

Drugs Affecting Lipid Metabolism

Edited by
R. Paoletti
D. Kritchevsky, W. L. Holmes



Drugs Affecting Lipid Metabolism

Edited by R. Paoletti,
D. Kritchevsky and W. L. Holmes

With 132 Figures



Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo

Professor Dr. RODOLFO PAOLETTI
Dean
School of Pharmacy
University of Milan
Via Balzaretti 9
20133 Milan, Italy

Professor Dr. DAVID KRITCHEVSKY
Associate Director
The Wistar Institute
3601 Spruce Street
Philadelphia, PA 19104, USA

Dr. WILLIAM L. HOLMES
238 Chatham Way
West Chester, PA 19380, USA

ISBN 3-540-17277-7 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-17277-7 Springer-Verlag New York Berlin Heidelberg

Library of Congress Cataloging in Publication Data. Drugs affecting lipid metabolism/
edited by R. Paoletti, D. Kritchevsky, and W.L. Holmes. p. cm. - (Proceedings in life sciences)
Includes index. ISBN 0-387-17277-7 (U.S.). 1. Hyperlipidemia-Chemotherapy. 2. Antilipemic
agents-Testing. 3. Blood lipoproteins-Metabolism. 4. Blood cholesterol-Metabolism. I. Paoletti,
Rodolfo. II. Kritchevsky, David, 1920-. III. Holmes, Williams L., 1918-. IV. Series. [DNLM:
1. Antilipemic Agents. 2. Arteriosclerosis. 3. Lipids-metabolism. 4. Lipoproteins-metabolism.
5. Metabolism-drug effects. QU 85 D794] RC632.H87D78 987 616.3'997061-dc 19

This work is subject to copyright. All rights are reserved, whether the whole or part of the
material is concerned, specifically the rights of translation, reprinting, re-use of illustrations,
recitation, broadcasting, reproduction on microfilms or in other ways, and storage in data
banks. Duplication of this publication or parts thereof is only permitted under the provisions
of the German Copyright Law of September 9, 1965, in its version of June 24, 1985, and a
copyright fee must always be paid. Violations fall under the prosecution act of the German
Copyright Law.

© Springer-Verlag Berlin Heidelberg 1987
Printed in Germany

The use of registered names, trademarks, etc. in this publication does not imply, even in the
absence of a specific statement, that such names are exempt from the relevant protective laws
and regulations and therefore free for general use.

Printing and Binding: Brühlsche Universitätsdruckerei, Giessen
2131/3430-543210

Preface

The recent symposium and the appearance of this new book on *Drugs Affecting Lipid Metabolism* take place at a very unusual time for the development of this area.

After the publication and wide acceptance of the results of the cholestyramine study by the Lipid Clinics in the USA, showing for the first time a direct association between drug induced reduction of plasma levels of total and LDL cholesterol and coronary heart disease in a high risk population, an unparalleled interest in drugs and other procedures able to control plasma cholesterol levels has been activated.

Two other significant events occurred during 1986 and 1987: the availability of compact instruments for the immediate determination of total cholesterol in plasma or total blood and the developments of new agents such as the inhibitors of HMG-CoA (hydroxymethylglutaryl CoA) reductase and ACAT inhibitors, with potentially great effect on plasma lipid levels after oral administration.

These new advances, together with the combined efforts of cell biologists and lipoprotein chemists, have set the pace for an exciting period of research and clinical applications of diets and drugs affecting lipids.

This volume, which includes the work of many of the leading world laboratories, represents an authoritative and up-to-date appraisal of the status of the art and a stimulus to future research at laboratory and clinical level in an area of opportunity for clinical and preventive medicine.

Milan, October 1987

Rodolfo Paoletti

Acknowledgements

We thank the contributors for their appreciable efforts in writing the papers for the Drugs Affecting Lipid Metabolism Meeting (Florence, Italy, October 22–25, 1986) upon which the chapters in this volume are based. We are particularly indebted to the Giovanni Lorenzini Foundation for its help and generous support, which made the meeting possible.

We are also grateful to the scientific secretaries, Drs. A.L. Catapano and C.R. Sirtori, and to the International Advisory Board for their valuable contributions.

The Editors

Roberto Paoletti

Milan, October 1987

Contributors

You will find the addresses at the beginning of the respective contributions

- | | | |
|-------------------------------|---------------------------|-------------------------|
| Albarede, J.L. 328 | Catapano, A.L. 126 | Gaion, R.M. 94 |
| Allievi, L. 131 | Cazzolato, G. 407, 433 | Galli, C. 131, 162 |
| Apebe, P. 442 | Chan, L. 52 | Galli, G. 126, 380, 394 |
| Austen, K.F. 167 | Chapman, M.J. 117 | Galli Kienle, M. 421 |
| Avogaro, P. 407, 433 | Chernick, S.S. 88 | Gebhard, R.L. 150 |
| Axthelm, M. 426 | Chesne, E. 338 | Genovese, S. 295 |
| Baggio, G. 355 | Ciuffetti, G. 291, 372 | Ghiselli, G. 63 |
| Balestreri, R. 283 | Cighetti, G. 421 | Gianfranceschi, G. 442 |
| Ball, M.J. 56 | Connor, W.E. 155 | Gianturco, S.H. 52 |
| Baralle, F.E. 56 | Crepaldi, G. 355 | Gibson, D.M. 9 |
| Barbara, L. 350 | Crestani, M. 126, 380 | Giudici, G.A. 358 |
| Bard, J.M. 333 | Crook, D. 215 | Glatz, J.F.C. 122 |
| Barter, P.J. 244 | Cuzzolaro, S. 283 | Godslan, I.F. 215 |
| Bass, N.M. 105 | Daga, A. 283 | Goto, Y. 247, 274 |
| Bazzoli, F. 350 | De Fabiani, E. 380, 394 | Gotto, A.M., Jr. 52, 63 |
| Bell, G.D. 223 | Del Puppo, M. 421 | Graham, K.J. 150 |
| Bengtsson-Olivecrona, G. 88 | Di Santo, C. 358 | Gregg, R.E. 236 |
| Bertolini, S. 283 | Dorigo, P. 94 | Grundy, S.M. 34, 415 |
| Beynen, A.C. 122 | Dostert, P. 324, 338 | Guichard, J.P. 328 |
| Bittolo Bon, G. 407, 433 | Douste-Blazy, P. 333 | Harris, W.S. 155 |
| Blane, G.F. 309 | DoVale, H. 1 | Heibig, J. 63 |
| Bogaievsky, Y. 343 | Drouin, P. 333 | Hibbard, D.M. 150 |
| Bondioli, A. 142 | Duane, W.C. 150 | Hoeg, J.M. 236 |
| Bonnefous, F. 343 | Dujovne, C.A. 136 | Hopkins, G.J. 244 |
| Bosisio, E. 21, 126, 380, 394 | Eisenberg, S. 48, 79, 305 | Houin, G. 328 |
| Bradley, W.A. 52 | Elicio, N. 283 | Hunninghake, D.B. 150 |
| Branchi, A. 278 | Fantappié, S. 126 | Illingworth, D.R. 155 |
| Brewer Jr., H.B. 236 | Fievet, C. 333 | Ito, T. 251 |
| Cacciaguerra, F. 223 | Fragiacomo, C. 394, 410 | Itoh, H. 260 |
| Caldwell, J. 324 | Franceschini, G. 442 | Javitt, N.B. 29 |
| Canavesi, A. 174 | Freeman, M.L. 150 | Jost, G. 343 |
| Cao Danh, H. 317, 338 | Fruchart, J.C. 333 | Kajinami, K. 260 |
| Capaldo, B. 295 | Fujita, H. 260 | Kamon, N. 260 |
| | Funke, P.T. 255 | Kashyap, M.L. 367 |
| | Gaddi, A. 442 | Katan, M.B. 122, 158 |

- Kawai, C. 251
 Kayden, H.J. 193
 Kita, T. 251
 Knight, B.L. 403
 Koizumi, J. 403
 Krehbiel, P. 136
 Kritchevsky, D. 197
 Krüger, B. 389
 Kume, N. 251
 Law, S.W. 236
 Legendre, C. 317
 Lehtonen, A. 219
 Lemmens, A.G. 122
 Lovati, M.R. 131, 174
 Lugli, R. 399
 Luoma, P.V. 210
 Lupattelli, G. 291, 372
 Luyeye, I. 333
 Mabuchi, H. 260
 Mahley, R.W. 59
 Malinow, M.R. 426
 Mancini, M. 295
 Mann, J.I. 56
 Mannarino, E. 291
 Manzato, E. 355
 Manzoni, C. 131, 174
 Marcovina, S. 333
 Marin, R. 355
 Marotta, G. 295
 Mazzella, G. 350
 McCay, P.B. 181
 McKinstry, D.N. 255
 McLaughlin, P. 426
 Medini, L. 162
 Mensink, R.P. 158
 Michishita, I. 260
 Middleton, B. 223
 Miller, N.E. 200
 Miller, S.J. 9
 Mitropoulos, K.A. 14
 Montagna, G. 283
 Montgomery, J.C. 215
 Mosconi, C. 162
 Nakaya, N. 274
 Neri Serneri, G.G. 437
 Nikkilä, E.A. 231
 Nilsson-Ehle, P. 83
 Nosedà, G. 394, 410
 Ockner, R.K. 105
 Olivecrona, T. 88
 Orcchini, G. 372
 Packard, C.J. 205
 Pagani, F. 358
 Pan, H.Y. 255
 Paroni, R. 421
 Parker, R.A. 9
 Pascal, M. 317
 Patti, L. 295
 Paulussen, R.J.A. 98
 Pekala, P.H. 88
 Phillipson, B.E. 155
 Pistocchi, G. 283
 Postiglione, A. 295, 403
 Pownall, H. 52
 Prigge, W.F. 150
 Price, S.R. 88
 Prisco, D. 437
 Puchois, P. 333
 Puglisi, L. 376
 Quack, G. 376, 380
 Radelli, A. 394
 Reichl, D. 227
 Reinke, L.A. 181
 Riccardi, G. 295
 Rivellese, A. 295
 Roda, A. 350
 Roda, E. 350
 Rogasi, P.G. 437
 Ronchi, M. 350
 Saku, K. 367
 Saldalamacchia, G. 295
 Salvioli, G. 399
 Schatton, W. 376, 380,
 385
 Schwaier, A. 376
 Schwartzkopff, W. 301
 Scow, R.O. 88
 Seifert, T. 385
 Selvini, C. 358
 Semb, H. 88
 Shepherd, J. 205
 Shoulders, C.C. 56
 Siepi, D. 291, 372
 Silber, J.R. 1
 Simoni, P. 350
 Siperstein, M.D. 1
 Sirtori, C.R. 131, 142, 174,
 442
 Sirtori, M. 442
 Slimane, N. 333
 Sommariva, D. 278
 Soutar, A.K. 403
 Sparrow, J.T. 52
 Sperling, R.I. 167
 Stefanoni, P. 358
 Steinberg, D. 42, 69
 Strolin-Benedetti, M.
 324, 328, 338
 Takeda, M. 260
 Takeda, R. 260
 Taskinen, M.-R. 231
 Thiemann, R. 389
 Thompson, G.R. 403
 Torossian, F. 343
 Traber, M.G. 193
 Tremoli, E. 162
 Tsujita, Y. 251
 Turturro, F. 63
 Upson, B. 426
 Valice, S. 283
 Van Zutphen, L.F.M. 122
 Veerkamp, J.H. 98
 Ventura, A. 291, 372
 Vergani, C. 358
 Vesselinovitch, D. 111
 Vilaró, S. 88
 Villanova, N. 350
 Wakasugi, T. 260
 Watanabe, Y. 251
 Weil, A. 324
 White, D.A. 223
 Willard, D.A. 255
 Wissler, R.W. 111
 Wittels, E. 63
 Wynn, V. 215
 Yamamoto, A. 269
 Yamamura, T. 269
 Yang, C.Y. 52
 Yokoyama, S. 269
 Zambon, S. 355
 Zech, L.A. 236

Contents

Relationship of Cholesterol to DNA Synthesis in Normal and Cancerous Cells M.D. Siperstein, H. DoVale, and J.R. Silber (With 3 Figures)	1
Turnover of HMG-CoA Reductase is Influenced by Phosphorylation R.A. Parker, S.J. Miller, and D.M. Gibson (With 2 Figures)	9
Regulation of ACAT K.A. Mitropoulos (With 2 Figures)	14
Dietary and Pharmacological Control of Cholesterol, 7 α -Hydroxylase E. Bosio (With 3 Figures)	21
Recent Advances in Metabolic Pathways of Bile Acid Synthesis N.B. Javitt	29
Bile Acid Sequestrants: Do They Have a Future? S.M. Grundy	34
Transport of Cholesterol and Cholesterol Esters by HDL D. Steinberg	42
Role of HDL in the Metabolism of the Plasma Lipoproteins S. Eisenberg (With 1 Figure)	48
The Structure of ApoB-100: Structure-Function Studies A.M. Gotto, W.A. Bradley, L. Chan, S.H. Gianturco, H.J. Pownall, J.T. Sparrow, and C.Y. Yang (With 2 Figures)	52
A Genetic Marker in the Apolipoprotein AI/CIII Gene Complex Associated with Hypercholesterolaemia C.C. Shoulders, M.J. Ball, J.I. Mann, and F.E. Baralle	56

Cellular and Molecular Biology of Apolipoproteins: Receptor-Mediated Regulation of Cholesterol Metabolism R.W. Mahley (With 1 Figure)	59
APOA-I and APOA-II Metabolism and Coronary Artery Disease G. Ghiselli, J. Heibig, F. Turturro, A.M. Gotto, Jr., and E. Wittels	63
Hypocholesterolemic Drugs and Lipoprotein Metabolism D. Steinberg	69
Hypotriglyceridemic Drugs and Lipoprotein Catabolism S. Eisenberg (With 1 Figure)	79
Lipolysis and Lipoprotein Metabolism P. Nilsson-Ehle (With 2 Figures)	83
Regulation of Lipoprotein Lipase Activity: Its Role in Lipid-Lowering Therapies Th. Olivecrona, S.R. Price, P.H. Pekala, R.O. Scow, S.S. Chernick, H. Semb, S. Vilaró, and G. Bengtsson-Olivecrona (With 3 Figures)	88
Lipolysis and Antilipolytic Drugs at Different Ages R.M. Gaion and P. Dorigo	94
Fatty Acid-Binding Proteins of Various Tissues J.H. Veerkamp and R.J.A. Paulussen (With 3 Figures)	98
Interaction of Lipid-Lowering Drugs with Fatty Acid-Binding Proteins N.M. Bass and R.K. Ockner (With 1 Figure)	105
Animal Models for Hyperlipidemia-Induced Atherosclerosis R.W. Wissler and D. Vesselinovitch (With 2 Figures)	111
Animal Species as Models of Spontaneous and Induced Hyperlipidemias: A Critical Appraisal M.J. Chapman	117
Rabbit Models Hypo- or Hyperresponsive to Changes in Diet A.C. Beynen, A.G. Lemmens, J.F.C. Glatz, M.B. Katan, and L.F.M. Van Zutphen	122

Plasma Lipoproteins and Cholesterol Metabolism in a Strain of Hyperlipemic Rats S. Fantappiè, E. Bosisio, M. Crestani, G. Galli, and A.L. Catapano (With 2 Figures)	126
Spontaneous Hypertriglyceridemia in a Non-Obese Rat Model: The IVA-SIV Rat M.R. Lovati, L. Allievi, C. Manzoni, C. Galli, and C.R. Sirtori (With 1 Figure)	131
Considerations for Controlled Clinical Testing of Safety and Efficacy of New Hypolipidemic Drugs C.A. Dujovne and P. Krehbiel (With 7 Figures)	136
Desirable Lipoprotein Parameters in Early Drug Trials C.R. Sirtori and A. Bondioli (With 4 Figures)	142
Metabolic Studies with Lovastatin in Patients with Primary Hypercholesteremia D.B. Hunninghake, D.M. Hibbard, W.C. Duane, M.L. Freeman, W.F. Prigge, K.J. Graham, and R.L. Gebhard (With 2 Figures)	150
Reduction of Plasma Lipids and Lipoproteins by Dietary Fish Oils in Patients with Hypertriglyceridemia B.E. Phillipson, W.E. Connor, W.S. Harris, and D.R. Illingworth	155
Effects of Monounsaturated Fatty Acids Versus Complex Carbohydrates on Serum Lipoprotein Subfractions and Apolipoproteins in Healthy Men and Women R.P. Mensink and M.B. Katan	158
Changes of Eicosanoid Formation in Relation to Dietary Lipids and in Hyperlipaemia C. Galli, C. Mosconi, L. Medini, and E. Tremoli.	162
Effects of Omega-3 Polyunsaturated Fatty Acids on Human Leukocyte Function and Biochemistry R.I. Sperling and K.F. Austen	167
Dietary and Biochemical Studies with Textured Soy Proteins C.R. Sirtori, A. Canavesi, C. Manzoni, and M.R. Lovati (With 3 Figures)	174
Detection of Reactive Free Radicals in Livers of Ethanol-Fed Rats: Potentiating Effect of High Fat Diets P.B. McCay and L.A. Reinke (With 6 Figures)	181

The Role of the Antioxidant Tocopherol in Lipid and Lipoprotein Metabolism H.J. Kayden and M.G. Traber	193
Newer Aspects of Fats and Lipid Metabolism D. Kritchevsky	197
Can We Retard Atherogenesis by Modifying High-Density Lipoprotein Metabolism? N.E. Miller (With 1 Figure)	200
Effects of Lipid-Lowering Drugs on High Density Lipoprotein Structure and Metabolism J. Shepherd and C.J. Packard (With 1 Figure)	205
Enzyme-Inducers and High-Density Lipoproteins P.V. Luoma (With 2 Figures)	210
Gonadal Steroids and Hormone Antagonists D. Crook, I.F. Godsland, J.C. Montgomery, and V. Wynn	215
The Effects of Adrenoceptor and Adrenergic Blocking Drugs on Plasma Lipoproteins A. Lehtonen	219
The Influence of Terpenes and Analogues on Parameters of Atherosclerosis D.A. White, G.D. Bell, F. Cacciaguerra, and B. Middleton (With 1 Figure)	223
Initial Stages of Reverse Transport of Cholesterol D. Reichl (With 1 Figure)	227
Lipolytic Enzymes and HDL: Influence of Drugs and Hormones M.-R. Taskinen and E.A. Nikkilä (With 2 Figures)	231
Human Apolipoprotein A-I and A-II Metabolism H.B. Brewer, Jr., R.E. Gregg, S.W. Law, J.M. Hoeg, and L.A. Zech (With 3 Figures)	236
Roles of LCAT and Lipid Transfer Protein in HDL Metabolism P.J. Barter and G.J. Hopkins	244
The Profile of an HMG-CoA Reductase Inhibitor, CS-514 (SQ 31,000) Y. Goto (With 2 Figures)	247

Induction of Hepatic Low-Density Lipoprotein Receptors in Heterozygous WHHL Rabbits Treated with CS-514 Alone or CS-514 in Combination with Cholestyramine T. Kita, N. Kume, Y. Tsujita, T. Ito, Y. Watanabe, and C. Kawai (With 2 Figures)	251
The Clinical Pharmacology of SQ 31,000 (CS 514) in Healthy Subjects H.Y. Pan, D.A. Willard, P.T. Funke, and D.N. McKinstry (With 3 Figures)	255
Long-Term Effects of CS-514 on Serum Lipoprotein Lipid and Apolipoprotein Levels in Patients with Familial Hypercholesterolemia H. Mabuchi, N. Kamon, H. Fujita, I. Michishita, M. Takeda, K. Kajinami, H. Itoh, T. Wakasugi, and R. Takeda (With 6 Figures)	260
Intensive Drug Treatment for Familial Hypercholesterolemia A. Yamamoto, S. Yokoyama, and T. Yamamura (With 3 Figures). 269	
Effect of CS-514 on Hypercholesterolemic Patients N. Nakaya and Y. Goto (With 5 Figures)	274
Hyperlipoproteinemia and Therapy: Results of a Multicenter Trial with Bezafibrate, a New Lipid-Lowering Drug D. Sommariva and A. Branchi	278
Lipoprotein Changes Induced by Bezafibrate – 200 mg t.i.d. – and by Bezafibrate in a Slow-Release Preparation – 400 mg Once a Day – in Patients with Primary Hyperlipoproteinaemia S. Bertolini, S. Valice, N. Elicio, A. Daga, S. Cuzzolaro, G. Montagna, G. Pistocchi, and R. Balestreri.	283
Modifications of Apoprotein, Lipoprotein Parameters and HDL ₂ and HDL ₃ Subfractions During Treatment with Bezafibrate Retard A. Ventura, E. Mannarino, G. Ciuffetti, D. Siepi, and G. Lupattelli.	291
Effect of Bezafibrate Retard on Plasma Lipoproteins in Hypertriglyceridemic Patients With and Without Diabetes Mellitus G. Riccardi, G. Saldamacchia, S. Genovese, L. Patti, G. Marotta, A. Postiglione, A. Rivellesse, B. Capaldo, and M. Mancini.	295
Long-Term Experience of a Single Daily Dose of Bezafibrate Retard 400 in Hyperlipoproteinaemia of Types IIa, IIb and IV W. Schwartzkopf	301

Effects of Bezafibrate on Lipoprotein Metabolism in Cell Culture S. Eisenberg (With 1 Figure)	305
Efficacy and Tolerance of Fenofibrate: A Ten-Year Experience G.F. Blane (With 4 Figures)	309
Mechanism of Action of Fenofibrate: New Data M. Pascal, H. Cao Danh, and C. Legendre (With 5 Figures)	317
Species Differences in the Metabolic Disposition of Fenofibrate A. Weil, J. Caldwell, M. Strolin-Benedetti, and P. Dostert (With 1 Figure)	324
Pharmacokinetics of Lipanthyl in the Elderly J.P. Guichard, M. Strolin-Benedetti, G. Houin, and J.L. Albarede (With 1 Figure)	328
Effect of Fenofibrate on Lipoprotein Particles Predictive of Coronary Atherosclerosis J.C. Fruchart, C. Fievet, J.M. Bard, S. Marcovina, P. Drouin, P. Douste-Blazy, I. Luyeye, N. Slimane, and P. Puchois (With 3 Figures)	333
Tentative Biochemical Approach to Fenofibrate Efficacy in Tinnitus Aurium M. Strolin-Benedetti, E. Chesne, P. Dostert, and H. Cao Danh	338
Clinical Effect of Lipanthyl on Tinnitus Aurium and Other Symptoms Related to Inner Ear Disorders Y. Bogaievsky, F. Torossian, G. Jost, and F. Bonnefous (With 1 Figure)	343
Effect of Gemfibrozil Administration on Biliary Lipid Secretion: A Crossover Study with Clofibrate L. Barbara, G. Mazzella, N. Villanova, P. Simoni, M. Ronchi, A. Roda, E. Roda, and F. Bazzoli	350
Plasma Lipids, Lipoproteins, and Apoproteins During Gemfibrozil Treatment in Primary Hyperlipidemias E. Manzato, S. Zambon, R. Marin, G. Baggio, and G. Crepaldi	355
Effects of Gemfibrozil on Lipoproteins in Patients with Dyslipoproteinemia G.A. Giudici, F. Pagani, C. Selvini, P. Stefanoni, C. di Santo, and C. Vergani (With 5 Figures)	358

HDL Deficiency, Atherosclerosis, and Stimulation of HDL Synthesis: Role of Gemfibrozil M.L. Kashyap and K. Saku (With 1 Figure)	367
Hemorheological Activity of Gemfibrozil in Primary Hyperlipidemias G. Ciuffetti, G. Orecchini, D. Siepi, G. Lupattelli, and A. Ventura	372
Evaluation of Hypolipidemic and Other Useful Pharmacological Properties of Various Nicotinic Acid Derivatives G. Quack, L. Puglisi, W. Schatton, and A. Schwaier (With 3 Figures)	376
Pharmacokinetics and Metabolism of 2-Tert-Butyl-4-Cyclohexyl-Phenyl Nicotinate (L-44) in Rats G. Galli, E. Bosisio, E. De Fabiani, M. Crestani, G. Quack, and W. Schatton (With 4 Figures)	380
Effects of Etofibrate on Risk Factors of Atherosclerosis T. Seifert and W. Schatton	385
Hyperaggregability of Platelets in Patients with Hyperlipoproteinemia Type IIb Under Treatment with Etofibrate Retard and Acetylsalicylic Acid B. Krüger and R. Thiemann (With 1 Figure)	389
Effect of Etofibrate on Platelet Function in Hyperlipidemic Patients G. Nosedà, C. Fragiaco, A. Radelli, E. Bosisio, E. De Fabiani, and G. Galli (With 3 Figures)	394
Importance of Phospholipids in Cholesterol-Solubilizing Capacity of High-Density Lipoproteins G. Salvioli and R. Lugli (With 1 Figure)	399
Effects of Polyunsaturated Phospholipid on Cholesterol Efflux in Vitro and in Experimental Animals and Human Subjects J. Koizumi, A. Postiglione, B.L. Knight, A.K. Soutar, and G.R. Thompson (With 1 Figure)	403
Phospholipids in Human Atherosclerosis P. Avogaro, G. Bittolo Bon, and G. Cazzolato	407
Effect of Polyunsaturated Phosphatidylcholine (PPC) on Plasma Lipoproteins in Patients with Type II Hyperlipoproteinemia G. Nosedà and C. Fragiaco (With 1 Figure)	410

Dietary Lecithin: Metabolism, Fate, and Effects on Metabolism of Lipids and Lipoproteins

S.M. Grundy. 415

Effects of Pantethine on Lipid Metabolism in Isolated Rat Hepatocytes

M. Galli Kienle, G. Cighetti, M. Del Puppo, and R. Paroni
(With 3 Figures) 421

Effects of Pantethine on Experimental Atherosclerosis in Rabbits

M.R. Malinow, B. Upson, M. Axthelm, and P. McLaughlin
(With 5 Figures) 426

Modified LDL in Humans: Effect of Pantethine

G. Bittolo Bon, G. Cazzolato, and P. Avogaro (With 1 Figure) . . . 433

Changes in Platelet Membrane Lipid Composition Following Pantethine Administration

D. Prisco, P.G. Rogasi, and G.G. Neri Serneri (With 3 Figures) . . . 437

Pantethine Treatment in Type III Hyperlipoproteinemia

G. Franceschini, P. Apebe, G. Gianfranceschi, A. Gaddi, M. Sirtori, and C.R. Sirtori (With 1 Figure). 442

Subject Index. 447

Relationship of Cholesterol to DNA Synthesis in Normal and Cancerous Cells

M. D. SIPERSTEIN, H. DOVALE, and J. R. SILBER¹

It has been known since 1950 that there is a striking correlation between the rate at which acetate is converted to cholesterol and the rate of cell growth. Specifically, in tissues such as the kidney, cell replication is very slow and such tissues have low rates of cholesterol synthesis. By contrast, baby brain and intestine replicate at rapid rates and have active cholesterol synthesis. As we showed some years ago, the very rapid cell growth of regenerating liver is accompanied by one of the highest rates of cholesterolgenesis seen in mammalian cells (1).

Our interest in the relation between cell replication and cholesterol biosynthesis developed from two observations. One was the finding that the primary site of feedback control of cholesterol synthesis is located at the synthesis of mevalonate (2,3). Second was our initial observation that this feedback control of mevalonic acid, at least in vivo, is consistently impaired or completely deleted in a series of malignant tumors (1,4,5). In contrast to the liver, where the feeding of cholesterol leads to a marked decrease in the conversion of acetate to cholesterol and a comparable decrease in the activity of HMG CoA reductase, in the slowly growing hepatoma 9121 feeding cholesterol does not inhibit either cholesterolgenesis or HMG CoA reductase activity (Table 1) (6,7). Similar data have been reported by Goldfarb and Pitot (7).

Table 1. Absence of feedback control of HMG CoA reductase in hepatoma 9121

Tissue	Diet	(2- ¹⁴ C) Acetate converted to cholesterol $\mu\text{mol g}^{-1} \text{h}^{-1}$	β -hydroxy- β -methylglutaryl CoA reductase $\mu\text{mol g}^{-1} \text{h}^{-1}$
Liver	Low cholesterol	45	0.77 ± 0.11
	5% cholesterol	0.8	0.007 ± 0.01
Hepatoma 9121	Low cholesterol	46	1.34 ± 0.14
	5% cholesterol	96	1.69 ± 0.17

1 University of California, San Francisco Metabolism Section, Veterans Administration Medical Center, San Francisco, CA 94121, USA

Table 2. Absence of cholesterol feedback control in rat hepatomas

Tissue	Diet	
	Normal Acetate $\rightarrow$ Chol ^a	Cholesterol 5% Acetate $\rightarrow$ Chol ^a
Liver	8	0.02
Hepatomas		
9618A	152	126
9633	72	54
7787	33	32
9121	27	25
5121	9	7
7795	6	7
7793	3	4
7794A	7	18
7316A	4	8
7800	7	9
H-35	6	9
7288C	0.9	1
3924A	0.5	0.6
3683	1	3

^a nmol 2-14 C acetate g⁻¹ h⁻¹.

This phenomenon can be demonstrated in a variety of minimal deviation hepatomas. As shown by the data in Table 2, in contrast to the marked decrease in the conversion of acetate to cholesterol characteristic of the livers of animals fed cholesterol, cholesterol feeding consistently has no significant effect upon cholesterol synthesis in hepatomas. Loss of cholesterol feedback control has been shown to occur in non-hepatic tumors (8) and has been confirmed and extended by a number of investigators (9–12). Moreover, loss of the cholesterol feedback system can be demonstrated even in the precancerous state (13,14). For example, feeding aflatoxin to a rat for a period of only 2 days, led to complete loss of feedback control of cholesterol synthesis and of mevalonate synthesis (15). This observation, too, has been confirmed with a wide variety of cancer-producing agents, primarily by Sabine's laboratory (16–18).

These observations raised the question of what might be the role of cholesterol synthesis in both normal and abnormal cell growth. It is known that cholesterol is required for cell membrane synthesis, and it was shown initially by Chen and Kandutsch (19,20) and by Brown and Goldstein (21) that treating cells in tissue culture with hydroxysterols, which inhibit sterol synthesis by blocking HMG CoA reductase, will also inhibit cell growth. This inhibition could be reversed by adding cholesterol in the form of lipoprotein, a finding that logically led to the conclusion that hydroxysterols prevent cell proliferation by depleting the cell of cholesterol.

Because of our earlier interest in the control of mevalonic acid synthesis, we decided to look at the question of whether mevalonic acid, independent of its function