

**HYPERCHOLESTEROLEMIA,
HYPOCHOLESTEROLEMIA,
HYPERTRIGLYCERIDEMIA,
IN VIVO KINETICS**

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Editorial Board:

NATHAN BACK, *State University of New York at Buffalo*

IRUN R. COHEN, *The Weizmann Institute of Science*

DAVID KRITCHEVSKY, *Wistar Institute*

ABEL LAJTHA, *N.S. Kline Institute for Psychiatric Research*

RODOLFO PAOLETTI, *University of Milan*

Recent Volumes in this Series

Volume 280

MYOBLAST TRANSFER THERAPY

Edited by Robert C. Griggs and George Karpati

Volume 281

FIBRINOGEN, THROMBOSIS, COAGULATION, AND FIBRINOLYSIS

Edited by Chung Yuan Liu and Shu Chien

Volume 282

NEW DIRECTIONS IN UNDERSTANDING DEMENTIA AND ALZHEIMER'S DISEASE

Edited by Taher Zandi and Richard J. Ham

Volume 283

BIOLOGICAL REACTIVE INTERMEDIATES IV: Molecular and Cellular Effects and Their Impact on Human Health

Edited by Charlotte M. Witmer, Robert R. Snyder, David J. Jollow, George F. Kalf, James J. Kocsis, and I. Glenn Sipes

Volume 284

ENZYMOLGY AND MOLECULAR BIOLOGY OF CARBONYL METABOLISM 3

Edited by Henry Weiner, Bendicht Wermuth, and David W. Crabb

Volume 285

**HYPERCHOLESTEROLEMIA, HYPOCHOLESTEROLEMIA
HYPERTRIGLYCERIDEMIA, IN VIVO KINETICS**

Edited by Claude L. Malmendier, P. Alaupovic, and H. Bryan Brewer, Jr.

Volume 286

TEMPERATURE AND ENVIRONMENTAL EFFECTS ON THE TESTIS

Edited by Adrian W. Zorngiotti

Volume 287

NEURORECEPTOR MECHANISMS IN BRAIN

Edited by Shozo Kito, Tomio Segawa, and Richard W. Olsen

A Continuation Order Plan is available for this series. A continuation order will bring delivery of each new volume immediately upon publication. Volumes are billed only upon actual shipment. For further information please contact the publisher.

HYPERCHOLESTEROLEMIA, HYPOCHOLESTEROLEMIA, HYPERTRIGLYCERIDEMIA, IN VIVO KINETICS

Edited by

Claude L. Malmendier

Research Foundation on Atherosclerosis
Brussels, Belgium

P. Alaupovic

Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma

and

H. Bryan Brewer, Jr.

National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging-in-Publication Data

International Colloquium on Atherosclerosis (5th : 1990 : Brussels, Belgium)
Hypercholesterolemia, hypocholesterolemia, hypertriglyceridemia, in vivo kinetics / edited by Claude L. Malmendier, P. Alaupovic, and H. Bryan Brewer, Jr.
p. cm. -- (Advances in experimental medicine and biology ; v. 285)
"Proceedings of the Fifth International Colloquium on Atherosclerosis, held March 14-16, 1990, in Brussels, Belgium"--T.p. verso.
Includes bibliographical references and index.
ISBN-13: 978-1-4684-5906-7
1. Atherosclerosis--Pathophysiology--Congresses.
2. Hypercholesterolemia--Congresses. 3. Hypocholesterolemia--Congresses. 4. Hypertriglyceridemia--Congresses.
5. Atherosclerosis--Molecular aspects--Congresses. I. Malmendier, Claude L. II. Alaupovic, P. III. Brewer, H. Bryan. IV. Title. V. Series.
[DNLM: 1. Atherosclerosis--etiology--congresses. 2. Cholesterol--blood--congresses. 3. Hypercholesterolemia--metabolism--congresses. 4. Hypertriglyceridemia--metabolism--congresses. W1 AD559 v. 285 / WG 550 I6033h 1990]
RC692.I4674 1990
616.1'36071--dc20
DNLM/DLC
for Library of Congress

91-2557
CIP

Proceedings of the Fifth International Colloquium on Atherosclerosis,
held March 14-16, 1990, in Brussels, Belgium

ISBN-13: 978-1-4684-5906-7 e-ISBN-13: 978-1-4684-5904-3
DOI: 10.1007/978-1-4684-5904-3

© 1991 Plenum Press, New York

Softcover reprint of the hardcover 1st edition 1991
A Division of Plenum Publishing Corporation
233 Spring Street, New York, N.Y. 10013

All rights reserved

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise, without written permission from the Publisher

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

CONTENTS

CHOLESTEROL METABOLISM

Transcriptional Regulation of the Human Apolipoprotein Genes.....	1
V.I. Zannis, D. Kardassis, K. Ogami, M. Hadzopoulou-Cladaras, and C. Cladaras	
Mutations and Variants of Apolipoprotein B that Affect Plasma Cholesterol Levels.....	25
T.L. Innerarity and K. Boström	
Molecular Genetics of Familial Hypercholesterolemia.....	33
K. Aalto-Setälä and K. Kontula	
Investigation of Structural Domains on Human Serum Low Density Lipoprotein and Apolipoprotein B100.....	39
M. Djavaheri and L.P. Aggerbeck	
Implications of Thiolester Linked Fatty Acids in Apolipoprotein B..	49
D.M. Lee	
Factors Regulating the Distribution of Cholesterol between LDL and HDL.....	59
P.J. Barter, L.B.F. Chang, and O.V. Rajaram	
Regulation of Hepatic Lipase Expression by an Intermediate of the Cellular Cholesterol Biosynthetic Pathway.....	65
S.J. Busch, G.A. Martin, R.L. Barnhart, M.A. Flanagan, and R.L. Jackson	
Human Plasma Lecithin:Cholesterol Acyltransferase (LCAT). On the Role of Essential Carboxyl Groups in Catalysis.....	71
M. Jauhiainen and P. J. Dolphin	
Plasma Lipoprotein Phenotype in Response to Cholesteryl Ester Transfer Protein Levels in Dyslipoproteinemia.....	77
Y.L. Marcel, A.R. Tall, M. Hogue, R.W. Milne, and R. McPherson	
HDL Receptor-mediated Cholesterol Efflux from Cells and its Regulation.....	81
E.L. Bierman, J. Oram, and A. Mendez	
Binding of Apolipoproteins A to Adipose Cells: Role of Receptor Sites in Cholesterol Efflux and Purification of Binding Protein(S)	85
R. Barbaras, P. Puchois, A. Pradines-Figuères, A. Steinmetz, V. Clavey, N. Ghalim, J-C. Fruchart, and G. Ailhaud	

Lipoprotein A-I Containing Particles.....	93
N. Duverger, N. Ghalim, N. Theret, P. Duchateau, G. Aguie, G. Ailhaud, G. Castro, and J-C Fruchart	
Distribution of Cholesterol within High Density Lipoproteins Fractionated by Immunoaffinity Chromatography.....	101
D. Pometta and R.W. James	
Metabolic Role of Human Apopoprotein A-IV.....	109
L. Lagrost, P. Gambert, A. Athias, and C. Lallemand	
Regression of Atheroma and Putative Role of CETP in Cholesteryl Ester Removal.....	117
Y. Stein and O. Stein	
Symmetry of the Surface, and Structure of the Central Core of Human LDL Particles, Analyzed by X-ray Small Angle Scattering.....	123
M.W. Baumstark, W. Kreutz, A. Berg, and J. Keul	
Role of Amphipathic Helixes in HDL Structure/Function.....	131
G. M.Anantharamaiah, C.G. Brouillette, J.A. Engler, H. De Loof, Y.V. Venkatachalapathy, J. Boogaerts, and J.P. Segrest	
Conformational Properties of Apolipoproteins Studied by Computer Graphics.....	141
J.L. De Coen, J.P. Kocher, C. Delcroix, J-F. Lontie, and C.L. Malmendier	
Alterations of High Density Lipoproteins Induced by Thyroid Hormones in Man and Rat.....	147
G. Ponsin, C. Vialle-Valentin, and F.Berthézène	
The HELP-system in the Treatment of Severe Hypercholesterolaemia: Acute and Long-term Experience.....	155
D. Seidel	
Familial Hypocholesterolemia and HDL Deficiency.....	161
M-F. Dumon, M. Freneix-Clerc, M-J. Maviel, and M. Clerc	
Mechanisms of Hypocholesterolemia.....	173
C.L. Malmendier, J-F. Lontie, and D.Y. Dubois	
Origin of Cholesterol and Bile Acids in the Diverted Bile of Two Patients with Total Small Bowel Resection.....	183
J. Férézou, P. Beau, M. Parquet, T. Hajri, T. Magot, C. Matuchansky, and C. Lutton	

IN VIVO KINETICS

Berman's Simulation Analysis and Modeling.....	189
L.A. Zech, D.J. Rader, and P.C. Greif	
Considerations in Designing and Analyzing Data from Apo-B Turnover Studies.....	201
D.M. Foster and P.H.R. Barrett	
What Is Meant by Overproduction of Apo B-containing Lipoproteins?..	213
S.M. Grundy and G.L. Vega	

Kinetics of Heterogeneous Populations of Particles.....	223
C.L. Malmendier, J-F. Lontie, C. Delcroix, and D.Y. Dubois	
HDL Metabolism in HDL Deficiency Associated with Familial Hypertriglyceridemia: Effect of Treatment with Gemfibrozil.....	233
M.L. Kashyap and K. Saku	
Recent Advances in Lipoprotein Metabolism and the Genetic Dyslipoproteinemias.....	237
H.B. Brewer, Jr, D.J. Rader, J.M. Hoeg, A. Mann, and G Tennyson	
Kinetic Studies of the Origin of Apolipoprotein (apo) B-100 in Low Density Lipoproteins of Normal and Watanabe Heritable Hyperlipemic (WHL) Rabbits.....	245
R.J. Havel and D.M. Shames	
Alterations in Cholesterol Metabolism in the Genetically Hypercholesterolemic RICO Rat: An Overview.....	257
K. Ouguerram, T. Magot, and C. Lutton	
HYPERTRIGLYCERIDEMIA	
Genetic Variation at the Lipoprotein Lipase Gene Associates With Coronary Arteriosclerosis.....	275
J.C. Chamberlain, J.A. Thorn, R. Morgan, A. Bishop, J. Stocks, A. Rees, K. Oka, and D.J. Galton	
The Lipid Surface of Triglyceride-Rich Particles Can Modulate (Apo)Protein Binding and Tissue Uptake.....	281
D.M. Small, S.B. Clark, A. Tercyak, J. Steiner, D. Gantz, and A. Derksen	
Structure and Metabolism of Low Density Lipoproteins from Normal and Hypertriglyceridemic Subjects.....	289
B.J. McKeone, J.R. Patsch, and H.J. Pownall	
The ApoB 100-apo(a) Complex: Relation to Triglyceride-Rich Particles.....	295
A.M. Scanu and G. Fless	
ApoB-Containing Lipoprotein Particles as Risk Factors for Coronary Artery Disease.....	299
P. Alaupovic, D.H. Blankenhorn, C. Knight-Gibson, M. Tavella, J.M. Bard, D. Shafer, E.T. Lee, and J. Brasuell	
In Vitro Binding and In Vivo Uptake of Chylomicron Remnants after their Hydrolysis by Hepatic Lipase.....	311
F. Sultan, D. Lagrange, and S. Griglio	
The Endocytosis of Lipoproteins by the Liver and their Intracellular Pathway in Comparison to other Ligands.....	319
S. Jäckle, B. Levkau, T. Lorenzen, F. Rinninger, W. Daerr, H. Greten, and E. Windler	
Concomitant Inhibition of VLDL Triglyceride and Apoprotein Secretion by Hepatocytes of Rats Adapted to a High-fat Diet.....	325
O.L. Francone, A.D. Kalopissis, and G. Griffaton	

Molecular Genetics of ApoC-II and Lipoprotein Lipase Deficiency....	329
S.S. Fojo, J.L. de Gennes, U. Beisiegel, G. Baggio, A.F.H. Stalenhoef, J. D. Brunzell, and H.B. Brewer, Jr	
What Factors Regulate the Action of Lipoprotein Lipase?.....	335
T. Olivecrona, G. Bengtsson-Olivecrona, M. Hultin, J. Peterson, S. Vilaro, R.J. Deckelbaum, Y. A. Carpentier, and J. Patsch	
PATHOGENESIS OF ATHEROSCLEROSIS	
Cytotoxicity of Remnants of Triglyceride-Rich Lipoproteins: An Atherogenic Insult?.....	341
B. H. Chung and J.P. Segrest	
The Role of Oxidized LDL in Atherosclerosis.....	353
J.L. Witztum	
Probucol and its Mechanisms for Reducing Atherosclerosis.....	367
R.L. Jackson, R.L. Barnhart, and S.J.T. Mao	
Proteoglycans, Lipoproteins, and Atherosclerosis.....	373
S.R. Srinivasan, B. Radhakrishnamurthy, P.Vijayagopal, and G.S. Berenson	
Immune Mechanisms in the Pathogenesis of Atherosclerosis.....	383
M.F. Lopes-Virella and G. Virella	
Cholesterol Level in Circulating Immune Complexes as a Marker of Coronary Atherosclerosis.....	393
A.N. Orekhov, O.S. Kalenich, V.V. Tertov, I.D. Novikov, and E.G. Vorob'eva	
Antibody-like Immunoglobins G against Low Density Lipoprotein that Stimulate Lipid Accumulation in Cultured Cells.....	399
A.N. Orekhov and V.V. Tertov	
Nutritional Regulation of Apolipoprotein Genes: Effect of Dietary Carbohydrates and Fatty Acids.....	407
A. Ribeiro, M. Mangeney, P. Cardot, C. Loriette, J. Chambaz, Y. Rayssiguier, and G. Bereziat	
Lipoprotein Structure and Metabolism During Progression and Regression of Atherosclerosis in Pigs Fed With Fish Oil-Derived Fatty Acids.....	417
A. Van Tol, T. Van Gent, L.M. Scheek, J.E.M. Groener, L.M.A. Sassen, J.M.J. Lamers, and P.D. Verdouw	
Contributors.....	423
Index.....	435