New insights into Gaucher's tricky course

In the 107 years since Philippe Gaucher wrote his doctoral thesis about a Parisian patient with an enlarged spleen, physicians have remained baffled by the disease that today bears his name. Gaucher's disease, an inherited enzyme deficiency, affects more than 20,000 people in the United States and is especially prevalent among Jews of Eastern European ancestry. Oddly, the disorder ranges in severity from almost asymptomatic to fatal. Even among members of a single family, physicians find little correlation between the apparent degree of biochemical abnormality and the disease's clinical course.

In the past two years, however, molecular biologists have identified a handful of specific mutations on chromosome 1 that alone or in combination can cause Gaucher's. Now, in the largest studies of their kind, two research teams have discovered significant associations between particular combinations of genetic mutations and the severity of Gaucher's disease. If further experiments confirm the findings, genetic tests may soon provide useful information to people with Gaucher's, at-risk women considering pregnancy, and researchers investigating new therapies.

Ari Zimran, Ernest Beutler and their colleagues at the Scripps Clinic and Research Foundation, working with Stratagene Cloning Systems in La Jolla, Calif., studied 47 unrelated patients with Type I Gaucher's disease. Type I represents the most common and least severe of three forms of the disease, but its symptoms still range from almost nonexistent (many cases probably never get diagnosed) to spleen and liver failure with periods of extremely painful bone disease. The researchers used gene amplification techniques to detect specific mutations in the gene coding for the enzyme glucocerebrosidase. A deficiency of that enzyme in Gaucher's patients causes a damaging accumulation of fats in bone marrow and other cells.

The researchers found that the most common Gaucher-related mutation, called 1226, usually causes only mild disease when inherited from both parents. More severe disease appears when a 1226 from one parent appears with a different mutation, called 1448, from the other parent. With two copies of 1448, even more serious symptoms arise, they report in the Aug. 12 LANCET.

Work by Gregory A. Grabowski and his colleagues at the Mount Sinai School of Medicine in New York City generally affirms the La Jolla researchers' findings. In their report in the August AMERICAN JOURNAL OF HUMAN GENETICS, they also suggest that a previously identified mutation of the glucocerebrosidase gene may in fact *lessen* symptoms in patients with another Gaucher's mutation.

"For a long time we've wanted to predict severity of disease early on," Grabowski says, noting that genetic tests capable of detecting Gaucher's in fetuses are in demand from pregnant women considering abortion and from mothers choosing among the limited therapies for an affected child. For example, some doctors recommend bone marrow transplants – despite a high risk of mortality – for children developing the most severe form of Gaucher's. And patients with confirmed poor prognoses may be good candidates for current experimental therapies that involve taking supplemental doses of laboratory-produced glucocerebrosidase, Beutler says.

The new findings don't fully solve the puzzle, say researchers studying the disease. Definitions of mild, moderate and severe Gaucher's remain frustratingly subjective, the number of patients studied remains small, and one or several as-yet-unidentified genes no doubt play an important role. "Someday we'll be able to apply genotypes to clinical prognoses," says Edward I. Ginns of the National Institute of Mental Health in Bethesda, Md. "But it's premature to say we're there already." – *R. Weiss*

Early AZT use slows progression to AIDS

Zidovudine (AZT) can delay disease progression in some outwardly healthy people infected with the AIDS-causing virus HIV, according to preliminary results of a large, multicenter drug trial.

Researchers reported last week that zidovudine therapy benefits asymptomatic, HIV-infected individuals who have fewer than 500 T4 lymphocytes per cubic millimeter of blood – a very early sign of the immune system destruction that eventually leads to full-blown AIDS. A cubic millimeter of blood from a person with a robust immune system normally would contain 800 to 1,200 of these disease-fighting white blood cells.

The new finding complements an earlier study showing zidovudine slows disease progression in HIV-infected people who have AIDS-related complex (ARC), an early stage of AIDS (SN: 8/12/89, p.102). Researchers still don't know how long the drug can keep the disease at bay. But taken together, the two studies suggest zidovudine therapy may prolong the lives of an estimated 600,000 people in the United States – a prospect that several health officials say underscores the importance of prompt HIV testing. Public health officials estimate 60 percent of the 1.5 million U.S. residents infected with HIV don't realize they carry the virus and thus can't consider early zidovudine treatment when their T4-cell count dips below normal.

The latest results emerged when a scientific panel appointed by the National Institute of Allergy and Infectious Diseases (NIAID) reviewed preliminary data from an ongoing NIAID-sponsored zidovudine trial, which has enrolled 3,200 asymptomatic people with HIV infection since July 1987. When the panel scientists looked at data collected on 1,300 participants who had fewer than 500 T4 cells upon entering the study, they found that people on zidovudine were about half as likely as those on placebo to develop symptoms of ARC or AIDS after one year in the study. Reviewers used a statistical method that showed 7.6 progressions to ARC or AIDS during one year for every 100 people in the placebo group, compared with 3.6 treatment failures for every 100 people taking 500 milligrams of zidovudine daily and 4.2 failures for every 100 people taking 1,500 mg of zidovudine daily.

On Aug. 16, the panel stopped the trial for participants with fewer than 500 T4 cells and offered all of them the lower zidovudine dose, which appears to slow disease progression while causing fewer side effects. Some people getting the higher dose developed bone marrow suppression and other serious zidovudine-related side effects, says NIAID's Daniel F. Hoth.

Researchers will permit all participants with T4 counts above 500 to remain in the study, where they will continue to receive either placebo or zidovudine under close observation. People with such counts run a "negligible" short-term risk of developing ARC or AIDS, according to Hoth, who says researchers have not established the drug's efficacy in this group.

Advocates for people with AIDS hail the new findings but note that many can't afford the $7,000- to $8,000-per-year cost of zidovudine, manufactured by the Burroughs Wellcome Co. of Research Triangle Park, N.C. Jude Payne of the Washington, D.C.-based Health Insurance Association of America predicts that some insurance companies will begin covering zidovudine for asymptomatic HIV-infected people, while others will wait for further research to confirm the preliminary study.

Benjamin Schatz of the National Gay Rights Advocates, a public interest law firm in San Francisco, takes a slightly different view: "I believe many insurance companies are going to fight this tooth and nail, and will try to hide behind FDA labeling restrictions."

The FDA has yet to approve zidovudine for HIV infection in asymptomatic people, although it has approved the drug for full-blown AIDS. – *K.A. Fackelmann*