LOWERING PLASMA CHOLESTEROL
BY RAISING LDL RECEPTORS

MEDICAL GRAND ROUNDS

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More than 93 percent of the body's cholesterol is located in cells, where it performs vital structural and metabolic functions; only 7 percent circulates in plasma, where it predisposes to atherosclerosis. All of the cholesterol in plasma is packaged within lipoprotein particles; two-thirds is in low density lipoprotein (LDL). The pathway for plasma cholesterol transport is shown in Fig. 1. Epidemiologic data and animal experiments implicate plasma LDL as a major cause of atherosclerosis. This is particularly true for the 1-in-500 individuals in the population who suffer from familial hypercholesterolemia (FH). Because of their elevated LDL levels, male heterozygotes with this dominant disease have an 85 percent chance of sustaining a myocardial infarction before age 60. Female heterozygotes also have a markedly increased risk (1).

The reason for the elevated LDL levels in FH became apparent several years ago when these subjects were found to have a defect in the gene for the LDL receptor (2). Normal cells produce this surface receptor when they require cholesterol for synthesis of new membranes, bile acids, or steroid hormones. Plasma LDL binds to the receptor and is taken into the cells and degraded, yielding its cholesterol for use in cellular metabolism. FH heterozygotes have only one functional gene for the LDL receptor and their cells therefore synthesize only half the normal number. In the body, heterozygotes compensate for their half-normal receptors by elevating their plasma LDL level by 2-fold. In the steady state, they degrade a normal amount of LDL through the receptor pathway but at the price of a 2-fold elevation in LDL levels, which eventually produces atherosclerosis (1).

The goal of therapy in FH is to reduce the concentration of LDL in plasma without disrupting cholesterol delivery to cells. The ideal approach is to stimulate cells to produce more LDL receptors. When the number of receptors increases, the rate of LDL degradation will initially increase. If the rate of LDL production does not change, the LDL level must decline. As the LDL level

declines, the rate of LDL degradation falls, since the rate of receptor binding is proportional to LDL concentration. Eventually a new steady state is attained in which the absolute rates of LDL degradation and cholesterol delivery to cells are the same as they were initially (and are equal to the LDL production rate), but the plasma LDL concentration has fallen roughly in proportion to the increase in LDL receptors. (Nonspecific or scavenger cell pathways are ignored for the purpose of this calculation) This new steady state is manifest as an increase in the fractional catabolic rate for LDL, which is the absolute rate of LDL degradation (in mg per day) divided by the total amount of LDL in intravascular fluid (in mg).

Since in the steady state the catabolic rate must equal the production rate, the LDL production rate ultimately determines the amount of cholesterol delivered to tissues by LDL. The number of LDL receptors does not affect the amount of cholesterol delivered; rather, it determines the plasma level of LDL at which this delivery will occur, and it determines which tissues take up LDL. To lower plasma LDL, it may not be necessary to severely decrease the amount of cholesterol transported; it may be adequate to increase the efficiency of transport by raising LDL receptors. For example, an animal such as the dog, which has a plasma LDL-cholesterol level of 20 mg/dl, produces as much LDL per kg body weight per day as does a man with an LDL-cholesterol of 80 mg/dl (1,3). The same amount of LDL-cholesterol is delivered to tissues. The difference in plasma levels is due to the high fractional catabolic rate in the dog (1.6 day^{-1}) (3) versus the low rate in normal man (0.4 day^{-1}) (1). This difference is due, at least in part, to a larger number of LDL receptors in the dog.

How can we increase LDL receptors in man? The production of LDL receptors is known to be regulated by hormonal and metabolic factors (4). Many agents that affect plasma cholesterol levels act by altering the number of LDL receptors, thereby changing the fractional catabolic rate for LDL. For example, thyroid hormone increases LDL receptors, which explains the classic finding of low

plasma cholesterol levels in hyperthyroidism and high levels in hypothyroidism (5). In rabbits and dogs, a high cholesterol diet decreases LDL receptors in the liver, a regulatory response that contributes to diet-induced hypercholesterolemia (4).

Pharmacologically, the production of LDL receptors can be stimulated by resins, such as cholestyramine or colestipol, that bind bile acids in the intestine and prevent their normal reabsorption. The liver responds by converting more cholesterol to bile acids, which tends to lower the hepatic content of cholesterol. To obtain additional cholesterol, the liver mounts a dual response: 1) it increases the synthesis of cholesterol by increasing the activity of a rate-controlling enzyme, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) (6); and 2) it produces a larger number of LDL receptors, increasing the fractional catabolic rate for LDL and causing plasma LDL levels to fall (3,7,8). FH heterozygotes can respond to cholestyramine because the single normal receptor gene is stimulated to produce additional LDL receptors, thereby increasing the fractional catabolic rate for LDL (8). However, the magnitude of this response is disappointingly small because the accelerated hepatic cholesterol production partially offsets the liver's need for LDL-cholesterol, causing the liver to produce a submaximal number of LDL receptors.

In this context the recent discovery of compactin (also called ML-236B) by Akira Endo, at the Sankyo Drug Company in Tokyo, assumes great importance (9). Isolated from a penicillin mold, compactin seems to have been designed by nature to be an ideal competitive inhibitor of HMG CoA reductase. The enzyme has a 10,000-fold higher affinity for compactin than it does for the structurally similar substrate HMG CoA. At micromolar concentrations, compactin abolishes cholesterol synthesis in cultured human and animal cells (10). Recently a related, but even more potent analogue, called monacolin K or mevinolin, has been isolated independently by Endo and by workers at the Merck Sharp and Dohme Research Laboratories in the United States (11).

Compactin and mevinolin reduce the plasma level of LDL in many animal species (3,9,11) as well as in humans (12). High density lipoprotein (HDL) is much less affected. The mechanism of LDL-lowering has been studied so far only in dogs (3). In this species mevinolin lowers LDL by a dual mechanism: 1) it decreases the rate of production of LDL by 50 percent; and 2) it stimulates the production of LDL receptors in the liver, thereby increasing the fractional catabolic rate for LDL (3). When given to dogs together with colestipol, mevinolin blocks the compensatory increase in hepatic cholesterol synthesis. As a result, hepatic LDL receptors increase 3-fold, and there is a remarkable 75 percent reduction in plasma LDL levels (3).

Mabuchi, et. al. have recently reported a detailed study of compactin's effects on lipoprotein levels in man (13). They used extremely low doses of compactin, less than one-tenth the amount used in the dog studies. Yet they observed a dramatic 29 percent reduction in plasma LDL levels in subjects with heterozygous FH. Plasma HDL levels did not change.

The important lesson from Mabuchi's study and the previous experience with compactin, mevinolin, and bile acid-binding resins is that normal regulatory mechanisms can be exploited to lower plasma LDL. A rise in LDL receptors, coupled with a modest decrease in LDL production, can lead to a profound fall in plasma cholesterol levels long before crucial body cholesterol stores are depleted. Based on previous experience with animals and humans, it seems likely that the fall in plasma LDL will slow the development of atherosclerosis. The availability of compactin should allow this hypothesis to be tested directly.

In addition to patients with FH, compactin offers hope to the large number of people whose plasma LDL levels are in the upper range for the population and who are predisposed to atherosclerosis, yet who do not have FH. The cause of such "multifactorial" hypercholesterolemia is unknown; it may be related indirectly to a high intake of fat and cholesterol. Even though such individuals eat a

high cholesterol diet, their bodies still synthesize 3 times more cholesterol than is absorbed from the intestine (14). Inhibition of cholesterol synthesis with compactin, with or without a bile acid-binding resin, may stimulate production of LDL receptors and reduce LDL levels in these individuals despite the continued consumption of a diet that is rich in cholesterol.

Many hurdles must be overcome before compactin or mevinolin can be accepted as a "penicillin" for hypercholesterolemia. No long-term toxicity studies have been reported in animals or man. It is possible that these compounds will produce unexpected side effects, and new analogues may have to be developed. Yet the studies with the parent compounds, compactin and mevinolin, have established a general principle: interference with cholesterol synthesis can trigger an increase in LDL receptors, thereby reducing the harmful 7 percent of cholesterol in plasma without depleting the 93 percent of body cholesterol that performs vital functions in tissues. And this is encouraging news, indeed.

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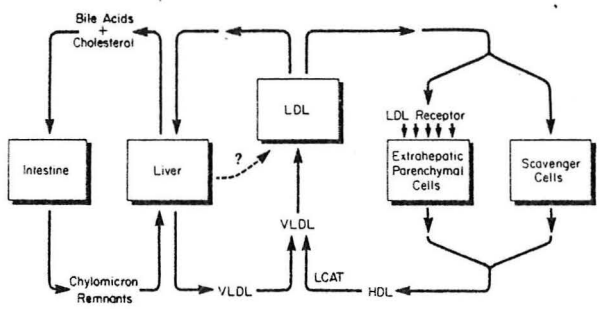

Fig. 1. Model for plasma cholesterol transport in normal man. The major site for control of plasma cholesterol transport resides in the liver. The liver receives dietary cholesterol in the form of chylomicron remnants, and it excretes cholesterol into the bile. The liver also secretes cholesterol into the plasma in the form of lipoproteins. The major lipoprotein secreted by the liver in man is very low-density lipoprotein (VLDL), which contains both triglyceride and cholesterol. The triglycerides of VLDL are removed in adipose tissue, and the VLDL particle is then converted into the cholesterol-rich lipoprotein, LDL. Circulating LDL acts as a storage bank for cholesterol. When extrahepatic parenchymal cells, such as kidney or lung cells, require cholesterol for membrane synthesis, it is believed that they synthesize LDL receptors, and this allows them to take up and degrade the lipoprotein and to use its cholesterol for membrane synthesis. The uptake of LDL through the receptor pathway suppresses cholesterol synthesis in these extrahepatic parenchymal cells. We believe that this mechanism explains the important earlier observations reviewed by Dietschy and Wilson in 1970 (6), when they showed in experimental animals that more than 70% of the cholesterol is synthesized in the liver and intestine and very little in extrahepatic cells. The liver also makes LDL receptors. The production of these receptors is regulated to help meet the liver's need for cholesterol for bile acid synthesis and VLDL secretion.