UT News
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****LDL receptor test developed to identify persons with familial hypercholesterolemia

DALLAS--Researchers in Dallas have developed a test that can identify the one in 500 persons who is born likely to have a heart attack before middle age.

Dr. Jennifer Cuthbert, collaborating with Drs. Cara East, David Bilheimer and Peter Lipsky, all of The University of Texas Health Science Center at Dallas' internal medicine department, has found a simplified way to identify people who have familial hypercholesterolemia (FH), or inherited high blood cholesterol.

People with FH have only half the normal number of specialized molecules called LDL receptors on their cells' surfaces. LDL receptors pull cholesterol-carrying low density lipoproteins (LDL) out of the blood and into the cells. In people with FH, excess cholesterol adheres to artery walls, narrowing the artery and slowing the flow of blood to the heart, a condition known as atherosclerosis. If a clot forms at the narrowed point, the blood flow is completely cut off, and a heart attack results.

Recent medical advances in treating FH have made it possible to lower cholesterol levels and help prevent the development of atherosclerosis. However, it has been difficult to differentiate people with defective LDL receptors from people having high cholesterol levels for other reasons. The only previous accurate test, using cultured skin cells, takes two to three months to complete. The new test developed in Dallas takes four to six days, and improved techniques may decrease the time even more.

Cuthbert explains that her test is based on the fact that lymphocytes, or white blood cells, need cholesterol to multiply. As the lymphocyte divides in two, it uses cholesterol to form the new cell membrane, or outer covering. In normal circumstances, the white blood cell can produce the necessary cholesterol internally or it can pull cholesterol-carrying LDL from the surrounding blood with its LDL receptors.

To test the efficiency of a person's LDL receptors, Cuthbert isolates lymphocytes from a blood sample and puts them in a culture that is free of LDL cholesterol. The lymphocytes' ability to manufacture cholesteral internally is suppressed by adding Mevinolin, a drug developed for that purpose in treating FH patients.

The lymphocytes, unable to produce their own cholesterol and unable to draw any from the culture medium, cannot reproduce.

At that point Cuthbert begins adding LDL cholesterol to the culture in tiny increments (one microgram per milliliter at a time). As the culture becomes richer in LDL cholesterol, the lymphocytes take it up through their receptors and begin to divide.

Lymphocytes drawn from individuals with average cholesterol counts begin to divide at a normal rate after three or four micrograms/ml. have been added. The same holds true for lymphocytes drawn from people with above average cholesterol levels but normal numbers of LDL receptors.

In contrast, the lymphocytes from FH patients require twice as much LDL--five to 10 micrograms/ml.--to be able to divide and reproduce at a normal rate.

The results of the first testing series was reported in the April 3, 1986, issue of the *New England Journal of Medicine*.

"Our original tests on 25 people proved very accurate," says Cuthbert. "Our next step, given funds, will be to test 300 to 500 people with high cholesterol levels

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during the next two or three years. That will prove whether the test retains accuracy on a wider population base.

"If it holds true, and we believe it will, we can use the test to screen young people who have high cholesterol levels or family histories of heart attacks at an early age. If we identify people with FH while they are young, with specific treatment we may be able to prevent heart disease later."

Identifying the people with FH among a large population with high cholesterol may also make it easier to isolate and identify other causes of high blood lipids, she says.

The new test will benefit children born with the milder, heterozygous form of FH, in which one parent contributes a normal gene for LDL receptors and the other contributes a defective gene. Heterozygous FH is fairly common, affecting about one in 500 people in most ethnic groups, possibly 400,000 persons in the United States. The LDL level in their blood is twice the normal level, and they begin to have heart attacks by the time they are 35. One in 20 persons who has a heart attack before age 60 suffers from heterozygous FH. It has been difficult to diagnose because the one good gene does contribute its share of functional LDL receptors, masking the symptoms.

The much more severe homozygous form of FH results when a child inherits defective LDL-receptor genes from both parents. Such children have circulating LDL levels more than six times higher than normal, and heart attacks can occur at the age of two. There has been no difficulty in diagnosing such cases even though they are extremely rare--about one in a million births.

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