LDL receptors bind particles carrying cholesterol and remove them from the circulation. Many Americans have too few LDL receptors, and so they are at high risk for atherosclerosis and heart attacks.

Half of all deaths in the U.S. are caused by atherosclerosis, the disease in which cholesterol, accumulation in the wall of arteries, forms bulky plaques that inhibit the flow of blood until a clot eventually forms, obstructing an artery and causing a heart attack or a stroke. The cholesterol of atherosclerotic plaques is derived from particles called low-density lipoprotein (LDL) that circulate in the bloodstream. The more LDL there is in the blood, the more rapidly atherosclerosis develops.

Epidemiologic data reveal the surprising fact that more than half of the people in Western industrialized societies, including the U.S., have a level of circulating LDL that puts them at high risk for developing atherosclerosis. Because such concentrations are so prevalent, they are considered "normal," but clearly they are not truly normal. They predispose to accelerated atherosclerosis and heart attacks or strokes.

What determines the blood level of LDL, and why is the level dangerously high in so many Americans? Some answers are emerging from studies of specialized proteins, called LDL receptors, that project from the surface of animal cells. The receptors bind LDL particles and extract them from the fluid that bathes the cells. The LDL is taken into the cells and broken down, yielding its cholesterol to serve each cell's needs. In supplying cells with cholesterol the receptors perform a second physiological function, which
is critical to the development of atherosclerosis: they remove LDL from the bloodstream.

The number of receptors displayed on the surface of cells varies with the cells' demand for cholesterol. When the need is low, excess cholesterol accumulates; cells make fewer receptors and take up LDL at a reduced rate. This protects cells against excess cholesterol, but at a high price: the reduction in the number of receptors decreases the rate at which LDL is removed from the circulation, the blood level of LDL rises and atherosclerosis is accelerated.

We have proposed that the high level of LDL in many Americans is attributed to a combination of factors that diminish the production of LDL receptors. Recognition of the central role of the receptors has led to a treatment for a severe genetic form of atherosclerosis, and it has also shed some light on the continuing controversy over the role of diet in atherosclerosis in the general population.

The story begins with the discovery of LDL receptors in 1973 in our laboratory at the University of Texas Health Science Center at Dallas. We were studying tissue cultures of the human skin cells called fibroblasts. Like all animal cells, cultured fibroblasts need cholesterol as a major building block of their surface membrane (the plasma membrane); they had been shown to get the cholesterol by extracting it from lipoprotein in the serum of the culture medium. There is a mixture of various lipoprotein in human serum, but we found that the fibroblasts derive most of their cholesterol from a particular lipoprotein: LDL. We were able to attribute this to the presence on the cells of highly specific receptor molecules that bind LDL and related lipoprotein.

LDL is a large spherical particle whose oily core is composed of some 1,500 molecules of the fatty alcohol cholesterol, each attached by an ester linkage to a long-chain fatty acid. This core of cholesteryl esters is enclosed in a layer of phospholipid and unesterified cholesterol molecules. The phospholipids are arrayed so that their hydrophilic heads are on the outside, allowing the LDL to be dissolved in the blood or intercellular fluid. Embedded in this hydrophilic coat is one large protein molecule designated apoprotein B-100.

It is apoprotein B-100 that is recognized and bound by the LDL receptor, a glycoprotein (a protein to which sugar chains are attached). The receptor spans the thickness of the cell's plasma membrane and carries a binding site that protrudes from the cell surface. Binding takes place when LDL is present
at a concentration of less than 10-9 molar, which is to say that the receptor can pick out a single LDL particle from more than a billion molecules of water. The receptor binds only lipoproteins carrying apoprotein B-100 or a related protein designated apoprotein E.

How is LDL taken into the cell? Our collaborator Richard G. W. Anderson discovered in 1976 that the receptors are clustered in specialized regions where the cell membrane is indented to form craters known as coated pits (because the inner surface of the membrane under them is coated with the protein clathrin). Within minutes of their formation the pits pouch inward into the cell and pinch off from the surface to form membrane-bounded sacs called coated vesicles; any LDL bound to a receptor is carried into the cell. (Receptor-mediated endocytosis, the term we and Anderson applied to this process of uptake through coated pits and vesicles, is now recognized as being a general mechanism whereby cells take up many large molecules, each having its own highly specific receptor.)

Eventually the LDL is separated from the receptor (which is recycled to the cell surface) and is delivered to a lysosome, a sac filled with digestive enzymes. Some of the enzymes break down the LDL's coat, exposing the cholesteryl ester core. Another enzyme clips off the fatty acid tails of the cholesteryl esters, liberating unesterified cholesterol, which leaves the lysosome. As we have indicated, all cells incorporate the cholesterol into newly synthesized surface membranes. In certain specialized cells the cholesterol extracted from LDL has other roles. In the adrenal gland and in the ovary it is converted into respectively the steroid hormones cortisol and estradiol: in the liver it is transformed to make bile acids, which have a digestive function in the intestine.

The amount of cholesterol liberated from LDL controls the cell's cholesterol metabolism. An accumulation of cholesterol modulates three processes. First, it reduces the cell's ability to make its own cholesterol by turning off the synthesis of an enzyme, HMG CoA reductase, that catalyzes a step in cholesterol's biosynthetic pathway. Suppression of the enzyme leaves the cell dependent on external cholesterol derived from the receptor-mediated uptake of LDL. Second, the incoming LDL-derived cholesterol promotes the storage of cholesterol in the cell by activating an enzyme called ACAT. The enzyme reattaches a fatty acid to excess cholesterol molecules, making cholesteryl esters that are deposited in storage droplets.
Third, and most significant, the accumulation of cholesterol within the cell drives a feedback mechanism that makes the cell stop synthesizing new LDL receptors. Cells thereby adjust their complement of receptors so that enough cholesterol is brought in to meet their varying demands but not enough to overload them. For example, fibroblasts that are actively dividing, so that new membrane material is needed, maintain a maximum complement of LDL receptors (some 40,000 per cell). In cells that are not growing the incoming cholesterol begins to accumulate, the feedback system reduces receptor manufacture and the complement of receptors is reduced as much as tenfold.

Our observations in tissue cultures were confirmed when the receptor system was shown to have an important role in the body. Soon after we found the LDL receptor on cultured fibroblasts it was shown to be present on circulating human blood cells and on cell membranes from many different tissues of mice, rats, dogs, pigs, cows and human beings. The relative number of receptors and their functioning can be assessed in living animals and in human volunteers by injecting into the bloodstream LDL labeled with a radioactive isotope and measuring its rate of removal from the circulation. The rate has been shown to depend on the total number of LDL receptors displayed on all cells in the body. This can be demonstrated by modifying the apoprotein B-100 before the LDL is injected, so that it can no longer bind to receptors. James Shepherd and Christopher J. Packard of the University of Glasgow showed that the modified LDL circulates much longer than normal LDL.

Where is the LDL taken up? Daniel Steinberg of the University of California School of Medicine at San Diego and John M. Dietschty of the Health Science Center at Dallas have shown that in rats, rabbits, guinea pigs and squirrel monkeys about 75 percent of the receptor-mediated removal of LDL takes place in the liver. We have measured the number of receptors directly, in cell membranes isolated from different tissues. Most tissues are found to have some receptors, but those of the liver, adrenal gland and ovary-the organs with particularly large requirements for cholesterol-have the highest concentration of receptors.

What is the origin of circulating LDL? The mechanism of its production is more complex, and as yet less well understood, than the mechanism of its uptake and degradation. LDL is one component of the system that transports
two fatty substances, cholesterol and various triglycerides, through the bloodstream. The fat-transport system can be divided into two pathways: an exogenous one for cholesterol and triglyceride absorbed from the intestine and an endogenous one for cholesterol and triglyceride entering the bloodstream from the liver and other nonintestinal tissues.

The exogenous pathway has been mapped by Richard J. Havel of the University of California School of Medicine at San Francisco and by others. It begins in the intestine, where dietary fats are packaged into lipoprotein particles called chylomicrons, which enter the bloodstream and deliver their triglyceride to adipose tissue (for storage) and to muscle (for oxidation to supply energy). The remnant of the chylomicron, containing cholesteryl esters, is removed from the circulation by a specific receptor found only on liver cells. This chylomicron-remnant receptor does not bind LDL or take part in its removal from the circulation.

LDL is a component of the endogenous pathway, which begins when the liver secretes into the bloodstream a large very-low-density lipoprotein particle (VLDL). Its core consists mostly of triglyceride synthesized in the liver, with a smaller amount of cholesteryl esters: it displays on its surface two predominant proteins, apoproteins B-100 and E, both of which can be bound by LDL receptors. When a VLDL particle reaches the capillaries of adipose tissue or of muscle, its triglyceride is extracted. The result is a new kind of particle, decreased in size and enriched in cholesteryl esters but retaining its two apoproteins: it is called intermediate-density lipoprotein, or IDL.

In human beings about half of the IDL particles are removed from the circulation quickly—within from two to six hours of their formation—because they bind very tightly to liver cells, which extract their cholesterol to make new VLDL and bile acids. Robert W. Mahley and Thomas L. Innerarity of the University of California School of Medicine at San Francisco have shown that the tight binding is attributable to apoprotein E, whose affinity for LDL receptors on liver cells is greater than that of apoprotein B-100. IDL particles not taken up by the liver remain in the circulation much longer. In time the apoprotein E is dissociated from them, leaving the particles, now converted into low-density lipoprotein (LDL), with apoprotein B-100 as their sole protein. Because of B-100's lower affinity for LDL receptors, the LDL particles have a much longer life span than IDL particles: they circulate for an average of two and a half days before binding to LDL receptors in the liver.
and in other tissues.

The central role of the LDL receptor in atherosclerosis was first appreciated when we showed that its absence is responsible for the severe disease called familial hypercholesterolemia (FH). In 1939 Carl Müller of the Oslo Community Hospital in Norway identified the disease as an inborn error of metabolism causing high blood cholesterol levels and heart attacks in young people; he recognized that it is transmitted as a dominant trait determined by a single gene. In the 1960's Avedis K. Khachadurian at the American University in Beirut and Donald S. Frederickson at the U.S. National Heart and Lung Institute showed there are two forms of the disease, a heterozygous form and a more severe homozygous form. Heterozygotes, who inherit one mutant gene, are quite common: about one in 500 people in most ethnic groups. Their plasma LDL level is twice the normal level (even before birth) and they begin to have heart attacks by the time they are 35; among people under 60 who have heart attacks, one in 20 has heterozygous FH.

If two FH heterozygotes marry (one in 250,000 marriages), each child has one chance in four of inheriting two copies of the mutant gene, one from each parent. Such FH homozygotes (about one in a million people) have a circulating LDL level more than six times higher than normal; heart attacks can occur at the age of two and are almost inevitable by the age of 20. It is notable that these children have none of the risk factors for atherosclerosis other than an elevated LDL level. They have normal blood pressure, do not smoke and do not have a high blood glucose level. Homozygous FH is a vivid experiment of nature. It demonstrates unequivocally the causal relation between an elevated circulating LDL level and atherosclerosis.

By what mechanism is the LDL level elevated? What is the particular function of the mutant gene? When we looked at cultured skin fibroblasts and circulating blood cells from FH homozygotes, we saw that the cells have either no functional LDL receptors at all or very few and therefore cannot bind, internalize and degrade LDL efficiently. The defective gene, in other words, encodes the protein of the LDL receptor. Homozygotes, having inherited two defective receptor genes, cannot synthesize any normal receptors. The cells of FH heterozygotes have one normal receptor gene and one mutant gene; they synthesize half the normal number of receptors and can therefore bind, internalize and degrade LDL at half the normal rate.
Although all FH patients studied to date have a mutation in the gene encoding the LDL receptor, the mutations are not always the same. Depending on the particular site that has undergone mutation, the receptor may not be synthesized at all or it may be synthesized but then fail to be transported to the cell surface, fail to bind LDL or fail to cluster in coated pits.

Studies with radioactively labeled LDL show that the particles survive in the bloodstream of FH homozygotes about two and a half times as long as they do in people with a normal LDL-receptor gene. (Eventually the LDL is removed from the circulation by alternate but much less efficient pathways.) The predictable slowdown in the removal and breakdown of LDL is one major reason for the extremely high LDL level characteristic of FH, but it does not account for the entire rise. In addition to degrading LDL more slowly, a person homozygous for FH actually produces about twice as much LDL per day as a normal person. How can a defect in the LDL receptor lead to the overproduction of LDL? The answer to this question came from markable strain of rabbits with a genetic defect resembling the one in human FH.

The rabbits were discovered in 1978 by Yoshio Watanabe of the Kobe University School of Medicine and are called WHHL rabbits (for "Watanabe heritable hyperlipidemic"). They are homozygous for a mutant LDL-receptor gene and produce less than 5 percent of the normal number of receptors; they have high circulating LDL from the time of birth and develop atherosclerosis leading to heart attacks by the age of two. Studies done by us in collaboration with Toru Kita and David W. Bilheimer and by Steinberg and his colleagues showed that the rabbits, like their human counterparts with homozygous FH, make too much LDL as well as taking too long to break it down.

To learn the reason for LDL overproduction, Kita injected radioactively labeled VLDL, a precursor of LDL, into WHHL rabbits and normal animals and tracked the radioactivity through the fat-transport pathway. He found that triglyceride was removed from the VLDL, generating IDL, at the same rate in both groups. In normal rabbits the vast majority of the IDL particles disappeared rapidly from the circulation as they bound to LDL receptors on liver cells. In the WHHL rabbits, however, the liver cells lack LDL receptors, and so more IDL particles remained in the circulation and were eventually converted into more than the normal amount of LDL. In other words, a reduction in receptors has two effects in the rabbits-increased production and decreased removal of LDL—that act synergistically to raise the LDL level,
which therefore rises disproportionately (see Figure 13.8). Nicholas B. Myant and his colleagues at Hammersmith Hospital in London have shown the same thing is true in FH homozygotes.

Knowledge of the receptor deficiency in FH suggested a way to help the large number of patients with the heterozygous form of the disease. Perhaps we could stimulate the heterozygote's one normal gene to direct the synthesis of twice as many receptors as usual and so provide the patient with a normal complement of functional receptors. The possibility of such treatment was raised by something we had learned from cultured skin fibroblasts, namely that the feedback regulation of receptor synthesis takes place at the level of transcription. An excess of cholesterol reduces transcription of the LDL-receptor gene into messenger RNA, the nucleic acid that is subsequently translated by the cell's protein-synthesizing machinery to make the receptor protein; a cholesterol deficiency stimulates transcription and thus steps up the manufacture of receptors. We found we could get cultured cells from FH heterozygotes to make a normal number of LDL receptors (by making more messenger-RNA molecules from their single receptor gene) when we reduced the amount of cholesterol in the culture medium. How might we create an analogous cholesterol deficiency in the FH patient?

The liver takes up and degrades more cholesterol than any other organ because of its large size and its high concentration of LDL receptors. The bile acids into which most of the cholesterol is converted are secreted into the upper intestine, where they emulsify dietary fats. Having done their work, the bile acids are not simply excreted, however; they are largely reabsorbed from the intestine, returned to the bloodstream, taken up by the liver and again secreted into the upper intestine. This recycling of bile acids ordinarily limits the liver's need for cholesterol. We reasoned that if the recycling could be interrupted, the liver would be called on to convert more cholesterol into bile acids and this should lead the liver cells to make more LDL receptors.

A class of drugs that interrupt the recycling of bile acids was already known. They are the bile-acid-binding resins, gritty polymers carrying many positively charged chemical groups. Taken orally, these resins bind to the negatively charged bile acids in the intestine; because the resins cannot be absorbed from the intestine, they are excreted, carrying the bound bile acids with them. The first bile-acid-binding resin, cholestyramine, was synthesized more than 20 years ago and was found to lower the blood LDL level by an
average of 10 percent. (A recent 10-year prospective study done by the National Heart, Lung, and Blood Institute indicated that such a reduction was enough to cut the incidence of heart attacks in a test group of middle-aged men by 20 percent.) What we had learned about LDL metabolism provided the missing rationale for such results: the interruption of bile-acid recycling increases the number of LDL receptors on liver cells.

The 10 percent drop in LDL level attainable with cholestyramine and other such resins was encouraging, but clearly a more profound reduction is necessary for treating FH heterozygotes. The limited efficacy of the resins stems from the dual response of the liver to a cholesterol deficiency. In addition to making more LDL receptors the liver increases its manufacture of HMG CoA reductase and makes more of its own cholesterol. We reasoned that this increased de novo synthesis of cholesterol partially satisfies the resin-induced demand for more cholesterol and so prevents the liver from maximally increasing the number of LDL receptors.

We thought inhibition of cholesterol synthesis might force the liver to rely more on LDL uptake and thus stimulate greater production of receptors. To block cholesterol synthesis we took advantage of the discovery by Akira Endo, now of the Tokyo University of Agriculture and Technology, of a remarkable natural inhibitor of HMG CoA reductase. In 1976 he isolated from a penicillin mold a substance called compactin. A side chain of the compactin molecule closely mimics the structure of the natural substrate of HMG CoA reductase, and so it binds to the enzyme's active site and inhibits the enzyme's activity. Alfred W. Alberts of the Merck Sharp & Dohme Research Laboratories and his colleagues isolated from a different mold a structural relative of compactin, called mevinolin, that is an even more potent enzyme blocker. Compactin and mevinolin were shown, by Endo and Alberts respectively, to lower the blood LDL level in animals. If our idea was correct, the drugs should be even more effective in conjunction with a bile-acidbinding resin.

In collaboration with Petri T. Kovanen we administered a bile-acid-binding resin to dogs either alone or along with one of the enzyme inhibitors. After two weeks we assessed the number of LDL receptors by measuring the ability of biopsied liver membranes to bind radioactive LDL. We found, as expected, that the resin alone generated a modest rise in the number of receptors. When the enzyme inhibitor was given too, the number of receptors
rose much more. At the whole-body level this led to a marked increase in the rate of removal of LDL from the circulation. Together the two drugs caused a remarkable 75 percent decline in the dogs' LDL level.

With Bilheimer and Scott M. Grundy we went on to administer a resin and mevinolin to patients with heterozygous FH (see Figure 13.10). Their LDL level fell by approximately 50 percent, into the normal range. Tests with radioactive LDL showed the drop was caused by an increase in LDL receptors. The single normal gene had been made to work twice as hard as usual, producing enough receptors to allow LDL to be removed from the circulation at a normal rate.

As might be expected, FH homozygotes, lacking even one normal receptor gene, do not respond to this two-drug treatment. Another approach must be found if they are to be helped. Thomas E. Starzl of the University of Pittsburgh School of Medicine has tested a surgical approach, following up on a suggestion that the homozygote's lack of receptors might be partially corrected if the patient could be given a liver from a normal donor. He transplanted the liver of a child killed in an accident into a sixyear-old girl suffering from severe homozygous FH. (The patient had already had several heart attacks and her heart was so weakened that a heart transplant was necessary at the same time). More than six months after the operation the patient was maintaining a total blood cholesterol level in the range of 300 milligrams per deciliter, compared with a preoperation level of about 1,200. Obviously liver transplantation is not an ideal treatment, but the results to date make it clear that receptors on the cells of the transplanted liver are functioning to remove LDL from the circulation.

What about the vast number of people in Western industrial societies who suffer heart attacks or strokes without having any genetic defect in the LDL receptor? Is what we have learned about FH relevant to the high incidence of atherosclerosis in the general population? We believe it is. The LDL-receptor hypothesis states that much of the atherosclerosis in the general population is caused by a dangerously high blood level of LDL resulting from failure to produce enough LDL receptors. The inadequate number of receptors can be attributed to subtle genetic and environmental factors that limit receptor manufacture even in people without FH. One environmental factor is a high dietary intake of cholesterol and of saturated fats derived from animal tissues.
Epidemiologic surveys done in many countries over the past 30 years have uniformly shown that atherosclerosis becomes severer as the mean LDL level rises in a population. As long ago as 1958 Ancel Keys of the University of Minnesota Medical School studied populations, in seven countries, in which the mean total cholesterol level varied from a high of 265 milligrams per deciliter to a low of 160. (He did not measure LDL cholesterol specifically, but because the level of lipoproteins other than LDL does not vary much, one can assume that the variations in total cholesterol reflected differences in LDL level.) Keys recorded the cholesterol level of 12,763 age-matched men in the seven countries, and 10 years later he determined which of the men had had a heart attack.

Two variables were found to correlate strongly with cholesterol level: the incidence of coronary atherosclerosis (as measured by fatal heart attacks) and the dietary intake of animal fats. In two villages (in Japan and Yugoslavia) where the mean total cholesterol level was 160 the incidence of fatal heart attacks was less than five per 1,000 men per 10 years. In eastern Finland, where the mean total cholesterol level was 265, the incidence of fatal heart attacks was 14 times as high. In populations with intermediate cholesterol levels (as in the U.S.) the incidence fell between the two extremes.

The correlation between cholesterol level and dietary intake of animal fats was even stronger than the correlation between cholesterol and atherosclerosis. Populations consuming small amounts of animal fats (as in Japan and Yugoslavia) had low cholesterol levels. Populations with a high intake of such fats (as in eastern Finland) had high levels. Subsequent studies of many different populations have confirmed Keys's findings: high LDL levels are the rule in populations that consume a large part of their calories as fats from meat and dairy products.

The LDL-receptor hypothesis provides a likely explanation of the epidemiologic data. A high average intake of cholesterol makes cholesterol accumulate in liver cells. The accumulation seems to be accentuated by ingestion of animal fats rich in saturated fatty acids. Even a modest accumulation of cholesterol in the liver would partially suppress the manufacture of LDL receptors. This could lead to an increase in the average LDL level that would be detectable in an entire population.

Animal experiments by our group and by Mahley and Innerarity support the hypothesis that a high-fat diet reduces LDL receptors in the liver. In baboons,
rabbits and dogs maintained on low-fat diets the number of LDL receptors is high and the animals degrade injected LDL rapidly; their LDL level is much lower than it is in human beings. When rabbits and dogs are fed diets high in cholesterol, their manufacture of receptors in the liver is suppressed by as much as 90 percent, and the result is a buildup of both IDL and LDL in the bloodstream. At birth human infants have LDL concentrations similar to those of other animal species; apparently newborn human beings make a large number of LDL receptors. During the childhood and early-adult years in industrialized societies, however, the LDL levels rises three- or fourfold. Studies in adults injected with LDL suggest that the increase is attributable to a decrease in the number of receptors with age.

The causes of the acquired receptor deficiency in human beings are not all known. The high dietary intake of animal fats seems to be an important factor, but it is not the only one: even in people raised on diets extremely low in fats the LDL level tends to be higher than it is in other species. Such hormones as estradiol and thyroid hormone are known to stimulate the manufacture of LDL receptors in the liver, and it is possible that subtle abnormalities in these and other hormones contribute to the age-related decrease in receptors.

The concentration of LDL eventually attained in most middle-aged adults in the U.S. and in similar societies is associated by epidemiological data with accelerated atherosclerosis. Experiments with cultured cells show why. The receptors bind LDL optimally when it is present in the blood at a concentration below 50 milligrams per deciliter. The receptors in animals and in humans (judging by the LDL level in human infants) have apparently been selected by evolution to function at just such levels. Yet in Western industrial countries the average "normal" LDL level in adults is about 125 milligrams per deciliter, considerably above the concentration at which receptors bind LDL most efficiently.

One finding that is consistent with the LDL receptor hypothesis has been reported by William R. Hazzard of the Johns Hopkins Hospital and his colleagues. They showed that ingestion by adults of a high-cholesterol diet (including three egg yolks per day) does lead to a decrease in the number of LDL receptors, which they measured directly in circulating lymphocytes. A definitive test of the hypothesis will, however, require a comprehensive and well-controlled study of the rate of metabolism of injected VLDL and LDL in
members of populations with low-fat and high-fat diets and with varying LDL levels. That has not yet been done systematically.

If the LDL-receptor hypothesis is correct, the human receptor system is designed to function in the presence of an exceedingly low LDL level. The kind of diet necessary to maintain such a level would be markedly different from the customary diet in Western industrial countries (and much more stringent than moderate low-cholesterol diets of the kind recommended by the American Heart Association). It would call for total elimination of dairy products as well as eggs, and for a severely limited intake of meats and other sources of saturated fats.

We believe such an extreme dietary change is not warranted for the entire population. There are several reasons. First, such a radical change in diet would have severe economic and social consequences. Second, it might well expose the population to other diseases now prevented by a moderate intake of fats. Third, experience shows most Americans will not adhere voluntarily to an extreme lowfat diet. Fourth, and most compelling, people vary genetically. Among those who consume the current high-fat diet of Western industrial societies, only 50 percent will die of atherosclerosis; the other 50 percent are resistant to the disease.

Some individuals resist atherosclerosis because their LDL level does not rise dangerously even though they consume a high-fat diet; they may inherit genes that somehow circumvent the usual feedback system and maintain receptor manufacture at an adequate level. Barbara V. Howard of the National Institutes of Health Clinical Research Center in Phoenix has shown, for example, that Indians of the Pima tribe have relatively large numbers of LDL receptors, and maintain low LDL levels, in spite of a high-fat diet. In other individuals the arteries apparently resist the damaging effects of elevated LDL. For example, 20 percent of men with heterozygous FH do not have a heart attack before the age of 60 even though their blood LDL is very high.

Given these reasons for constraint, what can be done to prevent accelerated atherosclerosis? One approach is to individualize dietary recommendations. A diet moderately low in animal fats would seem to be prudent for most people. The diet proposed by the American Heart Association, for example, would reduce blood cholesterol levels by as much as 15 percent and should somewhat lessen the incidence of heart attacks. On the other hand, people who have a strong family history of heart attacks or
strokes, and who may therefore be particularly susceptible to the damaging effects of LDL, might well be encouraged to follow a diet extremely low in cholesterol and saturated fats—even if their LDL level is near the mean "normal" level. One can hope additional research will identify factors that either sensitize people to the ill effects of LDL or protect them from those effects.

Finally, therapy with drugs that increase the number of LDL receptors may turn out to be appropriate for at least some people who do not have FH but in whom the number of receptors is reduced by diet or other factors. If it is shown that these drugs do prevent diet-induced suppression of receptors and if the drugs can be shown to be safe for longterm use, it may one day be possible for many people to have their steak and live to enjoy it too.