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Human Plasma High-Density Lipoproteins: Past, Present and Future

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High-density lipoproteins represent a class of plasma lipoproteins of high hydrated density commonly separated by ultracentrifugal flotation in media of density 1.063–1.21 g/ml. Two major subclasses have been recognized, with densities of 1.063–1.125 g/ml (HDL₂) and 1.125–1.21 g/ml (HDL₃). Both fraction HDL₂ and fraction HDL₃ have been intensively characterized by many chemical and physical techniques, although their relationship, whether physiological or merely an artifact, has not been established.

The demonstration that the apolipoprotein (referred to earlier as α P) of high-density lipoprotein can be isolated in an essentially lipid-free form and solubilized in aqueous media in the absence of surface-active agents or dissociating agents like urea or guanidine hydrochloride was a significant development in the understanding of the chemistry and the structure of high-density lipoprotein. Such an observation made possible the application to the apolipoprotein of the many techniques available in protein chemistry. It is now established that apo-(fraction HDL₂) and apo-(fraction HDL₃) each contain two major polypeptide chains, referred to in our laboratory as fractions III and IV, which are chemically and immunologically distinct from each other. Another minor class of polypeptides, fraction V, has been identified, and there is evidence for its derivation from the very-low-density-lipoprotein peptides as one of the consequences of the very-low-density lipoprotein-high-density lipoprotein exchange process.

From the structural viewpoint, the studies directed at defining the lipid-binding properties of fractions III and IV with the ultimate goal of reassembling *in vitro* high-density lipoprotein from its isolated constituents have been particularly fruitful. Methods have been described for the

reassembly of a high-density-lipoprotein-like complex with properties strikingly similar to those of native high-density lipoprotein. This has led to a detailed analysis of the mode of solubilization of cholesteryl esters in high-density lipoprotein, particular attention being paid to the role played by the apolipoprotein and phospholipids. Of no less significance have been the studies demonstrating that some of the polypeptide chains of the apolipoprotein centre in important enzymic reactions. For example, one of the polypeptides of fraction V has been shown to act as a cofactor in the activity of the enzyme lipoprotein lipase (clearing-factor lipase).

With regard to future trends, it is expected that important progress will be made in defining the structure and function of the various high-density-lipoprotein polypeptides. Reassembly methods, making use of ultracentrifugal, spectroscopic (n.m.r., spin-label methods, fluorescence etc.) and X-ray techniques for the analysis of the products obtained, are expected to provide some clarification of the molecular details of the protein-lipid interactions in high-density lipoprotein. Many of these studies are now under way.

The Argonne Cancer Research Hospital is operated by the University of Chicago for the U.S. Atomic Energy Commission.

Some Physical Approaches to the Structure of Serum High-Density Lipoproteins

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The serum lipoproteins have been subjected to an increasing range of physical techniques and physico-chemical approaches in recent years. These studies have had a dual motivation. On the one hand it was hoped that these approaches might lead to a detailed elucidation of the molecular structures of these systems, which in turn would lead to an understanding of their role in lipid metabolism. On the other hand the serum lipoproteins appear to be receiving increasing attention as models of lipid-protein interaction in general. This paper will be limited to the high-density lipoproteins of human serum, specifically the HDL₂ fraction, the major molecular components of which are protein, phospholipids (mainly phosphatidylcholine) and neutral lipids (mainly cholesteryl esters). The major questions to which the studies to be described refer are simply stated: what are the gross structural features and underlying molecular interaction in fraction HDL₂ that lead to a mutual solubilization of the otherwise water-insoluble phospholipids and cholesteryl esters?