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HYPERCHOLESTEROLEMIA, HYPOCHOLESTEROLEMIA, HYPERTRIGLYCERIDEMIA, IN VIVO KINETICS

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PREFACE

The past two decades have seen steady progress in our understanding of the pathogenesis of atherosclerosis. The role of low density lipoprotein (LDL) increase and of LDL receptor deficiency or malfunctions in familial hypercholesterolemia has been largely enlightened by the works of Brown and Goldstein. These authors postulated also that modification of LDL to a form recognized by the scavenger or acetyl-LDL receptor may be required for lipid loading of macrophage-derived foam cells in the lesions. A growing body of evidence suggests that oxidative modification of LDL could enhance its atherogenicity by its implication as a factor in the generation of foam cells.

Thus, if the role of LDL in the pathogenesis of hypercholesterolemia was well established a great deal of information appears currently on new approaches such as the mechanisms leading to the accumulation of foam cells, the impact of LDL structural alterations, notably oxidation and the role of gene mutations of apolipoprotein B and/or LDL receptor

The opening topic is devoted to these new avenues outlined in the field of hypercholesterolemia. The first part concerns the genetic aspects of atherosclerosis: mainly the genetics of apolipoproteins, their transcriptional regulation, the amino acid mutations of the apo B gene and of the LDL receptor gene, the structural domains and the acylation sites of apoprotein B. The second part of the topic is devoted more directly to cholesterol: the mechanisms regulating its distribution between lipoproteins in relation to the activity of the cholesteryl ester transfer protein, the role of its precursors in the hepatic lipase expression, the LCAT-mediated formation of its esters, the role of HDL receptor, of apolipoproteins A-I, A-II, A-IV and of CETP in its efflux from cells. The relation of structural characteristics (for instance amphipathic helices) and alterations with the function of LDL and HDL is also documented in this section.

A short second topic is dedicated to hypocholesterolemia. Surprisingly, while hypercholesterolemia has been the object of thousands of very competent papers, hypocholesterolemia which may be, when chronic and severe, harmful for the maintenance of normal membrane integrity and cell function and for adequate synthesis of steroid hormones has been often left out. It is worth remembering that a relationship has been long since suspected between hypocholesterolemia and cancer.

The third topic honors Mones Berman's contribution to kinetics. Whereas in vitro studies were often at the origin of basic discoveries, in vivo kinetic experiments made difficult by the very high number of variables appeared essential to be realized for our understanding of metabolism. Most "static" studies demonstrate the changes from normal of

many parameters without furnishing any view on their dynamics. In vivo kinetics is also submitted to a number of problems: ethical but essentially methodological. The use of tracers, the validity of their use as "physiological" markers have given rise to much controversy since many years, but despite these snags such studies, difficult of access, are irreplaceable. It is sure that Mones Berman a physicist of the NIH with a particularly high ability to apprehend physiology was a pioneer in the concept of compartmental modeling of physiological data, and of its application for identifying and quantifying metabolic routes in normal state and in a variety of pathologies, and also for assessing the prognosis, the mechanism of action of dietary conditions, of other risk factors and of hypolipidemic drugs. The fact that this approach is surely one of the most tedious has limited the number of teams and of studies devoted to these problems. Numerous examples are given showing the complexity of the subject, aggravated by the recent introduction of the concept of heterogeneity partly related to the new lipoprotein particle's theory.

The potential risk accompanying hypertriglyceridemia has not been until now well defined. Many contradictory studies have not allowed to result in a definite conclusion whether it is an additional or dependent risk factor. The fourth part of this volume deals with this question, particularly the role of genetic variation of the lipoprotein lipase gene, the factors regulating lipoprotein lipase, the effect of lipoprotein lipase and apoprotein C-II deficiency, the role of apoproteins in modulating the metabolism and uptake of triglyceride-rich particles, the relation with LDL composition, the potential role of Lp(a) pathogenicity, the influence of lipoprotein particles' apoprotein composition, the binding and uptake of triglyceride-rich lipoprotein remnants.

Finally the closing topics concerns some new approaches of atherosclerosis: -the cytotoxicity of triglyceride-rich remnants, the role of oxidized LDL and their preferential uptake by macrophages, the effect of certain drugs or vitamins on these modifications; -the relation between plasma factors and structural constituents of the arterial wall as the proteoglycans; -the contribution of immunocompetent cells to the atheromatous lesion and the formation of autoantibodies against endothelial cells, modified LDL, and circulating immune complexes.

If it is certain that atherosclerosis represents one entity the intricacy of the various mechanisms corresponding to many origins, isolated or combined, gives way to many further studies.

It is also highly desirable that these extraordinary strides in fundamental research will find a quick application in the diagnosis, prevention and treatment of atherosclerotic manifestations in routine clinics.

C. L. Malmendier

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