# Rusty Organs

## Researchers identify the gene for iron-overload disease

By KATHLEEN FACKELMANN

You've probably never heard of hereditary hemochromatosis. Your doctor knows about it but probably thinks it's rare. Yet this iron-overload disease afflicts about 1.5 million people in the United States.

"It is the most common inherited disease that is known," says researcher Bruce R. Bacon of the St. Louis University School of Medicine. Only a fraction of those with the disorder receive a correct diagnosis, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. Although a diagnostic procedure is available, it is seldom used.

Without treatment, people can and do die of hemochromatosis. The disease deposits iron in the heart, liver, and other organs of the body. By the fifth or sixth decade of life, those organs have literally rusted away.

In a back-to-the-future twist, an ancient treatment—bloodletting—can save the lives of people with hemochromatosis. In fact, regular bloodletting can completely prevent the complications of the disorder.

Now, a simpler, more reliable method of diagnosing this disease may be on the horizon. In August, a U.S. team announced that it had discovered a flawed gene that may be responsible for iron overload. In November, two research groups, one in France and the other in Australia, confirmed that finding. Such work is expected to lead to a genetic test for the mutant gene.

"With the techniques of molecular biology, it's not difficult to make a diagnosis," comments Philip Aisen, a hemochromatosis expert at the Albert Einstein College of Medicine in New York. "If you make the diagnosis, you can quite literally save someone's life."

For 20 years, researchers knew that the gene for hemochromatosis resided on chromosome 6, one of the 23 pairs of human chromosomes, but they were unable to pinpoint it. Then Roger K. Wolff of Mercator Genetics in Menlo Park, Calif., and his colleagues decided to jump into the race to find this iron-regulating gene. They suspected that most people with the disease had the same mutation.

"The majority of people with this disorder actually inherited the mutation from a common ancestor long lost in history," Wolff says.

The study focused on 178 people with iron-overload disease who had been diagnosed at 32 medical centers across the country. The researchers homed in on the segment of DNA that the patients had in common, a tactic that gave the scientists a shorter region of chromosome 6 to scour for the disease-causing mutation.

They then began a painstaking search of the segment's 250,000 base pairs, the chemical units that make up DNA. The team identified 15 genes, including one that appears to be the culprit. They called it *HLA-H*. A single flaw in the chemical units that make up this gene appeared in 85 percent of the patients studied. That mutation leads to an alteration—a substitution of the amino acid cysteine for a tyrosine—in the protein that the gene encodes.

The team also found a second, much less common mutation in *HLA-H*, but it's not clear how this change contributes to the disease, Wolff says. Together, the mutations account for 87 percent of iron-overload patients in the study. The researchers published their findings in the August NATURE GENETICS. At that time, they added the caveat that the *HLA-H* gene might not be the cause of the disease. They noted that a nearby gene could be at the root of the disorder.

That possibility seems unlikely now. An Australian group offered what it believes is solid proof of the link between the disease and *HLA-H*. Elizabeth C. Jazwinska of the Queensland Institute of Medical Research in Brisbane and her colleagues studied DNA taken from 112 iron-overload patients. All 112 had the major mutation identified by Wolff's team. At a recent meeting of the American Society for Human Genetics, Jazwinska called the findings "unequivocal proof" that the *HLA-H* gene causes hereditary hemochromatosis. Her group published its findings in the November NATURE GENETICS.

In that same issue, French scientists reported that among their patients with iron-overload disease, 59 out of 65 had the same mutation.

Taken together, the results argue strongly for the gene's role in iron regulation. "It is always possible that a mistake has been made," Aisen says, "but I think the preponderance of evidence is that [*HLA-H*] is really the gene."

Researchers have yet to figure out how a mutant form of the gene might cause the symptoms of iron-overload disease. Indeed, scientists admit they know very little about how a normal version of this gene works. They do know that *HLA-H* belongs to a family of immune system genes that encode a group of proteins called MHC class I. Such proteins alert killer blood cells to an infected or cancerous body cell that needs to be destroyed.

Why such a gene would play a role in iron regulation remains a mystery. The researchers speculate that the out-of-whack gene carries the blueprint for a faulty protein that somehow leads the gut to absorb too much iron, which then gets into the bloodstream.

"Iron is both toxic and absolutely essential," notes epidemiologist Sharon McDonnell of CDC. The body needs iron for many purposes, notably to synthesize hemoglobin, which transports oxygen to tissues. Normally, carrier proteins in the blood pick up iron and sequester it, a process that keeps it from causing harm.

In people with hemochromatosis, however, something goes wrong with that system. The carrier molecules become saturated with iron, and the excess spills over to the cells of the liver, pancreas, heart, and other organs.

Then the iron starts to oxidize the cells of those organs. "It's rust," McDonnell says. Over time, the rusty organs fail, leading to heart and liver disease and other complications, including insulin-dependent diabetes.

Iron is also deposited in the skin, making some people with the disease look like they have a year-round tan, McDonnell notes, hence the term "bronze diabetes."

Hereditary hemochromatosis is often diagnosed as another condition, says James D. Cook of the University of Kansas Medical Center in Kansas City. An iron-overload patient can be diagnosed with diabetes, heart disease, liver disease, or arthritis. Very rarely does a doctor ask whether the patient has an under-

lying problem of iron regulation, McDonnell adds.

In part, that's because most doctors were taught that hemochromatosis is uncommon, afflicting mostly white males. "I have a *Cecil Textbook of Medicine* from when I went to medical school," McDonnell says. "It's only 10 years old, and it still talks about this rare genetic disorder." More men than women do seem to suffer the symptoms of hemochromatosis, perhaps because women lose blood, and thus iron, on a monthly basis.

Recent studies have shown that hereditary iron loading is much more common than many doctors believe. The CDC now says it afflicts 1 in 200 people.

Furthermore, it is not just a disease of white men. A study in the Nov. 15 MORBIDITY AND MORTALITY WEEKLY REPORT shows that hereditary hemochromatosis is also very common in Hispanic populations. The investigation was the first to suggest that whites and Hispanics have a similar disease rate. Other studies have indicated that the disease also occurs in blacks. "The more you look for it, the more you find it," McDonnell says.

The prevalence of hemochromatosis has led to speculation that the mutation may originally have conferred some advantage on people who inherited it. Timothy Cox of the University of Cambridge in England suggests that the altered form of this gene is maintained by natural selection as a hedge against nutritional deficiency. A third of the world's population still suffers from a lack of iron, he notes.

Although people with one copy of the altered *HLA-H* gene typically don't suffer any symptoms, their intestines avidly absorb iron. A study in the Dec. 12 NEW ENGLAND JOURNAL OF MEDICINE shows that these carriers have higher-than-average concentrations of iron in their blood. This would be a boon in an environment where the metal was scarce.

Even for people who inherit both copies of the flawed gene, the consequences of iron loading often don't become apparent until later in life, Cox says. Especially for women in developing countries, a double dose of the iron-loading gene might prove helpful in warding off iron deficiency, he says.

Mercator Genetics says it will have a blood test available early this year. Judging by the scientific reports thus far, that test should identify at least 87 percent, and perhaps close to 100 percent, of the people who have both copies of the altered gene.

Most people with this disorder today don't get a correct diagnosis until it is too late—the iron deposited in their joints and organs has already done irreversible damage. But regular bloodletting—a procedure similar to donating blood—can outwit the disease. People with hemochromatosis must continue this therapy for life if they are to avoid the consequences of the disease.

The beauty of a genetic test is that it would detect people with the disease before symptoms appear. These could include members of a patient's family who don't have any symptoms but who nonetheless are accumulating a toxic load of iron, Cook says. With therapy, such people can live completely normal lives.

One person out of every 10 in the United States carries a flawed copy of the gene. These people can pass on the defect, but they generally will sustain no ill effects themselves. Only if they suffer from another liver-damaging disease, such as viral hepatitis or alcoholism, might it cause a problem.

*Throughout history, doctors have relied on bloodletting to treat humans (as well as horses) for a variety of medical conditions.*

For family members who don't have the mutant gene and thus can't pass the disease to their children, the test results would be even more reassuring, Aisen adds.

Mercator believes the genetic test is slated not just for families of hemochromatosis patients but for a much larger group. They hope that in the future, any patient going to the doctor for a physical exam would get a genetic test for the mutant *HLA-H*.

"It's the ideal test for a populationwide screen," says Bacon, a coauthor of the August NATURE GENETICS study. "Whether or not it will come to that, I don't know."

Questions about the genetic test remain. For example, does everyone with two copies of the flawed gene eventually suffer from the disease? Why do a few people get symptoms of the disorder in their twenties, while others show no hint of a problem until later? Will insurers or employers use the test result to discriminate against individuals with the disorder?

Furthermore, a genetic test would have to compete with the inexpensive blood test already available. The transferrin saturation test tells doctors when there is too much iron in a person's blood. This sign of danger is usually followed by a liver biopsy, to check for signs of liver damage due to iron deposits. Generally, the transferrin saturation test is not a routine part of a physical exam.

For years, Margit A. Krikker, medical director and founder of the Hemochromatosis Foundation in Albany, N.Y., has been urging federal officials to begin widespread screening for the disease. The foundation was so frustrated by lack of interest that it bought an ad in the New York Times to alert the public to this deadly condition. Krikker believes that the transferrin saturation test is sufficient for screening, at least for now.

Indeed, the CDC intends to recommend widespread screening for hemochromatosis this spring. It plans to advise doctors to order such a test for all patients age 18 and older, McDonnell says. It will also urge doctors to explore a diagnosis of iron overload for any patient with diabetes, heart disease, impotence, joint pain, or liver disease, she adds.

The agency has taken this step because the early symptoms of iron overload are absent entirely or easy to miss. Severe fatigue or abdominal pain can be the first sign of the disease, McDonnell says.

Whether the genetic test will offer an advantage over the transferrin saturation test remains to be seen. It will almost certainly be more expensive, Krikker says. The transferrin test typically costs between $10 and $20. Mercator has yet to price its genetic test, but the recently marketed test for two mutated genes that can cause breast cancer costs as much as $2,400.

Cook notes that results of the transferrin saturation test can vary from day to day. Thus, a diagnosis of iron overload can require a series of measurements, followed by liver biopsy. If Mercator works the bugs out of the genetic test, it would give patients the relief of a quick diagnosis, Cook says.

A genetic test for hemochromatosis also avoids the pitfalls presented by the much-touted breast cancer test, Aisen points out. Women who get a positive result from that test have no definitive way to avoid the disease (SN: 12/9/95, p. 394). In contrast, a positive test for hemochromatosis can be followed by a lifesaving course of action.

Such a test could even be given at birth. If a baby inherited both copies of the mutant *HLA-H* gene, he or she could receive the ancient treatment of bloodletting—a treatment that offers no less than a cure. □