Diet, drugs slow heart-felt 'insults'

Another piece of the cholesterol puzzle fell into place last week with the announcement that cholesterol-reducing drugs and decreased dietary fat together not only significantly lower blood cholesterol, but also slow the spread of fatty buildup in blood vessels. Based on a study of patients who had had coronary bypass surgery, the findings are expected to alter the standard treatment of patients after heart surgery. But they also raise questions about which of several groups considered at increased risk for heart disease — including asymptomatic individuals with moderate to high cholesterol levels — should follow the time-consuming and potentially expensive therapy regimen as a preventive measure.

Although elevated cholesterol levels have been tied to increased risk of heart disease for several years, the latest study is one of the first to lower blood cholesterol in patients who have had previous coronary bypass surgery. During a briefing at the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Md., institute director Claude Lenfant said this "very important" study, conducted at the University of Southern California (USC) in Los Angeles, also is the first designed to determine whether controlling cholesterol can regulate existing atherosclerotic lesions.

Called the Cholesterol-Lowering Atherosclerosis Study, the two-year test included 162 men — nonsmokers and exsmokers aged 40 to 59 years — who at the beginning of the study had blood cholesterol levels ranging from relatively low (185 milligrams per deciliter) to high (350 mg/dl) levels. Placed on similar low-cholesterol diets, half received a placebo, while the remainder were given a combination of colestipol hydrochloride and niacin.

In the drug-treated group, there was a 26 percent reduction in total cholesterol, a 43 percent reduction in low-density lipoprotein (LDL) cholesterol and a 37 percent increase in high-density lipoprotein (HDL) cholesterol. HDL cholesterol, the "good" kind, helps block the adverse effects of LDL cholesterol.

In contrast, parallel changes in the placebo group varied between 2 percent and 5 percent, said USC researcher David H. Blankenhorn at last week's briefing. Because of their history of heart disease, the men had been following a variety of low-cholesterol diets prior to beginning the study.

By injecting special dyes, the researchers also studied the size of atherosclerotic lesions in both native and "foreign" blood vessels, the latter added during bypass surgery to replace damaged vessels. Lesion changes, described in the June 19 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), showed either stabilization or shrinkage of lesions in the drug-treated group. According to Blankenhorn, actual regression of the lesions "as judged by perceptible improvement" occurred in 16.2 percent of the treated group, as opposed to 2.4 percent of the placebo group.

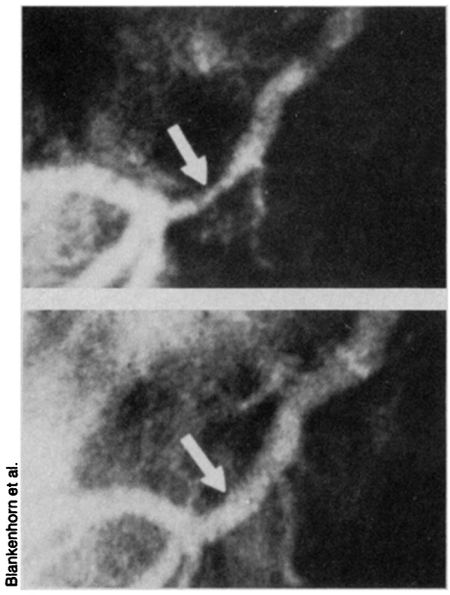
"We have the tools at hand to begin reducing the mortality of heart disease," says Blankenhorn, referring to various cholesterol-lowering drugs being tested. When given in large doses, niacin, which is one of the B complex vitamins, lowers total blood cholesterol and LDL cholesterol, while raising HDL cholesterol. Colestipol, a bile-acid binding resin, carries bile acids out through the intestine, forcing removal of cholesterol from the blood to help form new bile acids.

However, Blankenhorn and others emphasize that physician-mandated diet changes must precede drug use, and that the public should not begin taking large doses of the commercially available niacin. In the amounts used in the study, both niacin and colestipol can cause unpleasant side effects, including hot flashes, intestinal discomfort and joint pain. Scientists are hopeful that another drug group, which inhibits an enzyme important in cholesterol synthesis, will be better tolerated by the body. One of those drugs, called CS-514, reduced total average cholesterol levels between 11 percent and 25 percent (depending on dosage) in a clinical study at Japan's Tokai University Tokyo Hospital, according to a report in the June 12 JAMA.

In an editorial accompanying the USC report, NHLBI's Eugene R. Passamani writes that, although it suffers from flaws common in clinical trials, the study makes "a most persuasive argument for the aggressive use of lipid-lowering diet and drugs as important adjuncts to coronary artery bypass graft surgery," despite the "substantial effort" necessary to change diets and use the often-expensive drugs. Such treatment could benefit the estimated 220,000 patients undergoing coronary bypass surgery each year in the United States, and many of the 1.7 million who have had the procedure since it was first performed.

But what of the one out of four Americans who, according to NHLBI scientists, have elevated cholesterol levels yet may have no symptoms of heart disease? And what of the more than 6 million who do have symptoms? The study's data are drawn from too few subjects to determine whether there would be differences between the drug- and placebo-treated groups in the development of symptomatic heart disease, says Blankenhorn. But, he says, "the entire range of blood cholesterol levels between 185 and 350 mg/dl should be considered for vigorous treatment."

"The big issue facing us in the cholesterol study ... is the question of at what point does the benefit outweigh the risk," says Basil M. Rifkind of NHLBI, adding that a change in diet remains "by far the preferred approach" for most people with higher-than-healthy cholesterol levels. — *D.D. Edwards*



Blankenhorn et al.

Drug treatment has visibly increased blood flow in this patient's coronary arteries, say scientists. Taken in 1982, the top picture shows an artery narrowed by fatty accumulation; two years of drug therapy resulted in regression of the same lesion. Researchers say another angiogram taken in 1986 showed that blood-flow improvement was maintained.

New drugs with that enzymatic touch

Serendipity was key in the discovery nearly 60 years ago that a common mold produced a substance fatal to bacteria — leading to the broad availability of penicillin. But the present-day search for new drugs, combining computers with chemical acumen, is a far more premeditated pursuit. Two studies reported this week, which target specific enzymes essential to disease-causing microorganisms, show just how calculating drug design has become.

At Astra Alab in Södertälje, in Sweden, scientists have made finely tuned inhibitors of an enzyme needed in the synthesis of lipopolysaccharide (LPS). LPS is found exclusively in the cell walls of gram-negative bacteria, a broad classification that includes *Salmonella* species, *Escherichia coli* and many others. Because the inhibitor's target enzyme is not present in mammalian cells, the new class of synthetic drugs will attack certain bacteria and be nontoxic to the host, say the scientists in the June 25 NATURE.

But the group found that making the