Scientists find new HIV-host subtleties

Genetic variability is a well-known feature of the AIDS-causing virus, HIV. But new research described in Montreal this week at the Fifth International Conference on AIDS suggests that many of the variations scientists see among different strains of HIV — including apparently inconsistent responses to antibodies and changing preferences for various target cells — are part of the virus' predictable natural history in the human body. The new information both complicates an already daunting biomedical puzzle and presents some unforeseen opportunities to halt disease progression, researchers say.

During the course of an AIDS infection, HIV becomes progressively more toxic to cells and gains the ability to infect a broader variety of cells. Strains that infect only one kind of white blood cell called T lymphocytes can change very suddenly — within as little as one viral generation — so that they infect only monocytes and macrophages, other types of immune cells. Researchers remain baffled about how this targeting change occurs.

Ten Feizi of the MRC Clinical Research Center in Harrow, England, and others looked at macrophage- and T-lymphocyte-infecting versions of HIV. They report finding specific changes in the number and type of molecular side-chains on the protein spikes protruding from the viruses' outer envelopes, which allow viruses to gain access to new cell types. Moreover, Jay A. Levy of the University of California, San Francisco (UCSF) reports indirect evidence that factors in an infected person's blood may mediate such changes. He says individual variations in blood levels of these envelope-modifying factors could explain differences in the disease-causing potential of initially identical HIV strains in different individuals. Levy hopes to block these envelope changes, thus keeping the virus from spreading to different kinds of cells — such as brain cells — within the body.

Levy's team also looked at the role of an HIV gene called *nef*, which appears to suppress HIV replication during periods of latency. In specially engineered, cultured cells, the researchers compared *nef*'s influence on two strains of HIV. The less virulent came from patients in an early stage of infection; the other came from a later stage of infection. When *nef* was active, the early-stage HIV strains became almost totally latent, as expected. But late-stage HIV ignored *nef*'s commands. A better understanding of the *nef* gene, its product and the factors that make some HIVs insensitive to it may lead to an improved ability to force HIV into permanent latency, says Levy.

UCSF's Jacques Homsy and others also examined a phenomenon called antibody-dependent enhancement in individuals who harbor HIV. Unlike a typical immune reaction, in which "neutralizing" antibodies bind to and at least partially inactivate their targets, this poorly understood immune reaction — present in some AIDS patients — actually boosts HIV activity. Over the course of several years, the team studied 15 HIV-infected people at various disease stages ranging from asymptomatic to full-blown AIDS. They found that virus-enhancing antibodies gradually increased in patients as symptoms worsened. However, several patients' antibodies neutralized some virus strains while enhancing others.

That unpredictability, says Levy, could be very bad news for vaccine makers. Scientists will have to identify and disable at least some of the immune system elements involved in antibody-dependent enhancement before a safe AIDS vaccination program can be initiated, he says.

Homsy this week reported identifying one such molecule on white blood cells that appears critical to antibody-dependent enhancement. — *R. Weiss*

High 'I do' blood-test dues

Illinois public health researchers this week described their first year's costly experience with a state law requiring all marriage license applicants to prove they've been tested for antibodies to the AIDS-causing virus, HIV. The controversial law, which went into effect Jan. 1, 1988, requires that laboratories report to the state department of health the age, race and sex (but not names) of all HIV-positives, along with any history of high-risk sexual behavior reported by those applicants. The law demands that both parties to a proposed marriage inform each other of their test results.

Of 155,458 applicants, 26 tested positive for HIV antibodies — the same prevalence rate of 0.02 percent already observed for voluntary blood donors in Illinois, calculate Chet Kelly and Bernard J. Turnock of the state's department of health in Springfield. At an estimated cost of $35 per person, the expense of premarital testing comes out to $5.4 million annually. That's $217,641 per HIV-positive, or about 300 times the cost per seropositive identified through the state's AIDS counseling and testing program. The program of mandatory testing "has identified few seropositive individuals at enormous cost," Kelly and Turnock conclude in a paper presented in Montreal this week at the Fifth International Conference on AIDS.

The number of marriage licenses issued in Illinois decreased by 22 percent compared with the previous 12 months, the researchers add. □

Gene test foretells Type I diabetes risk

Scientists have developed a genetic test to predict a person's risk of developing Type I diabetes, the disorder's most serious form. The new test may help identify children with an inherited tendency to develop the disease.

Developed by Massimo Trucco and his colleagues at the University of Pittsburgh School of Medicine, the test may eventually permit doctors to intervene before damage occurs. As yet there is no cure for the disease, but researchers hope to perfect some type of immunosuppressive drug therapy in the future. Type I diabetes is thought to arise when immune cells mistakenly attack and destroy pancreatic beta cells. Beta cells produce insulin, the hormone needed to utilize sugar.

Trucco's test, unveiled this week at the meeting of the American Diabetes Association in Detroit, involves analyzing DNA taken from white blood cells. It doesn't diagnose Type I diabetes but picks out individuals who are likely to get the disease if they encounter a triggering factor. Scientists believe people inherit a tendency to develop Type I diabetes but that the actual disease must be set off by exposure to a virus or some other factor in the environment.

Confirmation of the test's accuracy should enable physicians to determine whether children in families with a history of Type I diabetes have a high risk of the disease, says Charles M. Clark Jr. of the Indiana University School of Medicine in Indianapolis. This knowledge could alert doctors and parents to watch for early signs of the disease, which often mimic the flu, he notes. Many children now are rushed to the emergency room in a diabetic coma because their symptoms went unrecognized, Trucco adds.

In the future, the test might enable physicians to begin immunosuppressive therapy early, Trucco says.

An antibody test developed last year detects the disease after beta-cell destruction has begun but before overt symptoms appear (SN: 6/18/88, p.389). Trucco's test predicts a person's risk before cell destruction takes place.

His work builds on research showing Type I diabetics have a genetic flaw resulting in the substitution of an amino acid occupying a specific position in a type of human leukocyte antigen protein (SN: 10/17/87, p.247). Researchers believe this amino acid, aspartic acid, protects against Type I diabetes by preventing immune cells from attaching to beta cells.

Trucco looks at a portion of the gene that codes for aspartic acid. People who have a specific alteration of the gene, he says, are 107 times more likely than others to develop Type I diabetes.

— *K.A. Fackelmann*