# Surgery, Drugs, Lifestyle, and Hyperlipidemia

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**Heart disease is the number-one cause of death in the United States, and more money is spent on its treatment each year than for any other condition. Both epidemiologic and experimental data clearly show that elevated plasma cholesterol levels increase the risk of death from coronary heart disease. Genetic insufficiencies can cause high blood cholesterol, but most people with high cholesterol do not have genetic abnormalities; rather, they have lifestyles that include high-fat diets and little exercise. Cholesterol can be managed aggressively with coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, partial ileal bypass, and even liver transplant. Antihyperlipidemic drugs include bile-acid-binding resins, nicotinic acid, fibric acid derivatives, hydroxymethyglutaryl coenzyme A-reductase inhibitors, and the antioxidant probucol. Strict programs of low-fat diets and exercise are also effective for reducing cholesterol, lowering blood pressure, and preventing heart disease without the side effects associated with surgery and drug therapy. Such lifestyle changes are critical to reducing the incidence of heart disease in this country.**

Heart disease continues to be the number-one killer of both men and women in the United States. As many as 1.5 million Americans will have a heart attack this year and 500,000 people will die of a heart attack. Approximately $52 billion per year is spent on treatment for heart disease—more than for any other condition. The costs include physician and nursing services, hospital and nursing home services, medications, and lost productivity resulting from disability. In 1990, the last year for which complete data are available, 392,000 coronary artery bypass surgical procedures were performed in this country.[1]

Hyperlipidemia—the presence of excess fat or lipids in the blood—is defined as hypercholesterolemia or hypertriglyceridemia or both.[2] This discussion centers primarily on hypercholesterolemia. Epidemiologic[3] and experimental data[4] have shown clearly that elevated total plasma cholesterol levels increase the risk of death from coronary heart disease.

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## EPIDEMIOLOGIC AND EXPERIMENTAL DATA

Leaf[5] has stated that in societies in which the mean cholesterol levels are 150 mg/dL or lower without the use of drugs, coronary heart disease is essentially unknown as a public health problem. Japan is a prime example. The Japanese population has an average cholesterol level of 150 mg/dL and only one tenth the incidence of coronary artery disease as do people living in the United States; however, when people from Japan move to the United States and adopt our diet and lifestyle, their incidence of coronary artery disease increases.[5] Americans consume approximately 1,000 calories more per day than the average Japanese person eating a traditional diet; and the extra calories in the American diet are mostly fat.[6]

A study of 9,000 Chinese living in China showed the average cholesterol level was 137 mg/mL.[7] A cholesterol level of 180 mg/dL is considered high by their standards. Heart disease in China is relatively unknown. In the United States, the average cholesterol level is 205 mg/dL, with 240 mg/dL considered high—and 27% of US citizens have cholesterol levels higher than 240 mg/dL. Of persons with coronary heart disease, 58% have blood cholesterol levels of 200 mg/dL or higher, and 40% to 50% have levels higher than 240 mg/dL.[8,9]

The Framingham Heart Study was begun in 1948 to determine risk factors for coronary heart disease. Dr. William Castelli,[3] who directed the study that included half of the 10,000 residents of Framingham, Massachusetts, noted that no one in the study whose total blood cholesterol level was less than 150 mg/dL has ever had a heart attack. To achieve a cholesterol level of 150 mg/dL, most adults must consume a low-fat vegetarian diet of approximately 10% fat. It was learned from this study that for every 1% that total blood cholesterol rises above 150 mg/dL, there is a 2% increase in the chance of developing coronary heart disease.

The American lifestyle has recently been described by Thomas Bodenheimer, MD[10] as the "TV-Automobile-Supermarket Society." We have become too sedentary, watch too much television, get too little exercise, eat too much fast, fatty food, and spend more time driving than walking. According to the findings from the third National Health and Nutrition Examination Survey from 1988 to 1991, 34% of US citizens are overweight, which is defined as 20% over ideal weight. From 1976 to 1980, only 26% of people were overweight. Currently, fewer than 10% of US citizens are at their ideal weight. Apparently, while Americans are talking health, they are eating a high-fat diet and leading sedentary lives.

Some people, however, are capable of metabolizing a high-fat diet well, and no matter how much fatty food or excess cholesterol they eat their total cholesterol level may remain below 150 mg/dL. Goldstein and Brown[11] won the Nobel Prize in medicine in 1985 for their discovery of low-density lipoprotein receptors (LDLR), located primarily on

the liver cells, that are capable of binding and removing cholesterol from the bloodstream. Their studies were done primarily with the Watanabe hereditable hyperlipidemic rabbit model, which closely resembles cases of severe homozygote hereditary hyperlipidemia among humans. Most persons with this disease and a cholesterol level in the 1,000-mg/dL range will die in their teens from advanced atherosclerosis whether or not they follow a strict, even vegetarian, diet. The defective or deficient LDL receptors in the liver cannot clear the cholesterol from the bloodstream, leading to plaque buildup in the peripheral arteries.

## GENETIC TRAITS AND HEART DISEASE RISK

Major genetic traits are now known to affect coronary heart disease risk. Some of them involve an increase in the LDLs, as with familial hypercholesterolemia (which is found in the heterozygote population and occurs in approximately 1 of 500 people) and with the familial defective Apo-B 100 trait (which is a heterozygote deficiency present in approximately 1 of 700 people). The genetic trait is also evident when there is an increase in both LDL and very-low density lipoproteins (VLDL) in familial combined hyperlipidemia, which occurs in approximately 1 in 100 people. Familial hypoalphalipoproteinemia, in which there is a decrease in high-density lipoprotein (HDL), also contributes to coronary artery disease, as does the genetic trait of an increase in lipoprotein little a, (Lp[a]), where there is a variation of the LDL molecule. The HDL cholesterol (HDLC) helps remove cholesterol from the plaque in the peripheral blood vessels and returns it to the liver where it can be removed and eliminated. The LDL cholesterol (LDLC), which makes up approximately 70% to 80% of the total cholesterol, is associated with plaque formation when it is elevated.

Although a genetic insufficiency of functional LDL receptors is one cause of high blood cholesterol, the majority of people who have high blood cholesterol do not appear to have genetic abnormalities and can, in fact, control their levels with diet. Diets high in saturated fat and cholesterol lead to high LDLC levels, promoting the accumulation of cholesterol in the liver and suppressing the manufacture of LDL receptors, thus decreasing the uptake of LDL from the blood.[12]

Among people with existing heart disease and a family history of death from coronary artery disease, the lowering of cholesterol levels has decreased the rate of mortality, according to secondary prevention trials.[13-22] A dose-response relation also appears to exist. Some health specialists suggest a total cholesterol level of 200 mg/dL or less and an LDLC level of 130 mg/dL or less for optimum health.[18] Superko[19] believes a total cholesterol level of 180 mg/dL or less and an LDLC level of 110 mg/dL or less is optimum, even for persons who are not in a high-risk group.

## MANAGING HIGH CHOLESTEROL WITH SURGERY

Aggressive cholesterol management is needed to reverse atherogenic disease, and some investigators believe that reversal requires an LDLC level of less than 100 mg/dL and an HDLC level of more than 50 mg/dL. The June 1993 National Cholesterol Education Program guidelines for secondary prevention in patients with evidence of coronary heart disease state that the optimal LDLC level should be 100 mg/dL or less. An HDL value of less than 35 mg/dL is considered an additional risk factor for coronary heart disease.

Coronary artery bypass surgery remains the procedure of choice when arteries are extensively blocked by atherosclerosis. The cost involved in this procedure averages $50,000 and requires a recovery time of 4 to 6 weeks. The mortality rate for the procedure is 1% to 2%. The patients who receive the most benefit from surgery, in terms of survival, are those with severe disease and a high risk of death without surgery, such as those with stenosis of the left main coronary artery or proximal left anterior descending coronary artery, multivessel disease, severe angina, abnormal left ventricular function, and a positive finding on exercise testing. The coronary artery bypass operation is basically an anatomic operation for a metabolic disease.[23]

Percutaneous transluminal coronary angioplasty (PTCA) with balloon-tip catheters tends to be used for patients with less extensive coronary disease, because the treatment of the coronary lesions is less certain, less complete, and less persistent than with bypass surgery.[23] Overall morbidity is less with PTCA, however, and it also requires a shorter time in the hospital and is less expensive. The average hospital stay is 2 to 7 days and the average cost is approximately $12,000. There are also newer intraluminal atherectomy techniques that use lasers, drills, and intraluminal stents to keep the coronary arteries open. When anticlotting drug therapies are used, the stents are very successful.

The partial ileal bypass (PIB) for hyperlipidemia advocated by Buchwald et al,[16] biomedical engineers at the University of Minnesota in Minneapolis, is a procedure where the distal 200 cm or one third of the small intestine, whichever is larger, is bypassed with restoration of intestinal continuity by an end-to-side anastomosis of the proximal small intestine to the cecum. The PIB causes cholesterol reduction by draining the cholesterol body pools. Cholesterol and bile salts are primarily absorbed in the distal small bowel. Because of the depletion of the cholesterol and bile salt pool, more cholesterol from the body reserve goes into making more bile salts, thus lowering the blood level of cholesterol.

The PIB operation has been shown to work especially well for heterozygous, type II-a hyperlipidemia patients whose total plasma cholesterol levels were above the 90th percentile for age and sex, and who were therefore at a markedly increased risk of death from coronary heart disease. The heterozygous form of familial hypercholesterolemia occurs in 1 of 500 people, and total cholesterol levels are generally in the 300- to 500-mg/dL range. In one study,[24] 58 heterozygote type II-b hyperlipidemia patients underwent a PIB operation and were then placed on a 25%-fat, phase-II American Heart Association diet with daily cholesterol intake restricted to between 200 mg and 250 mg. After 1 year, total plasma cholesterol level was reduced by 24%, LDLC was reduced by 34%, and HDLC level was increased by 5% in the PIB patients compared with 52 control heterozygote type II patients on the diet alone. The PIB operation costs approximately $2,000.

Dudrick,[25] in his work with hyperalimentation solutions and nutrition for wound healing in surgical patients, noted that regression of atherosclerosis can occur with the intravenous infusion of specific biochemical nutrient substrates high in arginine. His experiments were conducted with both animals and humans. The most effective solutions resembled plant or vegetable protein in their amino acid compositions, with L-arginine being the most effective amino acid component. It is now known that L-arginine causes endothelial relaxation by allowing the release of the endothelial-derived relaxing factor known as nitric oxide, which causes vasodilation. It also inhibits many processes involved in atherogenesis, such as platelet aggregation, vascular smooth muscle proliferation, elaboration of extracellular matrix, and foam cell formation. In an experimental animal model using rabbits fed a 1% cholesterol diet, a normal rabbit chow diet, or a 1% cholesterol diet supplemented with 2.25% L-arginine, Cooke et al[26] demonstrated that a sixfold increase in dietary arginine will cause a doubling of plasma arginine. The rabbits fed the arginine supplement with a 1% cholesterol diet not only had a reduction in atherosclerosis compared with the rabbits fed only a 1% cholesterol diet, but also had an improvement in endothelial-derived relaxing factor activity. Studies will be conducted among humans to see whether dietary arginine can raise plasma arginine levels enough to help reverse atherosclerosis.

In severe cases of homozygote familial hyperlipidemia where total cholesterol and LDLC levels are often elevated above 1,000 mg/dL, the manifestations of advanced atherosclerosis appear in childhood or early adolescence. For these patients, a transplant can be done to replace their liver, which has deficient or absent LDL receptors. The cost of this operation is approximately $115,000.[27]

### Gene Therapy

The latest solution for correction of the familial hypercholesterolemia-inherited disorder is gene therapy. Chowdhury et al[28] did a study that showed long-term improvement of hypercholesterolemia after rabbits deficient in LDL receptors (LDLR) were given ex vivo gene therapy. In an experimental model using Watanabe heritable hyperlipidemic rabbits, 30% of the liver was removed. The hepatocytes were then cultured and recombinant retroviruses were used to transduce a functional LDLR gene into the hepatocytes. The corrected hepatocytes were transplanted back into the animal from which they came by injecting them into the spleen. The infused cells then entered the portal circulation and seeded the liver. In the liver they became metabolically active, resulting in a cholesterol level reduction of 30% that lasted for the duration of the 122-day experiment. Since a possible complication of gene therapy is the development of an antibody response to the transplanted gene, sera from transplant recipients were analyzed for the formation of antibodies to the LDLR-expressing virus. No antibodies were detected.[28] The group, led by Dr. James Wilson, has now received NIH funding to perform pilot studies with gene therapy on humans with homozygote familial hyperlipidemia and has begun these studies.

## DRUG TREATMENT OF HYPERLIPIDEMIA

The adult treatment panel of the National Cholesterol Education Program has made recommendations that a high-risk patient with an LDLC level of more than 160 mg/dL, after reasonable and sincere attempts to lower it through modification of diet and exercise and reduction of other cardiovascular risk factors, should then be considered for antihyperlipidemic therapy. The goal is to reduce the LDLC to below 130 mg/dL.[13,18] A person considered high risk has a personal history of cardiovascular disease or two or more major risk factors which consist of hypertension, smoking, diabetes mellitus, severe obesity, family history of premature cardiovascular disease, low level of HDLC, and being male. It is thought by some investigators that patients who already have atherogenic cardiovascular disease should have an LDLC level <100 mg/dL and an HDLC level >50 mg/dL.

Medications used for the treatment of hyperlipidemia vary according to the type of hyperlipidemia and the patient's tolerance to the drug. The cost of medications varies from $500 to $3,000 per year. Patient compliance in taking these medications may be only 25%, depending on cost, palatability, side effects, and motivation. Following is a brief synopsis of some of the more commonly used medications for treatment of hyperlipidemia. Combination therapy using two or more of these drugs is not uncommon, and can be very effective in order to reduce cholesterol and triglygeride levels.

Bile-acid-binding resins such as cholestyramine and colestipol work by binding the bile acids in the intestine that are responsible for lipid absorption. They are good for lowering LDL, and their safety and efficacy have been documented by the Coronary Primary Prevention Trial.[29-30] The decreased enterohepatic circulation of bile acids changes the hepatic feedback loop, resulting in increased LDL receptor sites and consequently enhanced plasma LDLC clearance. A full dose was reported to reduce LDLC by 28%. The main side effects are gas, bloating, constipation, increased liver function test values, and gastrointestinal reactions that cause decreased absorption of medications taken at the same time as the bile-acid binder.

Nicotinic acid acts by reducing the hepatic VLDL secretion and free fatty acid mobilization from hepatocytes. Maximum doses can reduce LDLC by 20% and increase HDLC by 25%. Nicotinic acid can be used alone or in combination with other medications such as the bile-acid-binding resins to reduce cholesterol. The side effects include headaches and flushing secondary to vasodilation, gastrointestinal upset, skin rashes, and elevated liver enzymes. Aspirin can counteract some of the headache and flushing symptoms.

The fibric acid derivative gemfibrozil is used primarily to treat hypertriglyceridemia, and in these patients it can also raise HDL levels. Side effects include gallstones, gastrointestinal tumors, muscle pain, abdominal distress, and elevated creatinine kinase levels.

Hydroxymethyglutaryl-coenzyme A-reductase inhibitors act by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), which is the rate-limiting step in cholesterol biosynthesis. Side effects include elevated liver function tests, myositis, and cataracts. In patients with

type II hyperlipidemia, this medication can reduce LDLC by 39%, and the addition of a bile-acid-binding resin can reduce it by 54%.[31]

Probucol, one of the newer anticholesterol drugs, acts as a powerful antioxidant. It prevents the oxidation of LDL and consequently decreases foam cell formation and thereby limits the formation of atherosclerosis. It also works to increase the catabolic rate of LDL extraction from the bloodstream, a process called reverse cholesterol transport, and has been shown to actually reverse angiographically proven plaques. Its adverse side effects are negligible.[32]

In the 1994 coronary artery regression comparison study by Superko and Krauss,[33] randomized, controlled clinical trials were compared to assess the effect of lipoprotein manipulation on the rate of progression or regression of coronary atherosclerosis. These studies, using coronary arteriography, ranged from 5 to 10 years of follow-up. A total of 2,095 patients studied showed a mean regression of arteriographic disease of 20% and an average decrease in LDL of 28%, a decrease in triglycerides of 11%, and an increase in HDL of 11% compared with the controls. In addition, clinical cardiovascular events were fewer in the study subjects than in the controls. This review was made up of three nonpharmacological trials and eight pharmacological trials and included the Buchwald partial ileal bypass because of the aggressive nature of the intervention. Cost effectiveness was also analyzed in this review, and one estimate stated that if the 13% difference in the need for coronary artery bypass seen in the colestipol and lovastatin study were extrapolated to the estimated 1 million American men with coronary artery disease, an estimated $4.6 billion could be saved in a 2.5-year period because of fewer coronary artery bypass surgeries alone.

In postmenopausal women, hormone-replacement therapy appears to be associated with a favorable lipid physiologic profile that appears to have protective effects in relation to cardiovascular disease. Compared with nonusers, women who use hormones have higher levels of HDLC and lower levels of LDLC, with possible reductions of 42% in the risk of cardiovascular disease. The use of estrogen combined with progesterone appears to be associated with an even better profile than the use of estrogen alone.[34]

Two papers that have implications for drug therapy were presented at the October 1993 annual meeting of the North American Association for the Study of Obesity. Sarah Leibowitz of Rockefeller University in New York City reported having identified a protein in the brain, called galanin, which increases the appetite for fats.[35] The other study, by David York of Louisiana State University, described the discovery of a protein called enterostatin, which cuts fat intake 50% to 80% when injected into animals.[36]

## NEED FOR LIFESTYLE CHANGES

Dean Ornish, MD, a great proponent of lifestyle changes for the reversal and prevention of heart disease, found that only through comprehensive lifestyle changes, described in his book *Reversing Heart Disease,* can cholesterol and blood pressure be lowered and heart disease be reversed.[20] His program consists of a combination of a strict vegetarian diet of no more than 10% fat, and no animal products except one cup per day of nonfat milk or yogurt and egg whites. In addition, his program prescribes a moderate exercise program of one half hour per day; stress reduction exercises consisting of stretching, yoga, and meditation; an emotional support group; and the elimination of caffeine and smoking. Anyone with existing heart disease who wishes to reduce the risk of premature death, disability, and cost from heart disease is advised to follow this regimen.

Patients with documented heart disease and chest pain who did not have bypass surgery but who instead undertook this comprehensive program of lifestyle change have shown a significant reduction in their total cholesterol levels, and a reversal of their heart disease in just 1 year. In the 1980 study by Ornish et al[21] that enlisted 24 people in the treatment group and 24 people in the control group, the treatment group had a 91% reduction in angina and a 21% reduction in cholesterol levels compared with controls. They also had a 55% improvement in exercise capability. Patients not only became pain free, they reported feeling more energy and a greater sense of well being. In the following 3 years of the study supported by the NIH, these patients continued to show further improvement.[20-22]

To quote Dr. Thomas Bodenheimer,[10] "To begin the search for a truly broad public health approach to coronary heart disease, we must confront the entire TV-automobile-supermarket society. This syndrome results in a gross caloric imbalance: processed foods from the supermarket containing high levels of fat and calories, a lack of physical activity created by the replacement of human muscle power with the automobile as the principal means of transport, and a further lack of activity produced by watching TV, which also implores us to buy cars and high-fat foods."

Clearly there are environmental, dietary, behavioral, and inherent genetic factors involved in this multifactorial disease (hyperlipidemia) and the associated coronary artery disease. Significant progress is being made in its treatment, including advances in surgery and drug therapy. But perhaps the most critical factor—and one within the control of the patient—is lifestyle change. Preventive health care is known to be the most cost-effective approach to medicine, and lifestyle changes are no small part of that prescription. They have proven to decrease morbidity and mortality from heart disease at a significant rate.

At present, fewer than 5% of US citizens do vigorous exercise and fewer than 10% are at their ideal weight. But changes are occurring at an institutional level, evident by the fact that Mutual of Omaha, the nation's largest insurance company, has endorsed the Dean Ornish lifestyle change program. Lifestyle changes are also recognized as a critical factor in the Clinton health care plan. Already advocated by much of the European community, including Germany, Sweden, and Denmark, lifestyle changes now need to be promoted by all health care professionals in the United States. Healthful food in employee cafeterias is a must. Workout areas and stress-reduction facilities provided by employers in return for low number of sick days are other preventive health incentives that are being suggested with a real emphasis on wellness.

Miracle drugs and gene therapy for hypercholesterolemia are in the process of being developed and can also play a role in prevention. However, these therapies in general

have more side effects than do intrinsic lifestyle changes. Surgery in the form of partial ileal bypass can be preventive, and if the condition already exists, it can reverse the disease. But much of the surgery for coronary artery disease is done for cases that have already advanced too far. Eliminating heart disease is projected to increase life span by only 3 years.[37] But a person's functional capacity and quality of life are much better overall, because preventing heart disease can also prevent angina, coronary artery bypass surgery, complications of surgery, and pain and suffering. And the benefit to society in general is that the escalating cost of health care due to coronary artery disease would be decreased.

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