# BIOMEDICINE

*Julie Ann Miller reports from Monterey, Calif., at the Arnold O. Beckman conference on Genetic Disease*

## Update on Tay-Sachs screening

A little more than a decade of screening programs for the genetic disorder called Tay-Sachs disease now sets a model for other programs. Among the target group—the American Jewish population — the incidence of the fatal, nerve degenerative disease has dropped 65 to 85 percent during the past 10 years.

The success of the program of "prospective prevention" depended on three factors, says Michael Kaback of the UCLA School of Medicine. There was a defined population primarily at risk (people of European Jewish ancestry); a simple, accurate, inexpensive test to define carriers; and a "positive and acceptable" reproductive alternative for couples found to be at risk.

The test detecting carriers of Tay-Sachs disease measures enzyme levels in a person's blood. The enzyme missing in the disease is present at lower than the normal levels in carriers of the recessive gene. If both members of a couple are carriers, they are offered amniocentesis during pregnancy. Cultured amniotic cells of an affected fetus are deficient in the enzyme.

Kaback heads the international center that standardizes and surveys the 102 screening centers in 15 countries around the world. He reports that since 1970 almost 400,000 people have been screened, 5,000 carriers detected and 350 couples found to be at risk. More than 1,000 pregnancies have been monitored and 250 fetuses identified with Tay-Sachs disease and aborted. Most important, Kaback says, there are 800 healthy children, some of whom would not otherwise have been born.

Tay-Sachs disease in a child is devastating to the family, Kaback explains. The infant appears normal for the first five months, then stops acquiring new skills and by the age of one year begins losing ground. Affected children generally die before they reach the age of five. The missing enzyme allows a minor brain compound to accumulate in nerve cells. The cells become engorged with storage vesicles and brain function is disrupted. Families who have had one child with the disease generally stop having children, and the parents may turn to alcoholism or become divorced, Kaback says. But of 617 couples in which the woman had had a child with the disease and underwent amniocentesis in a subsequent pregnancy, 470 went ahead to have healthy children.

There are about 100 recessive genetic diseases that tend to appear in particular populations, Kaback says. Programs in Italy, Greece and Britain are reducing the incidence of the genetic disease beta-thalassemia. The experience with Tay-Sachs screening should be applicable also to future prospective prevention for diseases such as sickle cell anemia and cystic fibrosis, Kaback says. He concludes, "Certainly, until effective therapies, or even cures, for such tragic conditions can be developed, carrier screening and prenatal diagnosis provides an important, albeit imperfect, alternative approach."

## Chromosomes and mental retardation

Mental retardation has a wide variety of suspected causes, many involving chromosome abnormalities. Too many genes, or too few genes, in specific regions can lead to slowed and limited intellectual development. Finding the regions—and eventually the genes—responsible for specific types of mental retardation may not only provide insight into the syndromes, but also may explain aspects of normal behavior.

In the past two years a relatively rare, but striking, syndrome has caught the attention of physician-investigators, says Park S. Gerald of Harvard Medical School. In a typical case of Prader-Willi syndrome, the newborn is "floppy," having poor muscle tone, and eating poorly. As a toddler, however, the child converts to such a voracious eater that the parents have to lock the refrigerator and hide the pet food and any edible garbage.

The child with Prader-Willi syndrome has characteristic facial features, is short for its age and is mentally retarded, although not severely. The outstanding characteristic is extreme obesity. Teenagers and adults can weigh 300 pounds. The obesity frequently contributes to cardiorespiratory failure.

Recent analyses of the chromosomes of children with Prader-Willi syndrome have shown a variety of abnormalities, especially translocations of chromosome pieces between chromosome 15 and others. David H. Ledbetter of Baylor College of Medicine and colleagues reported earlier this year that several patients with the syndrome simply are missing a small piece of chromosome 15 (the segment between the band labeled 15q11 and 15q13) and they suggested that segment is lost during the reported translocations. In cases where no chromosomal abnormality is apparent, the genetic change may be too small to be detectable by looking at the chromosomes or it may be that the syndrome itself has multiple causes.

Determining the basis of a syndrome characterized by pathological appetite gives hope that investigators will reach an understanding of overeating, Gerald says. Recombinant DNA techniques allow scientists to isolate and reproduce for study specific portions of the human chromosome. While the work on Prader-Willi syndrome has not yet advanced this far, scientists have reproduced six different segments of the X chromosome. They are looking for the site of another form of mental retardation called "fragile X."

The syndrome named fragile X occurs in at least 2 percent of mentally retarded, institutionalized males and in one-third of families with a history of sex-linked mental retardation. The affected males have prominent jaws, enlarged ears but normal or slightly enlarged head circumference. They are usually heavy at birth and their IQs fall between 30 and 70. In some of their cells, X chromosomes appear to have a satellite at one end, due to constriction of the chromosome at a specific site. Gerald says that the current recombinant DNA work offers the possibility of pulling out the fragile site to see what's wrong.

## New ways to cushion metabolic errors

The harm of most inborn errors of metabolism comes in the accumulation of toxic metabolites of the abnormal processing. A common form of therapy is to restrict the patient's diet to eliminate the build-up of toxic precursors to a missing enzyme. Less frequently, diet and drugs are used to restore adequate levels of a missing enzyme's product. Now Stephen Cedarbaum of the University of California at Los Angeles describes the "newest wrinkle" on treatment. Investigators have developed means to encourage specific side reactions in a metabolic pathway and thereby "drain" the body of a toxic material.

Disorders of the urea cycle are currently the focus of the new approach. Ammonia is the toxic substance that builds up in the diseases. Mark L. Batshaw and Sol W. Bruselow of Johns Hopkins University devised means to trap the ammonia in a less toxic, more easily excreted substance. For example, they give patients sodium benzoate, a compound commonly used as a food preservative. The compound reacts with the amino acid glycine and the product is excreted. The body then uses up some of its excess ammonia making more glycine. "The therapy gives the body an edge so it can do better with handling ammonia," Cedarbaum says. He reports that with this new "diversion therapy" 50 percent of newborns with the urea cycle defect survive, whereas previously 86 percent died soon after birth and the rest died within six months. He says that he expects all the infants to survive once physicians learn to recognize the disorder, and begin therapy, a few days earlier.



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