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EDITORIAL

New Insights into the Homeostasis of Plasma Cholesterol

A Time for Changing Concepts

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Ever since the discovery of cholesterol in the atheromatous lesions in man, there has been a surge of interest in the metabolism of cholesterol. The association of increased levels of plasma cholesterol with early development of atherosclerotic lesions focused the attention of investigators on plasma cholesterol. Although it constitutes only a small fraction of the total body cholesterol, plasma cholesterol is still the only pool of cholesterol incriminated in coronary artery disease and its dreaded complications. Despite extensive work on cholesterol metabolism over the last few decades, the mechanisms responsible for homeostasis of plasma cholesterol in man still elude us. An understanding of its normal homeostasis, as well as of the mechanisms by which dietary factors influence levels of plasma cholesterol, is desirable concomitant with attempts to lower the plasma cholesterol level of the general population by public health measures.

Conventional Approach for Elucidating Homeostatic Control. The lack of progress in this area is mainly due to the approach that is usually taken for elucidating the factors controlling the levels of plasma cholesterol. The methods used for most such studies provide information on the turnover rates of total cholesterol in the body but not about the turnover rates of cholesterol in the plasma compartment. The parameters of cholesterol principally examined in these studies have been focused on the absorption, synthesis and elimination of cholesterol from the system as a whole. It is obvious that changes in these parameters of cholesterol metabolism will directly be responsible for changes in the amount of total cholesterol in the body; as such, they do not necessarily have direct effects on the levels of plasma cholesterol.

The Assumptions. In order to relate the changes in total body cholesterol to the changes in plasma cholesterol levels, it is assumed that when changes in total body cholesterol occur there is a concurrent

reequilibration of mass of cholesterol between tissue and plasma pools so that changes in plasma cholesterol correspond to the changes in total body cholesterol. This assumption is usually implied, but it has also been stated explicitly by a leading group in this field as follows: "The total body cholesterol is regulated by a complex dynamic interplay between absorption, synthesis and excretion. Any imbalance among the principal determinants might result in swelling or depletion of the exchangeable body pools of cholesterol, and it might be expected that the size of plasma cholesterol pool would reflect such imbalances" [1].

Traditional ("Overload") Hypothesis. Despite the importance of these assumptions in the traditional view of homeostasis of plasma cholesterol, they have never been subjected to systematic and direct experimental tests, although a large number of observations can be marshalled in support of the view. Thus, early studies of Beveridge et al. [2], Conner et al. [3] and Mattson et al. [4] provided the major support to this hypothesis. These studies demonstrated that increasing intake of dietary cholesterol is generally associated with increasing levels of plasma cholesterol. It was generally believed that, in contrast to experimental animals, man cannot compensate for the increased absorption by a decrease in endogenous synthesis [5]. Thereby, it was argued that increased intake "overloaded" the system which then manifested itself by higher levels of cholesterol in plasma. Similarly, increased synthesis and decreased elimination were considered to increase the load of cholesterol and to increase its concentration in plasma.

However, there is substantial evidence to indicate that there is a marked variation in the individual responses of plasma cholesterol when man is challenged by increased dietary cholesterol. In fact, a significant proportion of subjects may show no change or some may even show a decrease in plasma cholesterol [6,7]. Furthermore, recent studies demonstrate that man can and does compensate for the increased absorption of dietary cholesterol by decreasing endogenous synthesis, increasing elimination or both [6–8]. Indeed, the sum of the two compensatory mechanisms nearly equals the increase in absorption when dietary intake is not unusually large [7], so that there may in fact be no net increase in the total body cholesterol even in subjects who respond by an increase in plasma cholesterol [7]. However, these studies failed to show why plasma cholesterol levels increased in some subjects and not in others. The investigations in experimental species other than man also failed to demonstrate any consistent relationships between the changes in plasma cholesterol with high cholesterol diets and the changes in synthesis, absorption or elimination of cholesterol from the body [9–12].

Updated "Transport" Hypothesis. This updated view may be termed "transport" hypothesis since the approach based on this hypothesis is concerned principally with the transport of cholesterol by plasma lipoproteins into and out of plasma, and only secondarily with the absorption, synthesis and elimination of cholesterol. It is recognized that mechanisms must exist for the transport of cholesterol from tissues into plasma and from plasma into tissues, which do not directly involve the synthesis or degradation of the plasma lipoproteins. But to date, so little is known of these mechanisms that this editorial is purposely focused primarily on the relationship of cholesterol metabolism to the metabolism of plasma lipoproteins. The transport hypothesis is delineated by the following discussion.

Even when considering the effects of dietary cholesterol on its levels in plasma, by tradition, we think of levels of cholesterol in postabsorptive plasma obtained from 12 to 16 hours after the last meal. Therefore, any changes in the levels of cholesterol during the absorptive phase are not relevant to our discussion. However, if chylomicra and other intestinal lipoproteins or their remnants containing dietary cholesterol are still present in circulating plasma, and have not once been cleared from the circulation and then released at or 16 hours after a meal, they may contribute directly to the plasma levels of cholesterol without involving changes in absorption, synthesis or elimination of cholesterol from the system. Furthermore, if this were true, it might also explain the progressive increase in plasma cholesterol with the increasing intake of dietary cholesterol [4].

If, on the other hand, remnants of intestinal lipoproteins containing dietary cholesterol are rapidly cleared from the circulation, the dietary cholesterol or its same equivalent has to reenter plasma in hepatic lipoproteins for the dietary cholesterol to influence levels of plasma cholesterol. Furthermore, for the dietary cholesterol to increase the levels of cholesterol in postabsorptive plasma in man, it has to either increase the rate of entry of cholesterol from the liver into plasma as lipoproteins, or decrease the rate of its exit from plasma. Thus, increased absorption of dietary cholesterol would be associated with clearly defined changes either in the structure or the metabolism of plasma lipoproteins or both.

Proposed Unified Concept. In the final analysis it is the concentrations of different plasma lipoproteins which determine the levels of cholesterol in plasma. Therefore, the concentration of plasma cholesterol may not be caused primarily by changes in absorption, synthesis and elimination of cholesterol from the system, but by factors that directly influence the metabolism and levels of lipoproteins in the plasma. Indeed, the

energy requirements of peripheral tissues, or the metabolism of fatty acids, may dictate the metabolism of plasma lipoproteins [13] more than the needs of cholesterol by extrahepatic tissues as recently postulated [14]. All this points to the necessity of elucidating the factors controlling the metabolism of different plasma lipoproteins and of correlating the latter with absorption, synthesis and elimination of cholesterol before we can develop a complete understanding of the homeostasis of plasma cholesterol.

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