronic Lymphocytic Interstitial Pneumonitis (CLIP). The difference is that HIV is also associated with the development of a characteristic form of immune deficiency in certain persons. Interestingly, this deficiency seems to occur almost exclusively in persons who are already subject to some other form of immune stress, such as other infections or malnutrition. It is now known that Bovine Visna Virus, now Bovine Immunodeficiency Virus, also does this.

Immunologic enhancement

As far back as 1985, Dr. Mark Whiteside contended that the immunosupression seen in AIDS patients was very similar to that seen in patients infected with known insect-transmitted viruses, called arboviruses. Dr. Whiteside postulated that the development of AIDS in an HIV infected individual could occur by a process known as immunologic enhancement of infection, a process which had previously been thought to play a role in the development of disease from arboviruses.

In immunologic, or serum, enhancement the presence of antibodies against a given type of virus results in more severe disease when the host is exposed to a closely related, but not identical, virus. The prototype for such a disease was dengue hemorrhagic fever, a severe form of disease caused by the insect-transmitted dengue virus, which is known to exist in four subtypes. In a person with a low level of antibodies to one subtype, infection with a second subtype results in potentially lethal hemorrhagic fever, instead of the usual self-limited, if somewhat painful, febrile illness.

Since immunologic enhancement of infection had been demonstrated for animal retroviruses, similar to the AIDS virus, this author and others predicted that a similar situation would occur with HIV, especially since the AIDS virus was known to mutate so rapidly. When it developed that mutation occurred within the same host and that a dozen or more strains could be isolated from a single individual, all different from the initial infecting strain, the possibility became a certainty. It is now established that serum enhancement occurs with HIV and correlates with the development of disease.

This brings us up against one fundamental problem of trying to develop a vaccine against HIV. That is that a vaccine which raises antibodies against one type of HIV may in fact enhance infection by another HIV type.

One of Dr. Whiteside's other contentions was that infection by arboviruses would activate a latent infection by a retrovirus, such as HIV, and that this would account for the large number of AIDS cases in Belle Glade, Florida, where there was a high level of exposure to arboviruses among the population afflicted by AIDS. The CDC and other agencies denied that such "co-factors" played any role in the development of AIDS.

It is now firmly established that a number of viruses, such as the herpes viruses and others, in fact produce proteins which activate HIV which is otherwise latent and can lead to expression of the virus and development of Acquired Immune Deficiency Syndrome. Conversely, if such activation does not occur the AIDS virus can lie dormant for an extended period. This was known as far back as 1985-86 and was one of the arguments this author made to the opponents of Propositions 64 and 69 in California. Namely, widespread testing was necessary to identify individuals with latent infection before they became ill, so that their health status could be monitored and appropriate interventions made to prevent activation of their infections. This was roundly denounced by the same people who are now calling for more widespread testing, for precisely the same reason.

On the question of insect transmission of HIV it is now established that the virus can survive in ticks, mosquitoes, and bedbugs for up to 48 hours and that cells capable of being infected with the virus exist in the most superficial layers of the skin. The response to this has been to simply ignore the evidence and insist that insect transmission can be excluded on "epidemiologic" grounds, though in fact not a single such epidemiologic argument can stand up under close examination. The supposed lack of cases among pre-adolescent children is seen in such insect-transmitted diseases as malaria and a number of the arboviruses.

Antibody production delayed

One of the most disturbing facts which has recently come to light is that it is possible to be infected by HIV, to transmit it, and even develop symptoms of brain disease without having a positive antibody test. It was known at the time of the discovery of the virus that this particular group of viruses could establish a dormant, or latent, infection within a cell, but it was presumed that development of antibodies would occur within six weeks or so of initial infection and would precede the development of clinical illness. One conclusion which followed from this presumption was that the spread of

infection could be accurately monitored by studies based on development of antibodies to the virus in the population.

With the development of tests for the presence of the virus itself, both in its free form in the blood and in its latent form in infected cells, it became evident that there was a population of individuals who could carry the virus for an extended period of time without developing antibodies. This was known as far back as 1984. One case involved a woman who had acquired the virus from her impotent husband by kissing. Since this was not an officially accepted means of transmission of the virus, a way to discount it had to be found.

Apparently on repeat testing the virus failed to grow out of the woman's white blood cells and it was concluded that she had not been infected, even though the virus had previously grown from her cells. Subsequently it was found that a number of homosexual men showed the same phenomenon of virus growth from their white cells, followed by the inability to grow virus from their cells. In some cases, again among homosexual men, persons who were initially seropositive for antibodies to the virus subsequently tested negative for these antibodies. However since homosexual "sex" was an accepted means of transmission it was acknowledged that these people were in fact infected and that this represented another baffling manifestation of HIV infection.

Now it is conclusively established that infected persons can carry the virus for three years or more without developing antibodies. Not only that, but 2-5% of HIV-infected persons can develop symptoms of nervous system involvement before they develop antibodies. How can this happen? It goes back to those superficial skin cells. These cells, known as Langerhans cells, are members of the monocyte family and have been shown to be capable of being infected with HIV. Since they reside out of reach of the bloodstream, the virus can infect them without coming in contact with the blood. These cells can also pass the virus directly to other immune system cells, monocytes and lymphocytes, which then carry the virus throughout the body without directly exposing it to the bloodstream. These cells in turn can pass the virus directly to other such cells, and so forth.

This means that it is entirely possible for infection of the superficial skin to occur, and for the virus to ultimately make its way to the brain without ever stimulating the presence of antibodies. It also means that studies which are based on seroconversion (development of antibodies) as a means of determining the spread of HIV infection are seriously flawed; they are flawed precisely in terms of so-called casual, or environmental, transmission of HIV. As opposed to direct needle injection or sexual intercourse among persons who have genital sores from other venereal diseases, where there is direct blood-to-blood contact, environmental transmission is more likely to involve superficial infection which avoids direct bloodstream contact.

How was it possible to know that these antibody-negative persons were in fact infected? The answer is that more sophisticated tests, especially a test known as DNA amplification or the Polymerase Chain Reaction (PCR) are capable of detecting the virus when it exists as nothing more than a segment of DNA integrated into the genetic material of the host cell. The use of this test to detect seronegative, but infected, transfusion blood is being opposed on cost grounds even though cases of HIV infection by seronegative transfusions continue to be reported.

In terms of treatment, there is only one effective agent against the virus, AZT, which has been known since 1986. This drug does improve the clinical condition of patients with AIDS, reverses some of the HIV-associated changes in the brain, and prolongs the lifespan of patients treated with it. A number of other drugs are proving effective in treating some of the infections and tumors which actually cause the death of these patients. However, these drugs are not curative; patients on AZT still ultimately succumb to AIDS, and these drugs are expensive and in limited supply. There is evidence that they may be most effective in prolonging life if administered before the onset of frank disease.

A demographic policy?

As for the disease itself, its spread in the homosexual community appears to be slowing and it is now spreading most rapidly in Africa, Central and South America, and among racial and ethnic minorities in the United States. This is occurring at the same time as an increasing concern is being expressed about overpopulation, and many are advocating the stabilization or reduction of populations throughout the world, as a means of reducing environmental damage and financial costs.

If one looks at the present official position on how HIV is transmitted and the policies being adopted to stop the spread of the disease, it is interesting that they are policies which in and of themselves will decrease the birth rate—sex education for children, condoms for the minorities, and promotion of homosexuality; or increase the death rate—free needles for drug addicts and euthanasia. On the other hand, the denial that environmental co-factors are operative in the spread of infection and development of disease, in spite of evidence to the contrary, ensures that these conditions will not be addressed, especially in light of current budgetary constraints. When one considers that amelioration of environmental factors would also tend to create the conditions for an expansion of population, it is hard to escape the conclusion that considerations other than stopping the spread of HIV infection underlie the present vehement rejection of such public health measures as mass testing and appropriate quarantine.

As someone observed in Montreal, what we are suffering from is AIDS of AIDS, the imposition of policy considerations other than public health on a public health problem. Perhaps HIV infection is not necessary to develop "AIDS" dementia.