The regulation of cholesterol metabolism

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INTEREST in the metabolism of cholesterol has in recent years been stimulated by the belief, whether justifiable or not, that a rise in the plasma cholesterol level is a contributory cause of degenerative disease of the arteries. It may, therefore, be useful to summarize what is known of the physiological aspects of cholesterol metabolism and of the way in which the plasma cholesterol level is regulated under normal conditions.

Metabolism of cholesterol

Figure 1 shows how cholesterol is metabolized in the body as a whole.

FIG. 1. Pathways of cholesterol metabolism (cholesterol, —; bile salts, ----). (1) Cholesterol taken in food; (2) partial absorption of cholesterol via lymph followed by uptake by liver; (3) excretion of unchanged cholesterol in bile; (4) and (5) exchange between cholesterol in plasma, liver and tissues; (6) endogenous synthesis of cholesterol from acetate, controlled by feedback inhibition; (7) conversion of cholesterol into bile acids and excretion as bile salts; and (8) partial reabsorption of bile salts via portal blood, leading to inhibition of (7).

Absorption and endogenous synthesis

Cholesterol taken in the food is partially absorbed from the jejunum after esterification with long-chain fatty acids and incorporation into chylomicra. The chylomicra enter the bloodstream via the thoracic duct and are taken up in the liver. In the liver, cholesterol is detached from the chylomicra and returned to the plasma as a component of the plasma lipoproteins.

Cholesterol synthesized in the tissues from acetate also contributes to the plasma cholesterol and is, in fact, the only source when there is no cholesterol in the diet. The liver is probably the main source of endogenous plasma cholesterol, but cholesterol synthesized in the wall of the small intestine also enters the plasma. The possibility that synthesis in tissues other than liver and intestine contributes significantly to the plasma cholesterol cannot be excluded.

Removal from the body

The main route for the removal of cholesterol from the body is by excretion in the bile. The constant loss and replacement of cells lining the small intestine also leads to removal of cholesterol. The conversion of cholesterol into steroid hormones and their excretion in the bile and urine result in some loss of cholesterol, but this is negligible in comparison with the amount lost by other routes. Some of the cholesterol removed via the bile enters the duodenum without undergoing chemical change, but a variable proportion is first converted in the liver into bile acids. In rats, conversion into bile acids is the major biochemical pathway for the removal of cholesterol; in man, less than half the cholesterol lost from the body is removed as bile acids.

Enterohepatic circulation

Some of the cholesterol excreted in the bile is reabsorbed after mixing with cholesterol reaching the intestine from the food. The unabsorbed cholesterol is excreted in the faeces after partial conversion into coprostanol and other steroids by the action of bacteria in the large intestine. Bile salts are also partially reabsorbed in the ileum, the unabsorbed fraction passing into the

large intestine, where free bile acids are released by the hydrolytic action of bacteria. After further modification, the free bile acids are excreted in the faeces. There is thus an incomplete enterohepatic circulation involving cholesterol, both endogenous and exogenous, and bile salts.

The plasma cholesterol

About two-thirds of the plasma cholesterol is esterified with long-chain fatty acids and about one-third is free. In the fasting state, when there are no chylomicra in the blood, all the plasma cholesterol is held in solution by its association with protein and with other lipids to form the plasma lipoproteins. Experiments in which the plasma cholesterol is labelled, either by intravenous injection of radioactive cholesterol or by administration of a radioactive precursor of cholesterol, have shown that free and esterified plasma cholesterol and cholesterol in the different lipoprotein fractions are all exchangeable with one another and with the cholesterol in most tissues other than central nervous system. In some cases the exchange appears to take place by simple diffusion. In others, the mechanism of exchange is more complicated. Exchange between free and esterified cholesterol in the plasma, for instance, appears to be brought about largely by hydrolysis and re-esterification in the liver. The rate at which the plasma cholesterol exchanges with tissue cholesterol varies widely in different tissues. For example, in normal men free cholesterol in plasma and liver approaches complete equilibration with a half-period of about 20 min, whereas equilibration between the cholesterol in the plasma and that in the wall of the abdominal aorta takes several weeks to approach completion.

Constancy of the plasma cholesterol level

In most species the plasma cholesterol level remains constant within fairly narrow limits despite variations in the amount of cholesterol taken in the food. This is certainly true for men, rats, dogs and monkeys. Indeed, the slight effect of cholesterol feeding on the plasma cholesterol level in many species of laboratory animals has been a hindrance to the study of experimental atherosclerosis. Rabbits, it should be noted, are unusual in that their plasma cholesterol level rises rapidly when they are fed cholesterol.

Regulation of the plasma cholesterol level

Constancy of the plasma cholesterol level in the presence of a variable intake of cholesterol suggests the existence of regulatory mechanisms that adjust the amount of cholesterol in the body.

Experimental animals

In laboratory animals, synthesis of cholesterol in the liver is depressed by feeding a diet rich in cholesterol; if cholesterol constitutes more than about 2% of the diet, inhibition of cholesterol synthesis in the rat's liver is almost complete. This effect is due to inhibition, by cholesterol itself, of a single rate-limiting step in the chain of reactions through which acetate is converted into cholesterol. If, as seems likely, cholesterol synthesis in the liver is inhibited by endogenous, as well as by exogenous, cholesterol, this would provide the animal with a self-regulating system for controlling endogenous synthesis of cholesterol. Inhibition of cholesterol synthesis by exogenous cholesterol must also enable the liver to compensate to some extent for variations in the amount of cholesterol absorbed from the food. If, for example, a rat's liver synthesized 10 mg of cholesterol per day when there was no cholesterol in the diet, it could compensate fully for 10 mg of cholesterol absorbed from the food per day by reducing the rate of endogenous synthesis to zero. Regulation of cholesterol synthesis in the liver by feed-back inhibition has now been demonstrated in rats, dogs, monkeys and rabbits.

The results of experiments on animals also suggest that the rate of conversion of cholesterol into bile acids increases in response to an increase in the amount of cholesterol absorbed from the food. Clearly, this could act as an additional regulatory mechanism.

Cholesterol metabolism is influenced by several hormones, including thyroxine and some of the steroid hormones. However, it is not certain that these effects play any part in the regulation of cholesterol metabolism under normal conditions. It seems clear, on the other hand, that bile salts participate in a homeostatic mechanism by which the degradation of cholesterol to bile acids is regulated by feed-back inhibition. Thus, if the enterohepatic circulation of bile salts is interrupted by making a bile fistula, the rate of bile-acid synthesis from cholesterol increases. If a pure bile salt is then infused into the lumen of the intestine, bile-acid synthesis reverts to the normal level. As would be expected, the high rate of conversion of cholesterol into bile acids in bile-fistula animals is accompanied by a compensatory increase in the rate of synthesis of endogenous cholesterol from acetate.

Man

Despite its importance, we know very little about the way in which cholesterol metabolism is regulated in man. Our lack of knowledge is

due largely to the difficulty of measuring accurately the rates of flow of cholesterol and bile acids along the various pathways shown in Fig. 1. This applies particularly to measurement of the rate of endogenous synthesis of cholesterol. Only recently has it become possible to measure this at all reliably in man.

The evidence for the existence of feed-back control of cholesterol synthesis in man is contradictory. Experiments designed to test the effect of cholesterol feeding on cholesterol synthesis in the liver *in vitro* have given conflicting answers. Moreover, no-one has yet succeeded in showing an inhibitory effect of cholesterol feeding on the incorporation of radioactive precursors of cholesterol into the plasma cholesterol *in vivo*. Nevertheless, it is hard to believe that a mechanism present in several species of animals, including monkeys, is not also present in man, especially since it probably reflects a fundamental property of a key enzyme concerned in the biosynthesis of cholesterol. There is some evidence that the rate at which the human intestine can absorb cholesterol is limited; recent work suggests that a normal man cannot absorb more than about 0.5 g/day. This would tend to diminish the fluctuations in the plasma cholesterol level that might otherwise be brought about by variations in the amount of cholesterol taken in the food. Further, since endogenous and exogenous cholesterol mix completely in the lumen of the intestine, any limitation to the absorption of exogenous cholesterol would apply equally to the reabsorption of cholesterol excreted in the bile. Conceivably, this might act as a 'safety valve', enabling the body to remove excessive amounts of endogenous cholesterol.

Relevance to the problem of treatment

The measures now available for lowering the plasma cholesterol level leave much to be de-

sired. They are often ineffective, and when they do produce an effect we seldom understand fully how it is brought about. To take only one example, unsaturated fatty acids are used extensively in the treatment of patients who have symptoms of arterial disease and in whom the plasma cholesterol level is at or above the upper limit of the normal range. Yet we cannot exclude the possibility that the effect of this treatment on the plasma cholesterol level is due largely to displacement of cholesterol from the plasma into the tissues.

A rational approach to the problem of treatment would be based on what we know of the way in which cholesterol is metabolized. In view of the possibility that cholesterol synthesis in man is regulated by feed-back inhibition, it would be unreasonable, for example, to rely only on measures directed towards stimulating the removal of cholesterol from the body, since this would be expected to cause a compensatory increase in endogenous synthesis. For the same reason, it is hardly surprising that a cholesterol-free diet is not an effective method of treatment. A method acting merely to redistribute cholesterol from plasma to tissues would not, of course, be acceptable. Nor is it desirable to inhibit completely an early step in the synthesis of cholesterol, since some of the intermediates in cholesterol biosynthesis from acetate may be essential to the body. It may well be that advances in the treatment of essential hypercholesterolaemia will come by combining methods affecting cholesterol metabolism at several points. A practicable approach might be to try to depress endogenous synthesis of cholesterol, while at the same time stimulating its conversion into bile acids and diminishing its reabsorption from the intestine. We are not yet in a position to achieve this, but it may be better to aim at something of this sort rather than to concentrate on a single line of attack.