

YOUNG HEARTS

Researchers try new ways to prevent tomorrow's heart attacks

By CAROL ERON



Clear medical descriptions of hardening of the arteries have been recorded since the 16th century, and 20th-century researchers have found evidence of it in the mummified remains of ancient Egyptians. Yet not until 1984 did researchers succeed in proving that the risk of coronary heart disease can be lowered by lowering the blood level of cholesterol — in adults.

But what about children? Questions and debate surround childhood cholesterol levels and their implications regarding coronary disease, simply because fewer hard facts exist.

Although researchers lack conclusive evidence that elevated cholesterol levels in childhood lead to high cholesterol in adulthood, circumstantial evidence has now accumulated to the point where many physicians believe mass interventions to lower children's cholesterol levels will save lives. At major medical centers across the country, researchers are attempting to find the best ways to do this.

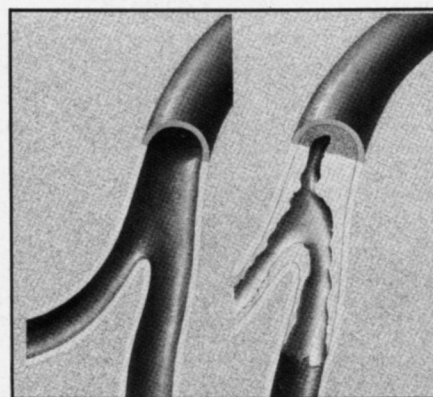
Cholesterol, which is manufactured by the liver and also acquired from food, is essential to growth. Present in the blood and most tissues, it forms a vital part of cell membranes and contributes to the production of bile acid, vitamin D and many hormones. Without sufficient fats, or lipids, young children may fail to grow to full height and can suffer neurologic damage. At the same time, evidence of potential heart disease — once thought to be confined to older people — is being found in some children as young as 3 years of age, in the form of fatty streaks in the heart's main artery, the aorta.

In teenagers, fatty streaks may develop in and under the layer of cells that lines

coronary artery walls. Most evidence suggests these fatty coronary streaks later become plaques, the fat-rich scar tissue that bulges in the arteries and blocks blood flow. Now-classic studies of young U.S. soldiers who died in Korea and in Vietnam revealed many had plaques and some even had severe arteriosclerosis, or hardening of the arteries. With this confirmation that the disease does begin at a young age, the question became: What can be done about it?

In adults with elevated cholesterol levels, every 1 percent decrease in blood cholesterol yields a 2 percent drop in the risk of coronary disease, according to the 10-year Lipid Research Clinics Coronary Primary Prevention Trial, reported in the Jan. 20, 1984 *JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION*. In children, however, physicians lack definitive evidence of such a benefit. No studies with sufficient numbers of children have lasted long enough — say, 50 years — to prove that lowering cholesterol levels reduces their risk of coronary heart disease as adults. And in light of the ethical issues raised by the use of "controls" who do not receive treatment at any age even if they appear endangered, it seems unlikely that such a study will ever be done.

"But all kinds of studies are suggestive," says James I. Cleeman of the National Cholesterol Education Program at the National Institutes of Health in Bethesda, Md. For instance, in populations with a low incidence of coronary disease among adults, cholesterol levels of both children and adults are lower than among groups with higher rates of heart disease. The Bogalusa (La.) Heart Study, an ongoing, long-term investigation of risk factors for cardiovascular disease in children, has shown that cholesterol lev-



A clear coronary artery (left) and a diseased one, narrowed by deposits of fatty substances, or plaque, on the inner artery wall.

els "track" well from childhood into adulthood. In other words, a given measurement tends to retain the same rank order as the child ages, and a child with high blood cholesterol is at greater risk for a high level in the future.

The Bogalusa project, conducted by researchers at the Louisiana State University (LSU) Medical Center in New Orleans, and other studies have determined definite childhood risk factors for arteriosclerosis. As with adults, the unalterable risk factors are age (older people run a higher risk), gender (male) and genetics (race, coronary anatomy and family history of disease). Potentially alterable risk factors include hypertension, high cholesterol levels, high blood sugar, obesity, "psychosocial tension" and lifestyle factors such as smoking, sedentary habits and a high-fat diet. Thus, says LSU researcher Frank A. Franklin, "a strong case can be made for the prevention of atherosclerosis, even in childhood."



Medical experts agree that children at high risk for future coronary artery disease should be tested for blood lipids, including total serum cholesterol, serum triglycerides and high-density lipoprotein (HDL). "But how high [a cholesterol level] is too high, and how you evaluate those levels in relation to the individual, and how you treat it have not been answered," Cleeman says. He anticipates that when researchers in the field convene late this year for the Treatment Panel on Children and Adolescents, a more definitive approach will be developed.

Of special concern in the high-risk group are obese children. "Obesity adds to whatever your genetic predisposition is," Franklin says, and obesity in U.S. schoolchildren is increasing. Between 1963 and 1980, obesity increased 54 percent in children aged 6 to 11, and 39 percent in adolescents aged 12 to 17, while superobesity increased in 6- to 11-year-olds by 90 percent, according to William H. Dietz of Tufts University School of Medicine in Boston. Children are classified as obese if the measurement of skin thickness at the back of the arm ranks in the upper 15 percent for their age and height; superobese children are those ranking in the upper 5 percent. While there may be a genetic component to obesity itself, environment is important as well because parents and children tend to share the same diet and exercise patterns. In either case, the parents are a critical factor: If one parent is obese, a child stands a 40 percent chance of being obese; if both parents are obese, the child's risk rises to 80 percent, according to Dietz. The condition is associated with higher low-density lipoprotein (LDL) and lower HDL levels, as well as increased blood pressure — all major risk factors for cardiovascular disease.

Heritability of the cholesterol level itself is estimated by Franklin and others at up to 50 percent. But research into the genetic aspects of coronary artery disease does not yet translate into practical application on a large scale. Researchers have isolated genes that code for proteins controlling cholesterol metabolism; now the hunt is on for genes that control variations in blood lipid levels. "Once we find this, then we can design tests to look for individuals who have this variation and find ways to treat it," says Jan L. Breslow of Rockefeller University in New York City, who has conducted extensive studies of the genes that control lipoprotein structure and function.

In one case, Breslow and Robert Norum, of Henry Ford Hospital in Detroit, studied a family with an unusually high rate of early, severe atherosclerosis. In two sisters who had heart attacks in their 20s, Breslow found extremely low HDL levels. He also found that the sisters lacked apo A-1, the major protein compo-

nent of HDL's apolipoprotein package. Examining DNA from the sisters, he found that part of a gene for another apolipoprotein had left its correct position and was inserted into the apo A-1 gene. This rearrangement inactivated both genes.

"It's pretty awesome to think of a single gene abnormality that can accelerate the age for a heart attack by 50 years," he has observed. How commonly such mutations cause low HDL levels in the general population, however, remains unknown. About 5 percent of U.S. 5- to 18-year-olds have total blood cholesterol levels above 200 milligrams per deciliter, and among these a smaller number have inherited lipid and lipoprotein disorders that can result in premature heart disease. An ideal blood cholesterol level for children is considered about 150 milligrams per deciliter.

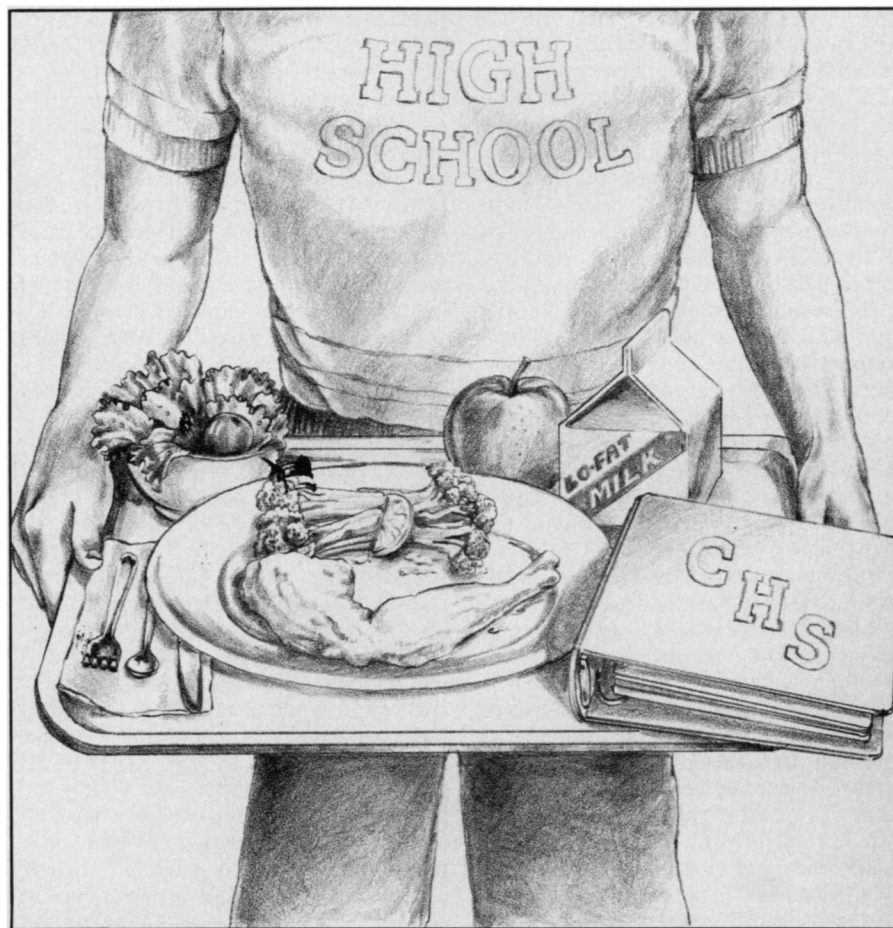


While medical opinion seems unanimous that high-cholesterol kids need special attention, not all physicians and researchers agree on what preventive measures to take with children in general — even on the basic question of whether

all children should be tested routinely for cholesterol levels. Later this month, the American Academy of Pediatrics will issue recommendations about such testing.

With two-thirds of adults registering blood cholesterol above 200 milligrams per deciliter (200 to 239 represents borderline high cholesterol), as many as two-thirds of children are also candidates for high cholesterol levels later in life, Franklin points out. This leads many experts to give center stage to the "population approach" to prevention — which means taking measures to reach large numbers of children at the school level and attempting to lower their cholesterol levels. The other approach, selecting out for doctors' treatment those at particularly high risk, is already well established, but it has limitations. For one, obtaining a family medical history in single-parent families can be difficult or nearly impossible. In Bogalusa, for example, family medical histories do not identify 70 percent of the children with elevated cholesterol levels.

The population approach calls for intervention at the school curriculum, parental and environmental levels, right down to what goes into school lunches, many of which are still high in fat and sodium, according to a September report by Public Voice for Food and Health



Some schools provide heart-healthy lunches, but many still offer high-fat fare.

Policy in Washington, D.C. Several large studies now in progress aim to develop models for intervention programs and to assess their effectiveness. A notable forerunner of these efforts, a 1972 study of high-cholesterol boys in a New England boarding school, showed that when dietary fat was reduced, the boys experienced some lowering in blood cholesterol levels. Once the diet ended, however, blood cholesterol returned to former levels. The study was led by Cynthia H. Ford, then at the Harvard School of Public Health in Boston.

More recently, investigators who studied 3,000 schoolchildren in and around New York City reported in the April 28 *NEW ENGLAND JOURNAL OF MEDICINE* that educational efforts could modify risk factors for coronary artery disease in children in a more typical setting. The researchers studied children beginning in the fourth grade for five years. About half of the 37 schools participating in each of two groups, suburban and inner city, received the "intervention": a curriculum focusing on diet, physical activity and not smoking. In all groups, cholesterol levels declined — a change the researchers say may have been related to normal hormonal changes in the age group studied. But those in the intervention groups showed a greater reduction than the others. For unknown reasons, the average change in the suburban intervention group was greater than that in the inner-city intervention group. The report, by Heather J. Walter of the American Health Foundation and her colleagues, suggests that if the results can be duplicated, such programs may be a promising way to lower children's cholesterol.

The Child and Adolescent Trial for Cardiovascular Health (CATCH), a four-city study now in progress, is an attempt to develop and implement a model school-based educational program for third- to sixth-graders, encompassing child education, school-lunch modifications and physical exercise, in addition to educational materials sent home to parents. If successful in changing children's cholesterol levels, the program will be expanded and ultimately could form the basis for a national program, says investigator Larry Webber of LSU, one of the participating medical centers.

A second major investigation now underway, the Dietary Intervention Study in Children (DISC), is a six-center project that seeks to determine whether a diet low in cholesterol and saturated fat will lower high levels of LDL on a long-term basis. The study will also attempt to determine if it is feasible for children and families to comply with the diet for 3½ years, and whether the diet is compatible with normal growth and development.

The study group consists of 600 boys and girls aged 8 to 10, whose LDL levels are consistently between the 80th and 98th percentiles. Half the children are

being assigned to a "special intervention" group, in which groups of families meet in the evenings to learn how to modify their saturated fat intake. The other 300 will receive only printed cholesterol-education materials to take home, and will remain under the "usual" care of their own physicians.



Meanwhile, contention brews over exactly what diet is best, in light of children's special nutritional needs. For children under 2, authorities agree, diet should not be restricted. Beyond age 2, the American Heart Association recommends limiting fat intake to 30 percent of calories, with 10 percent or less of calories from saturated fats. The American Academy of Pediatrics disagrees, arguing that a child's optimal total fat intake cannot be determined but that 30 to 40 percent of calories seems reasonable. (About 22 percent of U.S. children take in less than 30 percent of their calories as fat, and a similar number consume more than 40 percent, according to the academy.) The academy and others maintain that too restrictive a diet may interfere with normal growth and health.

"The concern here is that overzealous parents will go too far in the right direction," says Cleeman, of the National Cholesterol Education Program, which early this year issued guidelines for the diagnosis and treatment of adults but has yet to issue directives for children. Cleeman cites a group of 7- to 22-month-old infants in Manhasset, N.Y., whose parents — educated, suburban and able to provide food — decided to restrict their infants' calories and fat to 60 to 94 percent of recommended levels for their ages, resulting in inadequate weight gain and growth. Researcher Fima Lifshitz of Manhasset's North Shore University Hospital says the parents seemed to act out of fear that their children would become like them — prone to weight gain, chronically dieting and at risk for atherosclerosis. One set of parents expressed concern about creating children who were "junk food addicts."

"There has to be a significant understanding of the difference in nutrient intake among adults and children," says LSU's Franklin. "With too low-fat a diet you remove the calorically denser foods, and a child would have to increase bulk in order to get enough — and therefore might fall off in caloric intake. We need to emphasize the *right* fats. That's really the point. One is not trying to eliminate all fat but rather the *saturated* fat from children's diets. Children get a lot of their calories from snacks, so we need to choose snacks and desserts that contain the polyunsaturated and monounsaturated

Lipos and apos



Cholesterol travels in the blood packaged as lipoprotein — a form of fat, or lipid, surrounded by protein. Low-density lipoproteins (LDLs) carry cholesterol

from the liver to other parts of the body where it is needed. High-density lipoproteins (HDLs) — sometimes called the "clean-up squad" — carry it back to the liver for processing or removal from the body. Thus, the HDLs, which consist half of protein and are denser than the lipid-rich LDLs, are known as "good" cholesterol and LDLs as "bad" cholesterol.

In measuring cholesterol levels, the ratio of LDL to HDL is a better indicator of risk for coronary heart disease than is the total amount of cholesterol in the bloodstream. The higher the HDL level, the lower the risk; the higher the LDL, the greater the risk.

Another method of determining who is at risk for coronary artery disease is measurement of apolipoproteins, or apos (from the Greek *apo*, meaning derived from), which surround the lipoprotein package. Apos guide cholesterol and other lipids through the body's metabolic pathways. When a cell needs cholesterol, receptors on its surface bind with LDL apolipoprotein, allowing cholesterol to enter the cell (SN: 2/7/87, p.90).

Some researchers believe apos will be the best predictors of potential coronary artery disease because, while the cholesterol content of LDL particles can vary, each LDL particle has only one apo B molecule and each HDL particle has only one apo A-1 molecule. Therefore, says Peter Kwiterovich of Johns Hopkins University School of Medicine in Baltimore, "measurement of the ratio of apo A-1 to apo B might be proven to be the best indicator. But a true prospective study over many years would be necessary to prove this." — C. Eron

rated fats. Parents need to be a little more sophisticated. And one ought to monitor children's growth — that's the role of the child's physician."

In the midst of controversy over ideal diets and the need for large-scale testing, the urgency of the cholesterol problem remains clear. "Coronary artery disease and essential hypertension very clearly begin early. They are percolating in childhood," says Gerald S. Berenson, a medical researcher who directs the Bogalusa study. "Bogalusa shows that heart disease begins by 18 to 20 years of age. And if we don't do something about it now, our children will be the next generation of heart attacks." □