An infusion of hope

Genetic engineering is changing the lives of kids and adults with Fabry disease, an inherited enzyme disorder

▶ The specialist: Dr. Robert Desnick

A geneticist and pediatrician for more than 30 years, Desnick focuses on treating genetic diseases — like Fabry disease — that begin showing symptoms in childhood or adolescence. A professor at Mount Sinai and chairman of its Department of Genetics and Genomic Sciences, he treats patients from around the world, and performs clinical, molecular and biochemical genetics research.

▶ Who's at risk:

Fabry disease is an inherited disorder in which an enzyme deficiency allows the fatty substance globotriaosylceramide (GL-3) to build up in the blood-vessel walls. As the GL-3 deposits grow larger, they impair the function of the blood vessels and the organs they support.

The disease doesn't affect the sexes equally. "Like hemophilia, Fabry's is on the X chromosome," says Desnick, "and males are more heavily affected." When females have the disorder, their responses range from being totally asymptomatic to being as severely affected as males.

Fabry disease comes in two subtypes: classic early onset and later onset. Early-onset Fabry begins in childhood, usually between the age of 4 and 8, when kids begin to experience pain, skin lesions and gastrointestinal (GI) symptoms. "These children are often misdiagnosed," says Desnick, "And their pains are not often attributed to a specific disease." Patients with later-onset Fabry have some of the enzyme — enough to protect them from the early-onset symptoms, but not enough to prevent the GL-3 from building up over time.

"They don't have any of the hallmarks of the classic disease," says Desnick, "but they present late in life with heart disease, kidney disease and stroke." Studies have found that about 1 in 40,000 men have classic Fabry, and perhaps as many as 1 in 3,000 men may have the late-onset variety.

▶ Signs and symptoms:

With classic Fabry disease, children often complain about pain in their hands and feet, especially in their fingers and toes. Another warning sign is either absent or decreased sweating. Classic Fabry often causes gastrointestinal problems as well, like cramping and diarrhea after meals.

"Usually the patients are thin because they have diarrhea and abdominal discomfort," says Desnick.

The most distinctive symptom is a skin lesion called angiokeratoma that often looks like a red rash, especially between the navel and the knees. "The skin lesions may not be prominent in childhood but become increasingly prominent as kids age," says Desnick.

For females, the symptoms depend on the enzyme level. Those with a very low enzyme level can be symptomatic, while those with a higher level can show no symptoms.

Fabry is a progressive disease — as the GL-3 builds up, the blood vessels get narrower and narrower. The disease can eventually provoke potentially heart disease, renal disease and stroke.

▶ What you can do:

Get information.

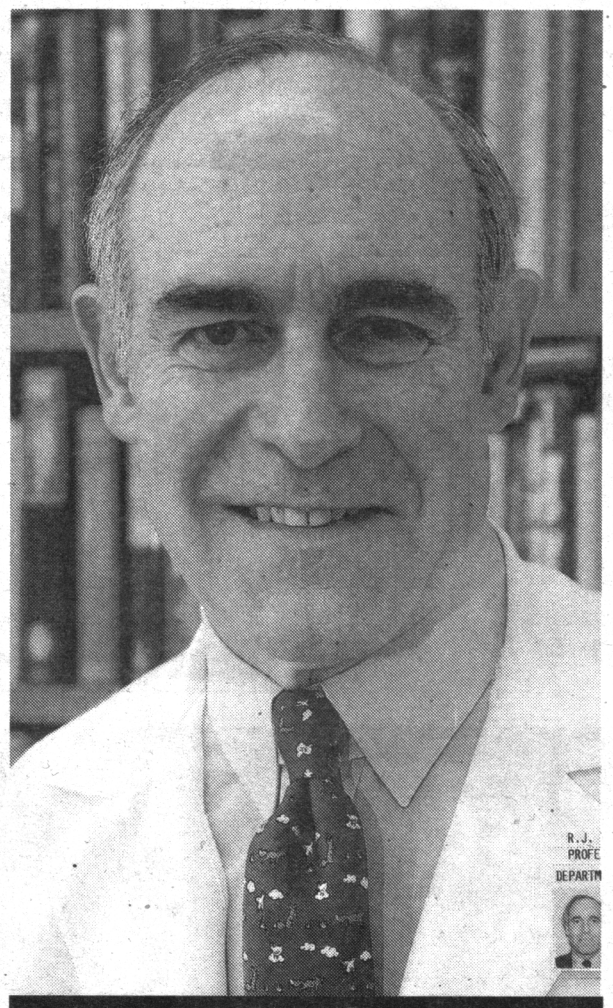
Mount Sinai is home to the International Center for Fabry Disease, and it offers great information on its Web site, including a helpful tutorial; go to www.mssm.edu/genetics/fabry. It also has a toll-free phone number that can put you in touch with a genetic counselor: 1-866-Fabry-MD (1-866-322-7963).

Get support.

Fabry is rare enough that many patients won't know anyone else with the disease. Support groups can help you find a community of peers; Desnick recommends the Fabry Support and Information Group (fabry.org).

Know your family history.

Fabry, as a genetic disease, runs in families. "One thing we want patients to do is focus on their family tree so they know the medical history of their relatives," says Desnick. "Then, when they do go to the doctor, they're prepared to explain what their relatives have."



Dr. Robert Desnick of Mount Sinai says treatment of Fabry disease has changed markedly.

TANYA BRAGANTI

▶ Traditional treatment:

For decades, doctors didn't have a treatment for Fabry that was effective in the long term. "We found the enzyme was present in normal blood, so we gave Fabry patients plasma transfusions," says Desnick. "It was effective but very short-lived."

The first step for most patients is preventive. Many of Fabry's painful symptoms are triggered by an external event like stress, exposure to heat or sun, physical exertion or fever, and doctors can help patients find ways to avoid these. This is not a a long-term solution either, however.

Thanks to genetic engineering, doctors are now able to make the enzyme that Fabry patients lack and give it to them through enzyme replacement therapy, a treatment developed by doctors at Mount Sinai. The enzyme is administered by IV infusion — patients give themselves injections at home once every two weeks.

Desnick has seen dramatic improvement in patients who start ERT when they are young. "Some of the first things that happen with treatment is that pain goes away or is decreased, they begin to sweat normally and they don't have GI problems," says Desnick.

For children, the benefits are especially pronounced. In the past they would have had to avoid exercise and sports, because they couldn't sweat and exercise could trigger a painful attack. "Now, kids with treatment can feel like all the other kids and participate in sports," Desnick says.

▶ Research breakthroughs:

After Mount Sinai researchers developed enzyme replacement therapy for Fabry, the method became a model for the treatment of some other illnesses.

"Now there are six different diseases with lysosomal involvement that are being treated effectively with enzyme replacement," says Desnick. "Fabry's was the first."

▶ Questions for your doctor:

Because Fabry disease shares some symptoms with far more common diseases, it's worth asking your doctor if he or she has considered Fabry as a possibility. For instance, if you have heart disease, renal failure or stroke, you might ask the doctor, **"Should I be screened for Fabry?"** Most patients with Fabry aren't diagnosed for 15 or 20 years. ◆

BY THE NUMBERS:

An estimated **10,000** Americans have Fabry disease

1 in 40,000 males has classic Fabry disease

Up to **5%** of males who have an early-onset first stroke may have undiagnosed Fabry's

A mother who is a carrier of Fabry disease has a **50%** chance of transmitting it to each son, and a **50%** chance that each daughter will be a carrier