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PREDICTING DISEASES

New Genetic Clues to Heart Disease, Cancer, AIDS And Other Killers Could Save Your Life

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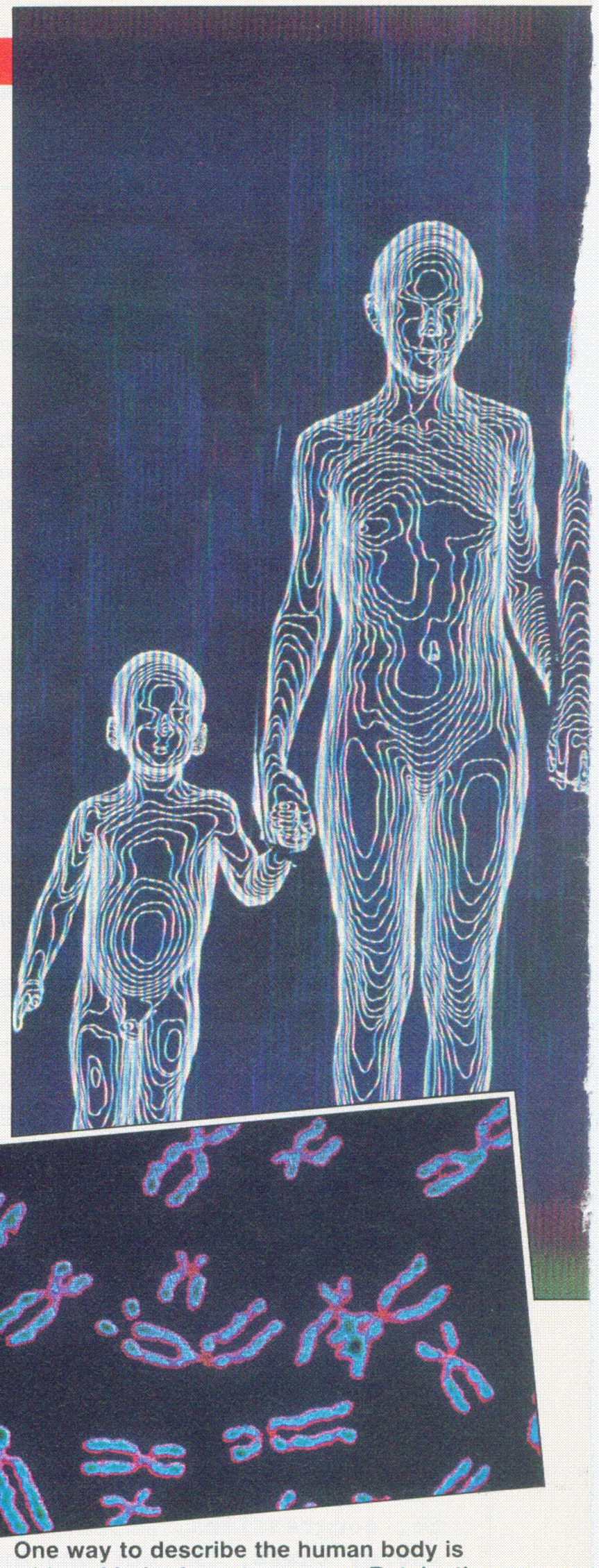
Medical researchers are nearing a dream of every physician since Hippocrates. Gene tests, performed even before birth, will let people know what health risks lie 10, 20, even 40 years ahead. The information could help prevent many illnesses before it's too late

PREDICTING DISEASES



One way to describe the human body is with a kind of contour map. But in the dance of the chromosomes lies true artistry. Each human chromosome like those above is a double strand of thousands of genes, strung like beads. The genes point to the future—to sickness and to health

■ "Why me? I take care of myself. Why am I sick?"

Why indeed? Why do some smokers get lung cancer while others puff away and live happily ever after? Why does one man die of a heart attack in his early 40s while his brother gorges on marbled steaks to no ill effect? Why do some carriers of the AIDS virus develop the full-blown disease while other infected individuals remain free of symptoms?

If doctors knew the answers, they could catch illnesses early, perhaps even prevent them altogether. But until recently, there was no way of knowing whether you had inherited Uncle Bert's gene for emphysema or Grandma's predisposition to manic depression.

That's all changing. With precision undreamed of even five years ago, medical scientists are rapidly zeroing in on the genes that influence, and occasionally dictate, an individual's health even into old age. In just the last few years, researchers have identified patterns of genes that raise a person's susceptibility to heart attacks, emphysema, juvenile diabetes, multiple sclerosis and certain rare cancers. Since January, scientists have found genes associated with Alzheimer's disease, cleft palate and two different types of manic depression. Two weeks ago, British researchers announced they had identified a pattern of inherited cell proteins that could explain why only some people exposed to the AIDS virus get the disease. Ten days later, a gene linked to schizophrenia came to light. "What will the gene of the week be?" quips Dr. Brenda Conner, a geneticist at the City of Hope National Medical Center in Duarte, Calif.

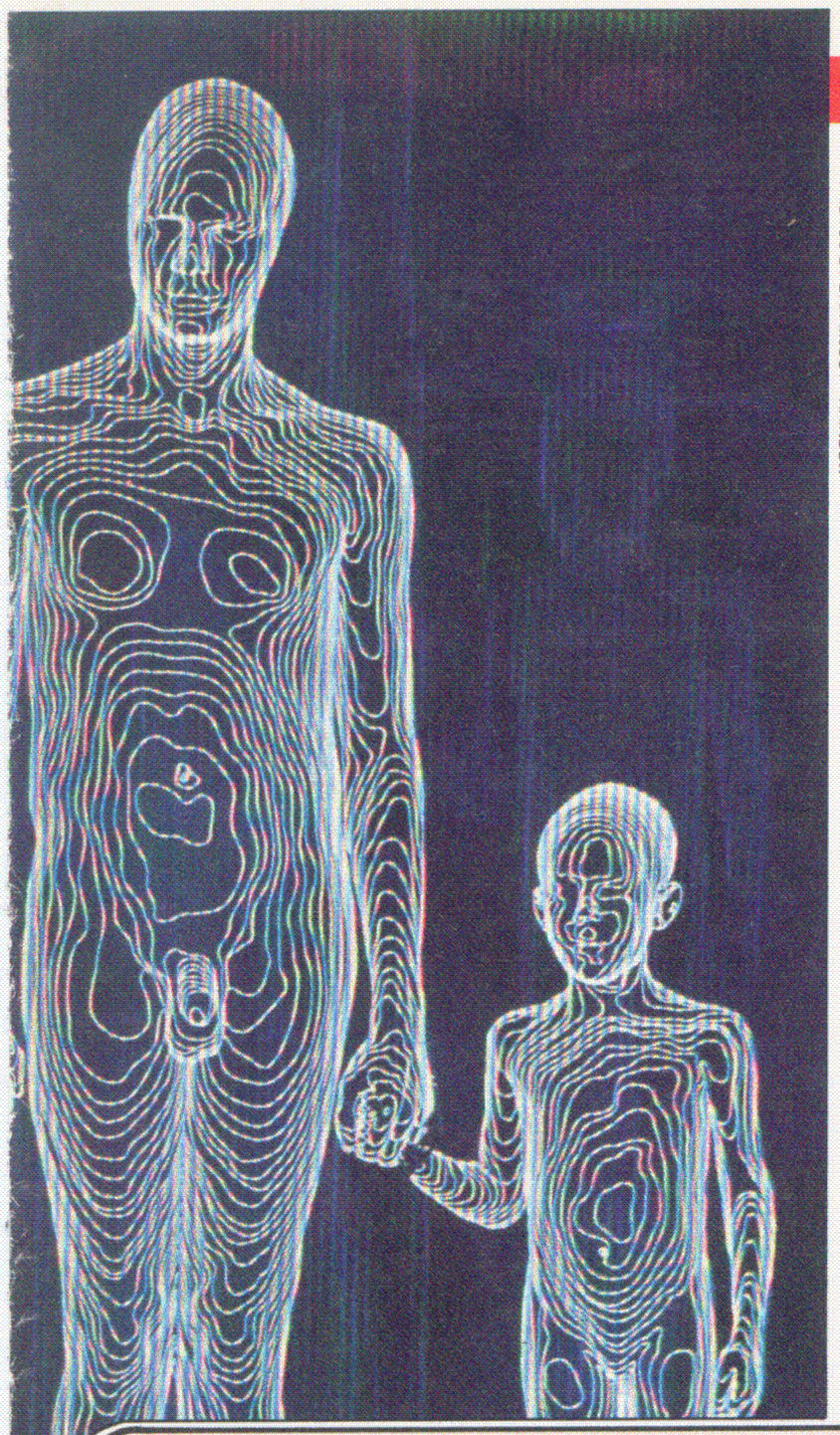
Collaborative Research, a company in Bedford, Mass., that leads in developing genetic tests, claims to be two years away from a complete map of the 23 pairs of human chromosomes. It will let scientists pinpoint all the genes associated with human illness, from obscure metabolic disorders to big killers like atherosclerosis or hardening of the arteries. If people are alerted to the genetic liabilities they and their children carry, they can develop healthy habits for life, or at least be treated at the earliest possible stage. "What we're working toward is genetic counseling for the common man," says Collaborative Research chairman and founder Orrie Friedman.

Portent of a vision

Such research is certain to lead to drug therapies that address the underlying causes of disease. In the distant future, it may even be possible to correct a handful of hereditary diseases by genetic engineering—substituting a healthy gene for a defective one.

Much must happen before even Friedman's vision becomes a reality. Most of the new genetic tests are still being evaluated and improved, and the few available are offered piecemeal. But in a portent of things to come, Focus Technology of Washington, D.C., is already incorporating genetic tests developed by commercial and academic laboratories into an innovative "wellness" program for 1,000 employes at Chesapeake & Potomac Telephone. Under the plan, computers analyze detailed family histories for volunteer participants. Then, the patient's blood is subjected to 32 tests for 14 diseases, including cervical cancer, gum disease and diabetes. One test sets a percentage risk that any particular woman will develop breast cancer. Finally, a "health advocate" reviews the results with the patient, who signs a "personal-health action plan" describing preventive steps he or she will take.

Most people will be getting genetic profiles by the year 2000, predicts Michael McGinnis, director of the U.S. Office of Disease Prevention and



PHOTOS BY DAN McCOY—RAINBOW

THE TEST–AND THE ILLNESS TOLL

Tests and total Americans affected—

NOW AVAILABLE	TOTAL CASES
Adult polycystic kidney disease	500,000
AAT deficiency *(emphysema)*	120,000
Fragile X syndrome	100,000
Sickle-cell anemia	65,000
Duchenne muscular dystrophy	32,000
Cystic fibrosis	30,000
Huntington's disease	25,000
Hemophilia	20,000
Phenylketonuria	16,000
Retinoblastoma *(childhood eye cancer)*	10,000

ON THE HORIZON

Hypertension	58 million
Dyslexia	15 million
Hardening of arteries	6.7 million
Cancer	5 million
Manic depression	2 million
AIDS carriers	1.5-4 million
Schizophrenia	1.5 million
Juvenile diabetes	1 million
Familial Alzheimer's	250,000
Multiple sclerosis	250,000
Myotonic muscular dystrophy	100,000

These listings don't include carriers, which in some cases dramatically increase the number.

Health Promotion. Health care will improve dramatically, he argues, because knowing one's risks will motivate lifestyle changes far more powerfully than warnings based on large groups of people. "It is one thing to tell a smoker he has a tenfold greater chance of getting lung disease based on national statistics," says McGinnis, "and quite another thing to tell him he lacks the gene for a lung-protective protein and will almost certainly get emphysema."

Sticky questions are bound to arise: Could it be that knowing your medical future—or your child's—might prove more traumatic than beneficial? Could it lead to a weeding-out of "unacceptable" fetuses through abortion? Will high-risk people be deprived of jobs or medical insurance? As testing for the AIDS virus has demonstrated, there are no absolute answers and plenty of room for abuse. With continuing publicity, the public may also come to expect too much too soon. Cautions Raymond White, a geneticist at the University of Utah School of Medicine: "We have a few more miles to go before translating interesting findings into practical significance."

For starters, most of today's probes aren't capable of pinpointing a bad gene. They can only detect sequences of healthy genes, called markers, that are usually found near a bad one. Finding an abnormal gene in such an indirect way is expensive and time-consuming. To determine how the marker is inherited, researchers must study many relatives, including at least one suffering from the disease. Getting results can take weeks or months. And because the marker can be inherited without the defective gene, findings may be misleading.

Once improved tests allow scientists to home in on a defective gene, much of the uncertainty should vanish. This could happen by the mid-1990s. Testing will be a one-step process, and the probes are likely to cut the cost of genetic screening to a fraction of its present price.

The finely targeted probes will first be used to screen fetuses and adult carriers for illnesses caused by a single gene, such as cystic fibrosis. Some 3,000 disorders fall into this category, but only a few—the ones that are relatively common—have received intense commercial attention. Besides cystic fibrosis, there are Duchenne muscular dystrophy and adult polycystic kidney disease, which accounts for one quarter to one third of the cases of kidney failure in the United States.

Heart disease, mental illness and most cancers aren't so easy, because they usually involve many genes. How these genes interact with smoking, diet and other environmental influences is also very poorly understood. Still, progress has come more swiftly than expected, and nowhere has it been more impressive than for genes that contribute to heart attacks.

HEART DISEASE

The last five years have witnessed a revolution in piecing together the inherited causes of heart disease. The first breakthrough came in 1983, when Dr. Michael Brown and Dr. Joseph Goldstein, geneticists at the University of Texas Health Science Center in Dallas, identified several mutations in a gene involved in the premature onset of atherosclerosis. People with this genetic defect cannot efficiently remove low-density lipoproteins, or LDL's—the "bad" combination of cholesterol and protein that contributes to heart disease. About 1 in 500 individuals carries the mutant gene. Such people are prone to heart attacks in their 30s.

> 'People will no longer be able to say, 'Why me?' Instead, they'll be having a say in why *not* me'
>
> **Federal health official Michael McGinnis**

There is often no warning. "It's known as the silent killer," says Goldstein, "because cholesterol builds up in the arteries for years before any symptoms become apparent. Indeed, the first symptom may be a heart attack."

Brown and Goldstein's discovery earned them the 1985 Nobel Prize in medicine, and their work has led to the identification of at least a half-dozen other genes with a role in heart disease. At Tufts University in Boston, for example, a team led by Dr. Ernest Schaefer and José Ordovas recently found a different defective gene, one associated with heart attacks that occur after age 40. The gene interferes with the body's ability to produce high-density lipoproteins, or HDL's—the "good" lipopro-

teins that transport cholesterol out of the bloodstream. The defect is carried by 1 in 25 people, making it the most common genetic cause of cardiovascular disease. Nearly a third of patients with confirmed heart disease have it.

Capitalizing on these advances, several bio-tech companies are competing to manufacture probes to detect the 12 or so genes now believed to have a major impact on the development of heart disease. With 1 in 4 Americans at risk, a huge demand for their product is virtually guaranteed. California Biotechnology of Mountain View, Calif., plans to introduce a genetic test for predisposition to atherosclerosis by 1989. The company has identified a series of genetic markers that increase an individual's risk of atherosclerosis by two to four times. It has also discovered markers that *lower* a person's risk of getting the disease by as much as one third.

Currently, cardiovascular disease often goes undiagnosed until the amount of cholesterol circulating in the blood jumps to dangerous levels, causing irreversible damage to the arteries. "If we could forewarn those at risk," says John Lewicki, vice president of research at California Biotech, "it would be a huge step forward. Stress, exercise, smoking, diet—all these factors relate to heart disease and unlike genes, are readily modifiable."

Beyond prevention, therapy could be fitted to the precise needs of the patient with heart disease. "We will see an explosion in the development of treatments tailored to the family's particular genetic disorder," says Nobel laureate Goldstein. Spurred by Goldstein and Brown's work in explaining the role of LDL's in some familial types of heart disease, the pharmaceutical house Merck, Sharp & Dohme resumed research on a long-shelved drug called Lovastatin. It is so effective in lowering blood-cholesterol levels that normally restrained physicians are describing the drug in such glowing terms as "great leap forward," "breakthrough" and "tremendous advance."

LAWRENCE MASON, JR., FOR *USN&WR*

FRAGILE X

It helped to find out, even if Adam stayed the same

At 9 months, Adam seemed laconic and didn't crawl. Annette Genovesi's husband accused her of being too impatient with the infant. She responded by constantly bursting into guilty tears. At 5½, Adam's problem was finally diagnosed: Fragile X syndrome, a chromosomal defect that causes retardation almost as often as Down syndrome. Mrs. Genovesi was relieved. "When I realized this kid was not going to be normal despite anything I did," she says, "I was freed to make some very constructive decisions." Now 7, Adam attends a school for the retarded and takes an experimental drug that could improve his language and eye contact. The Genovesis are considering having another child but don't know whether a fetus with fragile X will be unaffected or retarded. "It's a difficult decision," says Annette Genovesi. "I couldn't bear to go through this again."

CANCER

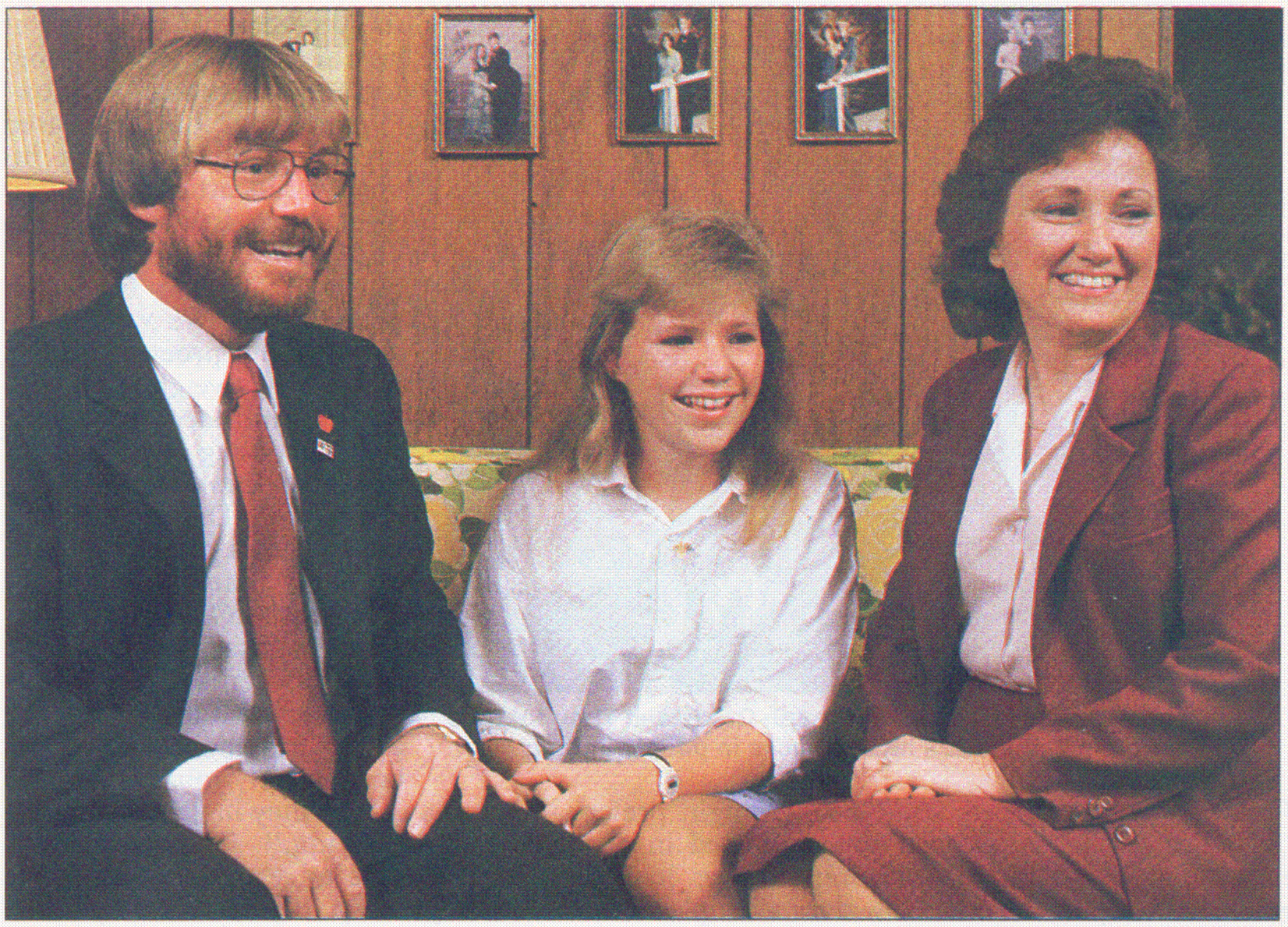
Since 1983, scientists have revealed some 36 human genes involved in different forms of cancer. These genes are essential for normal growth, but can be subverted to cause a tumor. Why an otherwise useful gene would declare mutiny on the body has been one of the hottest questions of modern science.

An explanation may be close, says Dr. Jorge Yunis of the University of Minnesota Medical School in Minneapolis. A pioneer of innovative techniques for studying the detailed structures of chromosomes, Yunis has found that 70 percent of oncogenes, or cancer-causing genes, are located near inherited weak points on chromosomes—regions where the genetic molecule is prone to breakages and rearrangements. Varying from individual to individual, these fragile sites are particularly vulnerable to attack by chemical carcinogens, X-rays, viruses and other cancer-inducing agents. "If a chromosome snaps apart in the immediate vicinity of an oncogene," says Yunis, "normal genetic control mechanisms break down and the stage is set for the formation of cancer."

Yunis has shown that such a sequence of events occurs at the onset of numerous leukemias, lymphomas and some tumors of the lung, colon and breast. By better understanding how internal and external factors contribute to these diseases, he believes it will eventually be possible to identify healthy individuals prone to cancer.

Yunis and other investigators have found that petroleum-based products—notably pesticides and insecticides—damage specific sites on chromosomes 5 and 7, two of the 23 pairs of human chromosomes that carry genetic information. In theory, farmers with fragile sites at those locations are more likely to get leukemia and could be warned to minimize their exposure to chemicals. Similarly, tobacco smoke tends to attack a part of another chromosome, so smokers with a fragile site in that portion may run an increased risk of lung cancer. If so, they might be encouraged to quit cigarettes. Even radiation produces selective chromosomal damage, raising the possibility of forewarning sunbathers prone to skin cancer.

Intriguing though these associations are, Yunis stresses that it will take 10 or more years of clinical trials to find out whether knowledge of personal risks can prevent cancer. Meanwhile, he is



CHAS CANCELLARE FOR *USN&WR*

DYSLEXIA

There's no gene for laziness

Maureen Peterson, right, knows what it means to be stigmatized. So do Edward, her oldest son, and Pammie, his daughter. All have dyslexia. "I dropped out of school because the nuns made me feel lazy and stupid," says Mrs. Peterson. "I was brilliant at mathematics, so everyone thought I was falling behind in reading because of lack of effort." Five years ago, researchers at the Mailman Center in Miami found she has a gene since tied to many dyslexia cases. "Once I knew the reason, it was easier to live with."

using his forecasting talent to help individuals whose disease has already been diagnosed. In particular, he has found chromosome rearrangements in leukemia and lymphoma cells that signal whether a patient will go into remission or, alternatively, die within a few months. The ability to predict the likely course of the disease will save lives by permitting clinicians to decide whether the patient needs an aggressive or milder treatment.

AIDS

Not everyone who carries the AIDS virus is certain to get the disease. An estimated 1.5 million to 4 million Americans have come into contact with the AIDS virus but remain free of symptoms. British researchers have just learned that the vulnerability of an individual, or of an entire ethnic group, to the lethal virus depends at least in part on genes. A team led by Lesley-Jane Eales of St. Mary's Hospital Medical School in London looked at six varieties of an inherited protein found on all human cell surfaces. The researchers concluded that one of the protein variations makes the people who carry it highly resistant to AIDS, while another makes them highly vulnerable. The other four variations fall in between.

The work may shed light on why the disease is spreading so rapidly among heterosexuals in Central Africa. Blacks from that region are nearly 10 times likelier than Caucasians to carry the "most susceptible" protein. Even people with the "most resistant" form of the protein aren't entirely safe from AIDS, so the practical value of a test is unclear. Lab technicians and medical professionals who work with the virus could be screened, says geneticist Stephen Daiger of the University of Texas in Houston. But he warns that information from the test "might actually be dangerous to those in high-risk groups, such as homosexuals, if it leads them to think they are protected when in fact they are not."

MENTAL ILLNESS

Emboldened by the discovery of genetic markers for dyslexia, Alzheimer's and manic depression, unprecedented numbers of geneticists are now being drawn to the study of mental and behavioral disturbances.

At the annual meeting of the American Psychiatric Association this month, researchers at the University of British Columbia in Vancouver reported finding a possible genetic marker for schizophrenia. Other research groups are hot on the trail of genetic markers for certain panic disorders that occur even without stress. And evidence of genetic underpinnings for alcoholism could lead to susceptibility tests for teenagers. "If it were me," says Friedman of Collaborative Research, "and I knew I was predisposed to alcoholism, I wouldn't take my first drink."

> 'Our discovery is great for science—but on a personal level, I'm no longer sure it's an advantage to know these things'
>
> **Molecular biologist José Ordovas**

The practicality of such tests will depend on whether genes are the main—or even frequent—cause of mental disturbances. Take Huntington's and Alzheimer's, two neurological disorders that strike late in life. "Huntington's disease is always caused by a gene, but only 10 percent of Alzheimer's cases have been clearly traced to heredity," says James Gusella, director of the Neurogenetics Laboratory at Massachusetts General Hospital in Boston and part of a team that discovered genetic markers for the two diseases. He believes that tests for predisposition to Alzheimer's will be limited to families with a history of the disease. When heredity plays a role, the disease is more likely to strike in the late 40s and 50s than after age 60, when the majority of cases occur.

It's hard to spot early warning signs of mental disease when a single diagnostic label might be pinned to a multitude of biochemical abnormalities. In one Pennsylvania Amish family with a history of manic depression, for example, the culprit gene was traced to chromosome 11. By contrast, a gene on the female sex

Sampled from the womb, the cells shed by a fetus can reveal some 200 diseases

Prenatal tests and where to get them

Clinics and centers that test for genetic defects will multiply over the next few years. For now, extensive tests are mainly performed on pregnant women. Most major medical centers offer the following prenatal tests:

• *Anencephaly* and *spina bifida.* A simple blood test of the mother at the end of the first trimester, or about the 13th week, of pregnancy can signal deformities in the fetal nervous system. These include anencephaly (literally "lack of brain") and spina bifida ("split spine"), in which the lower end of the spine and spinal cord fail to close properly. The test is also a flag for Down syndrome, a chromosomal disorder that causes mental retardation. The procedure detects abnormal levels of alfa-fetoprotein, a substance the fetus excretes through the placenta into the mother's blood. California now requires that the test be made available to all pregnant women, and currently about one third of pregnancies in the Northeast are being screened. The cost, which most health plans cover, is between $30 and $40. Because the test results are not always accurate, however, pregnant women with abnormal AFP levels should go for other tests, such as amniocentesis and ultrasound, for confirmation.

• *Amniocentesis.* This test is usually performed in the fourth or fifth month of pregnancy. The procedure is done together with ultrasonography, a painless technique that produces an image on a TV monitor by bouncing sound waves off the fetus. Guided by the picture, a clinician inserts a needle through the abdomen and into the womb—there's usually little or no sensation—to withdraw fetal cells floating in amniotic fluid. The test is offered routinely to women over 35, who have a 1-in-300 chance of having a child with a gross chromosomal disorder.

• *Chorionic villus sampling.* Fetal cells are removed through the vagina, so it is less invasive than amniocentesis. This method of obtaining the cells is still experimental, even though it is becoming an increasingly popular alternative to amniocentesis. CVS can also be done as early as the ninth week of gestation—when abortion is a less traumatic option.

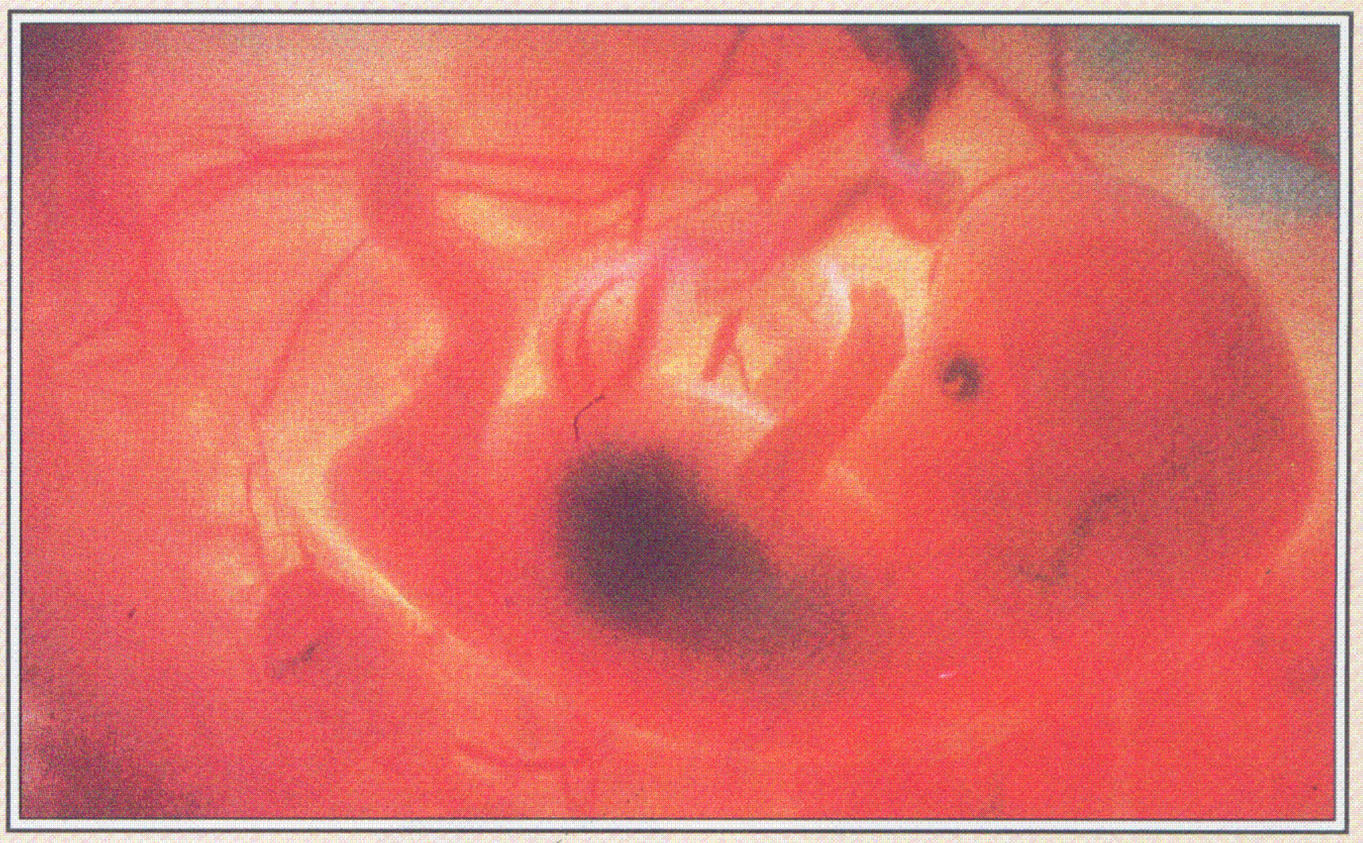


PHOTO RESEARCHERS, INC.

The well-being of this 4½-month-old fetus is foretold in the cells it sheds

The cost of both amniocentesis and CVS is around $900. Insurance companies will usually pick up the tab if a woman is in her 30s, has a family history of hereditary disease, or if her AFP test is abnormal.

Once fetal cells are obtained, either through amniocentesis or CVS, they are subjected to biochemical tests and microscopic analysis. If there is a family history of diseases, newly developed probes may be used that directly analyze the genetic material inside the fetal cells. Together, these screening methods can detect some 200 abnormalities. Because direct analysis of fetal genes is expensive and time-consuming, however, most pregnant women would only get a small fraction of the total number of tests available.

A few leading medical centers also offer genetic tests for healthy adults whose family history suggests that they are at high risk of developing certain diseases at a later age.

For more information about hereditary diseases and where to seek genetic counseling, contact the organizations listed at left.

FINDING HELP

Fragile X Foundation
P.O. Box 300233
Denver, Colo. 80220
(800) 835-2246 ext. 58

Cystic Fibrosis Foundation
6931 Arlington Rd.
Bethesda, Md. 20814
(301) 951-4422

National Tay-Sachs and Allied Diseases Association
92 Washington Ave.
Cedarhurst, N.Y. 11516
(516) 569-4300

Muscular Dystrophy Association
810 Seventh Ave.
New York, N.Y. 10019
(212) 586-0808

National Hemophilia Foundation
110 Greene St.
Room 406
New York, N.Y. 10012
(212) 219-8180

National Kidney Foundation
2233 Wisconsin Ave., N.W.
Suite 320
Washington, D.C. 20007
(202) 337-6600
Pamphlet on polycystic kidney disease

National Maternal and Child Health Clearing House
38th and R Sts., N.W.
Washington, D.C. 20057
(202) 625-8410
Pamphlets on hemophilia, phenylketonuria, sickle-cell disease, homocystinuria and other diseases

March of Dimes
1275 Mamaroneck Ave.,
White Plains, N.Y. 10605
Booklet on genetic counseling

Huntington's Disease Society of America
140 West 22d St.
(6th floor)
New York, N.Y. 10011
(800) 345-HDSA

Cooley's Anemia Foundation
105 East 22d St., Suite 911
New York, N.Y. 10010
(800) 221-3571 or (800) 522-7222 in New York

National Society of Genetic Counselors
Clinical Genetics Center,
Children's Hospital of Philadelphia
34th and Civic Center Blvd.
Philadelphia, Pa. 19104
(215) 596-9802