SCIENCE NEWS of the week

New Molecular Analysis for Genetic Disorder

A goal of medical genetics is to detect defective genes before they do irreparable harm. Such a task must involve screening large numbers of asymptomatic individuals. The jump from the powerful new genetic analyses being performed in research laboratories to practical population screening tests is proving difficult. In most cases, the new procedures at best help determine who carries a defective gene within a single family (SN: 8/18/84, p. 107). Now, Savio L.C. Woo of Baylor College of Medicine in Houston reports that in work on phenylketonuria (PKU), the "granddaddy" of inborn errors of metabolism, he and his colleagues have developed a family-based analysis and used it to perform the first prenatal diagnosis of PKU. They have also extended the analysis to derive a method that is expected to be useful for population screening, and they have begun work toward a genetic therapy. Their research may provide a model for work on other, more lethal diseases.

More than 50 years ago PKU was recognized as a cause of severe mental retardation. In the defect, lack of a single enzyme reduces the liver's ability to break down the amino acid phenylalanine, which has toxic effects at high doses. Today infants are given a blood test that screens for the disease, and those with PKU (about 1 in 10,000 Caucasians) are put on a rigid low-phenylalanine diet, beginning with synthetic milk. Most of these children do not become mentally retarded, but they still tend to fall short of their normal siblings in intellectual ability.

Last week in Baltimore at the Annual Congress for Recombinant DNA Research, Woo described the gene that underlies PKU. The normal gene, which encodes the enzyme called phenylalanine hydroxylase, has 13 coding regions (exons), which make up less than 3 percent of the gene's length. These exons are separated by long noncoding, or intervening, sequences. "This gene must have been designed by a committee," Woo quips.

The great length of the gene allows it to have many sites that vary from person to person, with or without functional consequences. Woo and his colleagues have identified 10 such sites by cutting the DNA with different specialized enzymes. Such cuts, usually much scarcer in a single gene, are the basis of the genetic technique called restriction fragment length polymorphism (RFLP) analysis (SN: 8/31/85, p. 140). Woo used this technique to determine that a fetus of a family with one PKU child also had the disorder.

In a population study in collaboration with Danish scientists, Woo analyzed the RFLP patterns of families containing members afflicted with PKU. He divided the RFLP patterns into 12 groups, called haplotypes. He reports that only four of these haplotypes are responsible for more than 90 percent of PKU-causing genes.

To substitute a simpler procedure for the laborious RFLP analysis, Woo determined that a specific alteration in the gene can be identified in at least one group. For this group, which he calls haplotype 3, Woo reports that the PKU gene has a single mutation at a junction between an exon and an intervening sequence. The change results in an abnormally short protein, which cannot act as an enzyme. This alteration is not found in normal, noncarrier members of haplotype 3 or in PKU patients or carriers who are of a different haplotype. "The association is fantastic," Woo says.

He speculates that this approach may be extended to the other three major PKU haplotypes. Then, instead of difficult family-RFLP studies, a simple test for four mutant genes could identify 90 percent of the PKU genes in a population.

Can the genetic defect be corrected in PKU victims? Woo and his colleagues have demonstrated that a human gene, minus the unwieldy intervening sequences, can be attached to a modified virus that infects laboratory-grown cells, where it directs production of functional enzyme. "The next step is to explore ways of introducing this gene into experimental animals," Woo says. *—J.A. Miller*

The AIDS virus: Equine similarities?

The virus associated with AIDS is in the same family as a virus that causes an infectious, sometimes fatal disease in horses, according to research from the federally supported Frederick (Md.) Cancer Research Facility. Determining the family to which the AIDS virus belongs is a question of more than academic interest: An understanding of the virus's closest relatives could suggest a way to deal with the virus itself.

Robert Gallo of the National Cancer Institute (NCI) in Bethesda, Md., has categorized the AIDS virus — which his group calls HTLV-III — within a family of leukemia-causing viruses. Other scientists, however, have maintained that the virus's structure and behavior in the body put it in a group of slow-acting, untreatable viruses called lentiviruses, a family that includes the equine infectious anemia virus (EIAV).

The Frederick group used a computer program to compare HTLV-III proteins with proteins from EIAV; from visna virus, a lentivirus that attacks sheep; and from two leukemia viruses, bovine leukemia virus (BLV) and HTLV-I. The computer analysis showed that EIAV had the most amino acid sequences in common with the AIDS virus. Visna virus ran second, with HTLV-I and BLV a distant third. The details of the analysis, made by Robert M. Stephens, James W. Casey and Nancy R. Rice, appear in the Feb. 7 SCIENCE.

This finding follows a discovery by Luc Montagnier and his colleagues at the Institut Pasteur in Paris that blood from people with the AIDS virus contains antibodies that react with one of the proteins manufactured by EIAV. Matthew A. Gonda, also of the Frederick laboratory, then showed that the AIDS virus was more similar to visna than to HTLV-I and -II (SN: 1/12/85, p. 22).

The similarity means the sheep and horse infections can be studied for their relevance to human AIDS, but it may be bad news for development of a vaccine, says Opendra Narayan of Johns Hopkins University in Baltimore. Narayan worked with Gonda, Gallo and others to show the visna virus similarity. "These viruses [lentiviruses] undergo a lot of mutation," he says. The constant changes may prove too much of a moving target for a vaccine.

More hopeful in terms of a vaccine, NCI researchers reported last week on a protein capable of stimulating AIDS-antibody production. According to a paper given by Flossie Wong-Staal at the Annual Congress for Recombinant DNA Research in Baltimore, regions of the gene that codes for the protein were identical in four different AIDS virus isolates, suggesting the protein might provide a basis for a vaccine.

While the Frederick work firms up the virus's position in the lentivirus family, it won't help in naming the virus, which is variously called HTLV-III, LAV (for lymphadenopathy-AIDS virus) or ARV (for AIDS-related virus). According to Harold Varmus of the University of California at San Francisco, who is heading a nomenclature group sponsored by the International Committee on the Taxonomy of Viruses, the name will not depend on the virus's exact classification. The problem of what to call it "should be coming to a resolution in a few weeks," says Varmus. *—J. Silberner*