Monoclonals Detect Likely Rheumatic Fever Victims

Rheumatic fever seems to run in families and for nearly 100 years investigators have looked for evidence that some people are genetically predisposed to get the disease. John Zabriskie of Rockefeller University reports that he and his colleagues have now found such evidence in the form of a clear-cut marker on cell surfaces. In addition Zabriskie has made monoclonal antibodies against the marker, thus making possible a test to screen newborn babies for rheumatic fever susceptibility.

Rheumatic fever follows an infection with streptococcal bacteria—usually a strep throat. In some people antibodies to the strep cross-react with heart tissue, causing permanent damage to heart valves. A typical scenario is for a child, aged 4 or 5, to come down with a sore throat and fever stemming from a strep infection. The sore throat goes away in a week to 10 days and the child feels fine. But in 3 to 6 weeks, the child complains of fatigue or swollen joints. By then, damage to the heart has occurred.

If the child had been given an antibiotic to knock out the strep infection in the first place, the heart damage would never have occurred. But, particularly in poor countries where antibiotics are at a premium, many children with strep throats simply are not treated. "There are large cardiac surgery clinics in underdeveloped countries in which 80 percent of valve surgery is done for rheumatic fever damage," Zabriskie says.

Zabriskie and his associates, working with Manuel Patarroy in Bogotá, Colombia, decided to look for a genetic marker for rheumatic fever. They would screen blood from rheumatic fever patients, looking for antibodies that might bind to antigens in the serum from other rheumatic fever patients.

In 1979, they had a success. The 883rd patient's blood they tested had antibodies that bound to an antigen present on B lymphocytes in 75 percent of all rheumatic fever patients but which was present only in 15 percent of nonrheumatic fever patients. They then made a monoclonal antibody, clone 19.23, with all the properties of the original antiserum. And they developed another monoclonal antibody, clone 256-10, that picks up many susceptible individuals that clone 19.23 misses.

Zabriskie and his associates report that clone 19.23 identified 70 to 75 percent of all rheumatic fever victims when it was tested on populations in New York, New Mexico, and India. This indicates that the antigen is distributed worldwide. Persons who carry the antigen on their cells have 15 times greater risk of getting rheumatic fever. It is possible, says Zabriskie, to test for the presence of the antigen at birth, using umbilical cord blood.

Zabriskie and his colleagues now are investigating how the presence of these antigens contributes to the development of rheumatic fever. For example, they are conducting experiments to determine what role the antigen plays in the immune response to strep infections. They are asking whether the marker might be a receptor for the adherence of strep to cells such as those of the tonsils. And they are asking whether different antigenic markers for rheumatic fever susceptibility have anything to do with the likelihood that individuals will develop long-term cardiac damage.

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Exercise During Pregnancy Reassessed

The evidence at first seemed so clear-cut and so logical: pregnant women who exercise vigorously may be depriving their babies of blood because blood will flow preferentially to the exercising muscles, so retarding the babies' growth. But, as James Metcalfe of the Oregon Health Sciences University in Portland pointed out, this apparently logical argument may be unfounded. Metcalfe's report is a story of how he and other investigators inadvertently misled themselves through a small, but crucial, element of experimental design.

After World War II, Metcalfe notes, physicians began reporting that babies born to women with rheumatic fever tend to be abnormally small. Then it was reported that small babies are characteristic of women who live at high altitudes, women who smoke, and women with cyanotic heart disease. "All those observations inferentially suggest that oxygen is what is missing—the common denominator is either a poor blood supply or blood with insufficient oxygen being carried to the uterus," Metcalfe says.

About 10 years ago, Metcalfe and his associates began to study pregnant women during exercise. They found that the fetal heart rate increases significantly but transiently after pregnant women do even mild exercise. It was likely, researchers thought, that the fetus was responding to a diminished blood supply.

Metcalfe decided to test this hypothesis with an experimental animal. A member of his group trained pregnant pygmy goats to exercise on a treadmill so that they increased their oxygen consumption to four times the amount consumed at rest. This is equivalent to walking briskly up a flight of stairs. For the last half of their pregnancies, the goats exercised for 10 minute periods three times a week. The results? "The goats carrying only one fetus delivered kids of normal size. Goats carrying twin fetuses delivered kids that were abnormally small," Metcalfe reports.

"These results strengthened our conviction that blood was drawn away from the uterus. Then other workers confirmed the fact that exercising of pregnant animals diminishes the growth of the fetus. This was shown for sheep and guinea pigs. We decided to investigate the oxygen supply to babies while the mother exercises," Metcalfe says.

But by this time the member of the group who had trained the pygmy goats to exercise had left the Oregon University group and a new trainer had been hired. The new trainer was dissatisfied with the standard method of teaching animals to exercise, that is by giving them an electric shock. She decided to teach them by rewarding them if they exercise.

The blood flow to the goats' uteruses decreased during exercise but—to everyone's amazement—all their babies, including the twins, were of normal size. Metcalfe believes that the blood flow to the placenta was maintained although the blood flow to the rest of the uterus was not. Thus the fetuses were not deprived of oxygen.

Next Metcalfe began studying preg-

nant women who exercise regularly. He enrolled them in a program in which they exercise three times a week. After studying 80 such women, he reports that their babies are entirely normal and healthy.

Asked if exercise is uniformly good or uniformly bad during pregnancy, Metcalfe replied, "I really don't know how to answer that question. The average woman used to exercising can continue to exercise while she feels good without jeopardizing her baby's health. But the women we studied were really great. They did everything right. They didn't smoke, they had good diets, they were very healthy. The way to find out whether exercise makes a difference is to get some of these women to stop exercising during their pregnancies. But try and get them to stop—we couldn't do it."

So, in the end, the only conclusion Metcalfe can draw is from the goat studies: women who feel that exercise is a punishment should not exercise when they are pregnant. Women who feel that exercise is a reward should go ahead.

What Is the Meaning of Childhood Hypertension?

A few years ago, a National Institutes of Health task force recommended that pediatricians start taking blood pressure measurements of children aged 3 years and older. Some medical researchers have suggested putting children whose blood pressures are in the high range on low-salt diets or even, possibly, giving them antihypertension drugs if their diastolic blood pressure goes over 90.

The implication in these discussions of what to do about childhood hypertension is that the children with high blood pressure will grow up to be hypertensive adults. But that is not at all established. Mary Jane Jesse of the University of Miami School of Medicine, who is the new president of the American Heart Association, says, "We still do not have predictors of hypertension that can be identified in the young and can be proven to be harbingers of adult hypertension."

When she and her associates looked at blood pressure distributions in children, she reports, "we were very surprised to learn that by age 13, children in the upper fifth percentile of blood pressures had diastolic blood pressures greater than 90 and systolic blood pressures greater than 140." But when Jesse repeated the blood pressure measurements 1 month later, only 1 percent of those in the upper fifth percentile based on the first measurements were still there. "Blood pressure tends to be fairly labile," she says. "You cannot identify from one or even two measurements who will get high blood pressure." Moreover, although more black adults than white adults have hypertension, Jesse found that there is no significant difference between the blood pressures of black and white children.

Jesse's conclusion is that studies are needed of young adults to see when a tendency to develop high blood pressure becomes apparent. "My major concern is that there is a lost generation. We clearly need more information on young people between the ages of 18 and 30. We need to follow them to see which teenagers at which blood pressure levels ultimately will have hypertension."

So why, then, did the NIH task force, of which Jesse was a member, place so much emphasis on taking blood pressure measurements of children? Jesse replies that the task force wanted to assure that those children with rare, but correctable, physiological defects causing high blood pressure, such as coarctation of the aorta, will be detected and treated. In addition, she says, the task force wanted to get pediatricians and parents used to thinking about high blood pressure.

Genetics and Cholesterol Metabolism

By bringing the tools of cell biology and genetics to bear on the problem of understanding cholesterol metabolism, a number of investigators hope to learn why some people have high concentrations of blood cholesterol and why this leads to an increased risk of heart disease.

Robert Mahley and his associates Stanley Rall, Karl Weisgraber, and Thomas Innerarity at the University of California in San Francisco recently made progress with this approach when they learned that a single amino acid substitution in a cholesterol-carrying protein is the cause of a well-known inherited disorder—type III hyperlipoproteinemia, which is characterized by large amounts of cholesterol in the blood and early death from heart disease. About 1 in 100 Americans is homozygous for the hyperlipoproteinemia mutation.

The cholesterol-carrying protein that is affected is called apo-E. Like other apolipoproteins, apo-E binds to specific receptors on the surfaces of certain cells. When it binds, it and the cholesterol it carries are taken up by the cells and metabolized.

Small particles, called chylomicron remnants, contain apo-E and cholesterol and are normally taken up by liver cells and metabolized. In patients with type III hyperlipoproteinemia, however, a substitution of cysteine for arginine at position 158 of the apo-E molecule prevents the liver receptor from binding apo-E. As a result, chylomicron remnants build up in the blood.

What happens to these chylomicron remnants? "One possibility, although it is not yet proved, is that macrophages in the arterial wall take up the chylomicron remnants," Mahley says. An atherosclerotic plaque consists of an accumulation of cholesterol in and around the cells of the artery wall. Some of these lipid-laden cells are macrophages, or scavenger cells. And macrophages will take up chylomicron remnants even when they contain the mutant apo-E protein typical of type III hyperlipoproteinemia.

Mahley and his associates are now working with Gerd Assmann of the University of Münster in Germany to screen for other apolipoprotein mutations that may be of biochemical significance. So far, the German group has analyzed blood samples from about 2000 individuals and has found three mutations in apo-AI, which is the major apolipoprotein associated with high-density lipoprotein—the "good" lipoprotein that removes cholesterol from the blood. But none of these mutations yet appears to be clinically significant.

Mahley is studying a family in Italy that carries a mutation in a gene coding for apo-AI. As a result, members of this family make only about half the normal amount of high-density lipoprotein. But, Mahley says, "there is no evidence of increased risk of heart disease in this family."

Gina Kolata