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Pharmacological Control of Lipid Metabolism

Edited by William L. Holmes, Rodolfo Paoletti and David Kritchevsky

PHARMACOLOGICAL CONTROL OF LIPID METABOLISM

Proceedings of the Fourth International Symposium on Drugs Affecting Lipid Metabolism held in Philadelphia, Pennsylvania, September 8-11, 1971

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The generosity of these organizations made it possible for us to arrange this Symposium, which was attended by more than four hundred scientists working on problems of lipid metabolism.

The Organizing Committee

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PREFACE

This Symposium was the fourth in a series which began in Milan, Italy, in 1960. Each meeting has introduced or developed some new concepts in the areas of lipid metabolism and drugs. The meetings have served as a springboard for new ideas which have, between meetings, become accepted and exploited. This meeting has been no exception. Principal among the many new concepts discussed were lipoprotein synthesis and metabolism, apoprotein structure and function, whole body metabolism of cholesterol, and aspects of myocardial and aortic metabolism. The Symposium also included a summary of current thought on management of hyperlipemias and atherosclerosis. Data on more than 30 drugs were introduced and discussed. We have every expectation that the next Symposium will include material which is now only in the formative stage.

The Organizing Committee would like to acknowledge the invaluable assistance of Miss Mary Constant, Mr. Ralph H. Hollerorth, Mrs. Carolyn P. Hyatt and Miss Jane T. Kolimaga, whose efforts contributed significantly ($p < .001$) to the success of this Symposium.

W. L. Holmes
R. Paoletti
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OPENING REMARKS

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In opening this Symposium on Drugs Affecting Lipid Metabolism, I thought it might be of interest to reflect for a moment on some of the past developments in this field. It was in 1931, exactly 40 years ago, that Dr. Paul Dudley White published the first edition of his celebrated book entitled "Heart Disease." In discussing the treatment of arterial disease, Dr. White said the following concerning arteriosclerosis: "For arteriosclerosis itself there is as yet no known therapy; some believe that the age-long use of potassium iodide or other drug of traditional value may some day prove to have a scientific basis. If the condition is rapidly progressive or pronounced, it is probably wise to prevent overexertion, overeating, and overexposure to infections without restricting too much the activities of life which in themselves favor health and happiness." Since that time, and particularly during the past twenty years, we have witnessed a tremendous explosion in the development of new basic knowledge concerning many facets of atherosclerosis, which in turn have led to new approaches to its treatment and even to its prevention. Testimony to this is seen in the ever increasing literature devoted to either the nutritional-hygenic or pharmacological approaches to the control of atherosclerotic vascular disease.

The recognition of a possible causal relationship of elevated serum cholesterol to atherosclerosis together with the demonstration in the early 1950's that soy sterols could inhibit atherogenesis in rabbits led to an intensified search for hypocholesterolemic

agents. Of necessity, many of these studies were quite emperical in nature; however, during the latter part of this decade, somewhat more rational approaches to the problem began to emerge. These were based on an ever increasing knowledge of the biochemical pathways involved in cholesterol biosynthesis, and of the factors concerned with its absorption, degradation and excretion. By 1960 a number of potential leads had been uncovered and formed a large portion of the subject matter for the first of these symposia. Of the ten or so potential drugs discussed at that meeting, only two or three have survived the test of time.

During this period we were beginning to hear rumblings of the possible relationship of triglyceride to certain types of vascular disease. Also, new knowledge of the chemistry and physical properties, and of the role of lipoprotein in lipid transport was unfolding. The low density lipoproteins were recognized as the culprits which invade the aorta and deposit their lipid therein—we began to think in terms of hyperlipoproteinemia and of decreasing circulating low density- and very low density lipoproteins rather than cholesterol or triglyceride alone.

Another milestone was achieved in 1965, when Fredrickson, Levy and Lees classified hyperlipoproteinemias into five distinct phenotypes. It soon was shown that the different phenotypes did not necessarily respond to the same type of therapy. This technique has proved to be of immense value, not only to the physician in planning therapeutic regimens for his hyperlipoproteinemic patients, but also to the research scientist searching for new lipoprotein lowering drugs.

Now to say a few words about the present meeting. When it was planned by the Organizing Committee, it was felt that the subject matter should be limited to two rather broad areas: (1) new basic information providing it is relevant, and (2) newer aspects of drugs affecting lipid metabolism. The Program Committee has attempted to organize the program within these guidelines, and we hope that you will find the result intellectually stimulating and satisfying.

Finally, a cursory inspection of the program shows that the effect of some thirty pharmacologic agents on various aspects of lipid metabolism will be discussed, some for the first time.

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Further, it can be seen that contributions have been received from researchers representing seventeen different countries, which attests to the fact that this Symposium truly has become the international forum for this new but important area of medical research.

NEWER DEVELOPMENTS IN LIPID BIOCHEMISTRY

SYNTHESIS AND SECRETION OF PLASMA LIPOPROTEINS

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Virtually nothing is known about the initial intracellular events that lead to the formation of a nascent lipoprotein particle. However, recent technical advances in electron microscopy, cell frationation, and the biochemistry of apolipoproteins are providing subcellular probes for identifying and characterizing both the plasma lipoprotein secretory mechanisms and the newly made secretory products. Evidence for an extremely close relationship between nascent plasma lipoproteins and the membrane lipoproteins constituting the secretory mechanism is beginning to emerge.

It is generally recognized that there are two different forms of lipoproteins: 1) those of cells which constitute the membrane lipoproteins of subcellular organelles; 2) the soluble lipoproteins of extracellular fluids (1). Membrane lipoproteins are probably formed chiefly by planar sheets of phospholipid bilayers. The long fatty acid chains of each phospholipid occupy the inner core of the sheet as a non-polar phase. Polar head groups of the phospholipids, spaced about 40-45 Å apart, provide a hydrophilic surface on each side of the sheet (2,3). The heterogeneous proteins of biological membranes associate with the phospholipid bilayer structure in different ways. Some proteins are extended on the surface, others penetrate partially and still others may penetrate the full thickness of the lipid bilayer (3).

The soluble lipoproteins of blood plasma and lymph serve transport functions and differ from membrane lipoproteins in that they are specialized products of only two cells: hepatic parenchymal cells and absorptive cells of the small intestine. One might expect soluble lipoproteins to differ greatly in structure from membranes since they occur as spheroidal particles measuring between

50-5000 Å in diameter. Although the structure of plasma lipoproteins is not established, many probably exist as a miniature droplet of oil containing triglycerides and cholesteryl esters surrounded by a thin surface film of phospholipid, protein and free cholesterol. Recent studies give evidence that this surface film is a monolayer of invariant thickness of about 21-22 Å, precisely one-half the thickness of a phospholipid bilayer (4). This model suggests the working hypothesis that plasma lipoproteins might originate from a phospholipid bilayer by expansion of the nonpolar core.

In order to discuss subcellular mechanisms of origin of soluble lipoproteins, it is first necessary to classify plasma lipoproteins into functional groups. Four major groups of lipoproteins isolated from plasma are generally recognized on the basis of their ultracentrifugal and electrophoretic properties. These include 1) chylomicrons; 2) very low density (VLDL) or pre-beta lipoproteins, 3) low density (LDL) or beta lipoproteins; 4) high density (HDL) or alpha lipoproteins. Each group can be isolated and characterized by measurements of the proportions of the major lipid components and total protein (5).

SECRETION OF VLDL AND CHYLOMICRONS

The formation of VLDL and chylomicrons may be discussed together. The liver develops as an outgrowth of the primitive foregut and from the standpoint of ultrastructure, hepatic parenchymal cells share many morphologic features with absorptive cells of the small intestine (Fig. 1 and 2). Functionally, these two cells are unique in their special capability to export triglycerides and cholesteryl esters in soluble particles. Both liver and small intestine respond to availability of extracellular free fatty acids (FFA) by increasing their uptake and esterification, and by increased release of triglycerides in particulate form back into the extracellular spaces. The secretory products released by these cells, VLDL and chylomicrons, are generally similar in gross chemical composition:

Rat Lipoproteins	Triglycerides	Chol. Esters	Chol.	Phospholipids	Protein	Mean Diameter
Serum VLDL	70	6	3	11	10	400 Å
Lymph Chylomicrons	90	2	1	6	1	2000 Å
	"Core"		"Surface"			

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