

Clinical Diagnosis of Atherosclerosis

Quantitative Methods of Evaluation

Edited by

M. Gene Bond

William Insull, Jr.

Seymour Glagov

A. Bleakley Chandler

J. Fredrick Cornhill

86834

Clinical Diagnosis of Atherosclerosis

Quantitative Methods of Evaluation

Edited by

M. Gene Bond
William Insull, Jr.
Seymour Glagov
A. Bleakley Chandler
J. Fredrick Cornhill

With 103 Figures



Springer-Verlag New York Heidelberg Berlin

M. Gene Bond, Ph.D., Associate Professor of Comparative Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27103, U.S.A.

William Insull, Jr., M.D., Department of Medicine, Baylor College of Medicine; Director, Lipid Research Clinic, Methodist Hospital, Houston, Texas 77030, U.S.A.

Seymour Glagov, M.D., Professor of Pathology, Pritzker School of Medicine, University of Chicago; Autopsy Service, University of Chicago Hospitals and Clinics, Chicago, Illinois 60637, U.S.A.

A. Bleakley Chandler, M.D., Professor and Chairman, Department of Pathology, Medical College of Georgia, Augusta, Georgia 30912, U.S.A.

J. Fredrick Cornhill, D. Phil., Associate Professor of Surgery, Laboratory of Experimental Atherosclerosis, Ohio State University, College of Medicine, Columbus, Ohio 43210, U.S.A.

Sponsoring Editor: Chester Van Wert

Production: Anthony Buatti

Library of Congress Cataloging in Publication Data

Main entry under title:

Clinical diagnosis of atherosclerosis.

Includes index.

1. Atherosclerosis—Diagnosis. I. Bond, M. Gene.

[DNLM: 1. Arteriosclerosis—Diagnosis. WG 550

C641 1982]

RC692.C54 1982 616.1'36'075 83-382

ISBN 0-387-90780-7

© 1983 by Springer-Verlag New York Inc.

All rights reserved. No part of this book may be translated or reproduced in any form without written permission from Springer-Verlag, 175 Fifth Avenue, New York, New York 10010, U.S.A.

The use of general descriptive names, trade names, trademarks, etc., in this publication, even if the former are not especially identified, is not to be taken as a sign that such names, as understood by the Trade Marks and Merchandise Marks Act, may accordingly be used freely by anyone.

Typed by the Bowman Gray School of Medicine, Winston-Salem, North Carolina

Printed and bound by Halliday Lithograph, West Hanover, Massachusetts

Printed in the United States of America

9 8 7 6 5 4 3 2 1

ISBN 0-387-90780-7 Springer-Verlag New York Heidelberg Berlin

ISBN 3-540-90780-7 Springer-Verlag Berlin Heidelberg New York

Preface

This volume is the product of a February 1982 conference, cosponsored by the American Heart Association, the National Institutes of Health, and the Bowman Gray School of Medicine, which examined techniques for delineating quantitatively the natural history of atherosclerosis. Against the background of current pathologic and clinical knowledge of atherosclerosis, invasive and noninvasive evaluative methods now in use and under development are surveyed in depth.

Correlative clinicopathologic studies of atherosclerosis pose special questions with respect to both luminal and plaque characteristics that are addressed in this volume. An old observation, based on the examination of arterial casts, suggested that the so-called nodose lesion of atherosclerosis may be at first flattened into the wall of a weakened, dilated artery, rather than raised into the lumen. This is now fully confirmed in vivo by ultrasonic and other imaging techniques. The morbid anatomist is challenged anew to describe lesions as they are likely to occur in vivo. To achieve closer correlation with natural conditions, perfusion fixation of arteries under arterial pressure is becoming more widely used and has already demonstrated more valid quantitation of the composition and configuration of lesions.

While the noninvasive methods of B-mode and Doppler ultrasound are suitable only for the clinical study of superficial arteries, such as the carotid or femoral, the new and relatively noninvasive procedure of intravenous digital subtraction angiography can be effectively used for the examination of deep systems, such as cerebral vessels. The application of nuclear magnetic resonance and positron emission tomography to the metabolic evaluation of lesions and to the assessment of blood flow is just beginning to unfold. Unlike noninvasive methods, the invasive technique of direct arterial angiography is usually employed after the appearance of symptoms, when the disease has reached an advanced stage at the site of involvement.

With such rapid strides in technology taking place, it is apparent that a revolution in the ability to measure the progres-

sion and regression of atherosclerotic lesions is at hand. Noninvasive approaches have the potential of achieving an economy of scale by sequentially following precisely located lesions in individuals on therapeutic regimens, thus obviating the need for large, enormously costly and complicated clinical trials. Moreover, the opportunity to discover and trace the evolution of lesions by these means in asymptomatic but high-risk populations will allow for early intervention. At the same time, this will underscore the often ignored fact that atherosclerosis is an insidious disease that progresses silently for years before becoming overtly manifest in its advanced stages.

The technology discussed herein may itself open new avenues for investigating the pathogenesis of atherosclerosis. Witness the remarkable demonstration by pulsed Doppler ultrasound of the whirlpool effect that disturbed blood flow produces in the carotid sinus, where atherosclerosis is so common. Witness the demonstration by B-mode ultrasound of the jerking arterial pulsations that rub together opposing lesions of the carotid artery, an area of high risk for the development of ulcerative plaques and mural thrombosis. Observations like these have added a new dimension to the study of thromboarterial disease.

The concluding chapters find an urgent need for pathologists and clinical investigators to develop acceptable reference standards for the measurement of lesions in vivo and ex vivo. Concepts of progression and regression of lesions must be carefully defined and made open ended to allow for multiple and additional methods of assessment by quantitative morphometry. This volume reflects the success of the conference, which did much to fulfill an initial challenge: "If by joint efforts image and tissue morphologists are to succeed in arriving at a reproducible means of quantitating lesions in the living subject, they must understand each other and know precisely what is and what is not being measured."

A. Bleakley Chandler

Acknowledgments

The conference on Quantitative Evaluation of Atherosclerosis and the publication of this volume were made possible by support from the following organizations and from private industry.

The Council on Arteriosclerosis of the American Heart Association
The National Heart, Lung and Blood Institute
The Bowman Gray School of Medicine of Wake Forest University

American Cyanamid Company
Boehringer Ingelheim Limited
Burroughs Wellcome Company
Carolina Medical Electronics
Ciba-Geigy Corporation
H.R.L., Incorporated
Hoffman-LaRoche Incorporated
Lilly Research Laboratories
Merck, Sharp & Dohme
Merrell Dow Pharmaceuticals Incorporated
Revlon Health Care Group
A.H. Robins Company
Sandoz, Incorporated
Schering Corporation
G.D. Searle and Company
Smith Kline Corporation
The Upjohn Company
Warner-Lambert Company

The Organizing Committee and the editors of this volume gratefully acknowledge their debt of gratitude to the following individuals: Dr. Sheldon A. Schaffer for local arrangements; Sarah Johnston, Office of Information and Publications, Bowman Gray School of Medicine, for brochure preparation; Mrs. Hugh B. Lofland for her excellent editorial assistance; Mrs. Shirley Pegram, Ms. Maria F. Hiller, and particularly Mrs. Lona Ellis for preparation of the final manuscripts; Ms. Hermína Trillo, Mrs. Jean Gardin, Ms. Sharon Wilmoth, Mrs. Dianna Swaim, and Ms. Loren Bynum for their invaluable assistance during the Workshop. Particularly, the

cochairmen of the Workshop wish to acknowledge their debt of gratitude to Mrs. Janet Kaduck Sawyer, whose exceptional skill and effort resulted in a well-organized meeting and in the preparation of this book.

The members of the Organizing Committee also gratefully acknowledge the permission granted by W. L. Gore and Associates, Inc. to use "The Vascular Man" as the symbol for this symposium.

The conference on Quantitative Evaluation of Atherosclerosis and the publication of this volume were made possible by support from the following organizations and from private industry:

The Council on Atherosclerosis of the American Heart Association
The National Heart Lung and Blood Institute
The Bowman Gray School of Medicine of Wake Forest University

American Cyanamid Company
Boehringer Ingelheim Limited
Burroughs Wellcome Company
Ciba-Geigy Corporation
H.R.L. Incorporated

Hoffman Laboratories
Lilly Research Laboratories
Merck Sharp & Dohme
Methel Dow Pharmaceuticals Incorporated
Reckon Health Care Group
A.H. Robins Company
Sandoz Incorporated
Schering Corporation
G.D. Searle and Company
Smith Kline Corporation
The Upjohn Company
Warner-Lambert Company

The Organizing Committee and the editors of this volume gratefully acknowledge their debt of gratitude to the following individuals: Dr. Sheldon A. Schrier for local arrangements; Sarah Johnston, Office of Information and Publications, Bowman Gray School of Medicine for brochure preparation; Mrs. Hugh B. Holland for her excellent editorial assistance; Mrs. Shirley Egan, Mrs. Marie E. Foster and particularly Mrs. Jean Ellis for preparation of the final manuscript; Mrs. Patricia Trille, Mrs. Jean Gault, Mrs. Susan Whitner, Mrs. Barbara Swann, and Ms. Lynn Dylam for their invaluable assistance during the Workshop. Finally, the

Contributors

Organizing Committee

Chairmen

M. Gene Bond, Ph.D., Department of Comparative Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

William Insull, Jr., M.D., Department of Medicine, Baylor College of Medicine; Lipid Research Clinic, Methodist Hospital, Houston, Texas

Members

Robert W. Barnes, M.D., F.A.C.S., F.A.C.C., Department of Surgery, Medical College of Virginia, Virginia Commonwealth University; Noninvasive Peripheral Vascular Laboratory, Medical College of Virginia; Department of Vascular Surgery, McGuire VA Medical Center, Richmond, Virginia

David H. Blankenhorn, M.D., Department of Medicine, Atherosclerosis Research Division, University of Southern California School of Medicine, Los Angeles, California

A. Bleakley Chandler, M.D., Department of Pathology, Medical College of Georgia, Augusta, Georgia

J. Fredrick Cornhill, D.Phil., Laboratory of Experimental Atherosclerosis, Ohio State University College of Medicine, Columbus, Ohio

Assaad S. Daoud, M.D., Department of Pathology, Albany Medical College, Union University, and Laboratory Service, VA Medical Center, Albany, New York

Seymour Glagov, M.D., Department of Pathology, Pritzker School of Medicine, University of Chicago; Autopsy Service, University of Chicago Hospitals and Clinics, Chicago, Illinois

James F. Greenleaf, Ph.D., Department of Biophysics and Medicine, Biodynamics Research Unit, Mayo Foundation, Rochester, Minnesota

C. Alex McMahan, Ph.D., Department of Pathology, University of Texas Health Sciences Center, San Antonio, Texas

C. Richard Minick, M.D., Department of Pathology, Cornell University Medical College, New York, New York

William P. Newman III, M.D., Department of Pathology, School of Medicine, Louisiana State University Medical Center, New Orleans, Louisiana

Sheldon A. Schaffer, Ph.D., Medical Research Division, American Cyanamid Company, Pearl River, New York

D. Eugene Strandness, M.D., Department of Surgery, University of Washington School of Medicine; University Hospital, Seattle, Washington

Robert W. Wissler, M.D., Ph.D., Department of Pathology, University of Chicago, Chicago, Illinois

Participants

Mark L. Armstrong, M.D., F.A.C.P., Department of Medicine, Cardiovascular Division, University of Iowa College of Medicine; University Hospital, Iowa City, Iowa

Marshall R. Ball, M.D., Department of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Ralph W. Barnes, Ph.D., Department of Neurology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

James B. Bassingthwaight, M.D., Ph.D., Center for Bioengineering and Biomathematics, University of Washington School of Medicine, Seattle, Washington

Errol M. Bellon, M.D., Department of Radiology, Case Western Reserve University School of Medicine; Cuyahoga County Hospital, Cleveland, Ohio

Alan Berson, Ph.D., Devices and Technology Branch, Division of Heart and Vascular Diseases, National Heart, Lung and Blood Institute, Bethesda, Maryland

Thomas F. Budinger, M.D., Ph.D., Department of Medical Research, Donner Laboratory; Department of Bioinstrumentation, Electrical Engineering and Computer Sciences, Lawrence Berkeley Laboratory, University of California, Berkeley, California

Bill C. Bullock, D.V.M., Department of Comparative Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Anthony J. Comerota, M.D., Department of Surgery, and Vascular Laboratory, Temple University Hospital, Philadelphia, Pennsylvania

Jerry G. Davis, B.S.E.E., Department of Biomedical Engineering, Clinical Research Division, Lovelace Medical Foundation, Albuquerque, New Mexico

Ralph G. DePalma, M.D., Department of Surgery, George Washington University, Washington, D.C.

James A. DeWeese, M.D., F.A.C.S., Department of Surgery, Division of Cardiothoracic Surgery, University of Rochester School of Medicine and Dentistry, Rochester, New York

Marlowe W. Eldridge, M.S.M.E., Research Division, Lovelace Medical Foundation, Albuquerque, New Mexico

Titus C. Evans, Jr., M.D., Ph.D., Department of Internal Medicine, Mayo Medical School; Division of Cardiovascular Disease and Internal Medicine, Mayo Clinic, Mayo Foundation, Rochester, Minnesota

Domenick J. Falcone, Ph.D., New York Hospital-Cornell Medical Center, New York, New York

C. Miller Fisher, M.D., Department of Neurology, Harvard Medical School, and Massachusetts General Hospital, Boston, Massachusetts

Lloyd D. Fisher, Ph.D., Department of Biostatistics, School of Public Health; Coronary Artery Surgery Study Coordinating Center, University of Washington, Seattle, Washington

Katherine E. Fritz, Ph.D., Department of Pathology, Albany Medical College, Union University; Atherosclerosis Research Laboratory, VA Medical Center, Albany, New York

Edward Ganz, M.D., Donner Laboratory, University of California, Berkeley, California

Don P. Giddens, Ph.D., School of Aerospace Engineering, Georgia Institute of Technology, Atlanta, Georgia

E. Richard Greene, Ph.D., Department of Medicine, University of New Mexico School of Medicine; Department of Physiology and Biophysics, Clinical Research Division, Lovelace Medical Foundation, Albuquerque, New Mexico

David P. Hajjar, Ph.D., New York Hospital-Cornell Medical Center, New York, New York

Elmer C. Hall, Ph.D., Department of Biometry, Emory University School of Medicine, Atlanta, Georgia

Gary J. Harpold, M.D., Department of Neurology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

M. Daria Haust, M.D., F.R.C.P.(C), Departments of Pathology, Paediatrics, and Obstetrics and Gynaecology, University of Western Ontario; Department of Pathology, Children's Psychiatric Research Institute, London, Ontario

Ruth Hegyeli, M.D., Division of International Programs, National Heart, Lung and Blood Institute, Bethesda, Maryland

William Hollander, M.D., Department of Medicine and Biochemistry, Boston University School of Medicine, Boston, Massachusetts

Barbara B. Hrapchak, Ph.D., Department of Biochemistry, Chemical Abstracts Services, Columbus, Ohio

John Jarmolych, M.D., Department of Pathology, Albany Medical College, Union University; Anatomic Pathology Section, Laboratory Service, VA Medical Center, Albany, New York

J. Ward Kennedy, M.D., Department of Cardiology, University of Washington; Department of Medicine, Division of Cardiology, Cardiovascular Disease Section, Seattle VA Hospital, Seattle, Washington

Thomas Killip, M.D., Department of Medicine, Henry Ford Hospital, Detroit, Michigan

Raelene L. Kinlough-Rathbone, M.D., Department of Pathology, McMaster University, Hamilton, Ontario

Robert S. Lees, M.D., Department of Cardiovascular Disease, Massachusetts Institute of Technology; Division of Peripheral Vascular Disease, New England Deaconess Hospital, Boston, Massachusetts

Martin Lipton, M.D., Department of Radiology, University of California Medical Center, San Francisco, California

William M. McKinney, M.D., Department of Neurology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Gardner C. McMillan, M.D., Division of Heart and Vascular

Diseases, National Heart, Lung and Blood Institute, Bethesda, Maryland

Fernando G. Miranda, M.D., University of New Mexico Medical School; Department of Neurosciences, Lovelace Medical Center, Albuquerque, New Mexico

Michael B. Mock, M.D., Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Mayo Foundation, Rochester, Minnesota

Brian R. Moyer, M.D., Department of Biomedicine, Donner Laboratory, University of California, Berkeley, California

J. Fraser Mustard, M.D., Ph.D., F.R.C.P.(C), Department of Pathology, McMaster University, Hamilton, Ontario

P. David Myerowitz, M.D., Department of Surgery, Division of Cardiothoracic Surgery, University of Wisconsin School of Medicine, Madison, Wisconsin

Theron W. Ovitt, M.D., Department of Radiology, University of Arizona Health Sciences Center, Tucson, Arizona

Marian A. Packham, Ph.D., Department of Biochemistry, University of Toronto, Toronto, Ontario

Rodolfo Paoletti, M.D., Università di Milano, Istituto di Farmacologia e di Farmacognosia, Milano, Italy

David C. Price, M.D., Department of Biomedicine, Donner Laboratory, University of California Medical Center, San Francisco, California

John M. Reid, Ph.D., Department of Electrical and Computer Engineering, College of Engineering, and Biomedical Engineering and Science Institute, Drexel University, Philadelphia, Pennsylvania

Richard W. St. Clair, Ph.D., Department of Pathology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Janet K. Sawyer, B.S., Department of Comparative Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Colin J. Schwartz, M.D., F.R.A.C.P., Department of Pathology, University of Texas Health Sciences Center, San Antonio, Texas

Robert H. Selzer, M.A., M.S., Observational Systems Division, Jet Propulsion Laboratory, California Institute of Technology; Southern California School of Medicine, Pasadena, California

Donald M. Small, M.D., Biophysics Institute, Boston University School of Medicine, Boston City Hospital; University Hospital, Boston, Massachusetts

Merrill P. Spencer, M.D., Institute of Applied Physiology and Medicine, Department of Clinical Physiology, Providence Medical Center; Vascular Laboratory, Northwest Hospital, Seattle, Washington

David S. Sumner, M.D., Department of Surgery, and Peripheral Vascular Service, Southern Illinois University School of Medicine, Springfield, Illinois

James F. Toole, M.D., LL.B., Department of Neurology, Bowman Gray School of Medicine, Wake Forest University; North Carolina Baptist Hospital, Winston-Salem, North Carolina

Dragoslava Vesselinovitch, D.V.M., Specialized Center of Research on Arteriosclerosis, Department of Pathology, Pritzker School of Medicine, University of Chicago Medical Center, Chicago, Illinois

Wyatt F. Voyles, M.D., Clinical Research Division, Lovelace Medical Foundation, Albuquerque, New Mexico

John Watson, Ph.D., Devices and Technology Branch, Division of Heart and Vascular Diseases, National Heart, Lung and Blood Institute, Bethesda, Maryland

David A. Waugh, M.D., Biophysics Institute, Boston University School of Medicine, Boston, Massachusetts

Christopher P. L. Wood, M.B., B.S., F.R.C.S., Department of Radiology, Clinical Research Centre, Northwick Park Hospital, Harrow, England

Yukio Yano, M.D., Department of Biomedicine, Donner Laboratory, University of California Medical Center, San Francisco, California

Christopher K. Zarins, M.D., Department of Surgery, Pritzker School of Medicine, University of Chicago; Department of Vascular Surgery, University of Chicago Medical Center, Chicago, Illinois

Michael A. Zatina, M.D., Department of Surgery, University of Chicago Medical Center, Chicago, Illinois

Contents

Preface ix

Acknowledgments xi

Contributors xiii

- 1 Workshop Overview 1
D. Eugene Strandness
- 2 Quantitating Atherosclerosis: Problems of Definition 11
Seymour Glagov and Christopher K. Zarins

Part I

Critical Review of Current and Prospective Quantitative Methods for Evaluating Atherosclerosis

- Introduction 39
Robert W. Barnes and James F. Greenleaf
- 3 Atherosclerosis Quantitation by Computer
Image Analysis 43
Robert H. Selzer
Discussion: Thomas F. Budinger 65
- 4 Morphology: Morphometric Analysis of
Pathology Specimens 67
J. Fredrick Cornhill and M. Gene Bond
- 5 Physical Biochemistry of the Lesions of Man, Subhuman
Primates, and Rabbits 79
David A. Waugh and Donald M. Small
Discussion: Richard W. St. Clair 94
- 6 Angiography in Experimental Atherosclerosis: Advantages
and Limitations 99
Ralph G. DePalma
Discussion: Errol M. Bellon 124

- 7 Digital Intravenous Subtraction Angiography 127
Theron W. Ovitt
Discussion: P. David Myerowitz 136
- 8 Quantitative Evaluation of Atherosclerosis Using Doppler
Ultrasound 139
E. Richard Greene, Marlowe W. Eldridge, Wyatt F. Voyles,
Fernando G. Miranda, and Jerry G. Davis
Discussion: John M. Reid 169
- 9 B-Mode Ultrasound Interrogation of Arteries 173
William M. McKinney and Gary J. Harpold
Discussion: Titus C. Evans, Jr. 183
- 10 Radionuclide and Nuclear Magnetic Resonance Methods of
Evaluating Atherosclerosis 189
Thomas F. Budinger, Edward Ganz, David C. Price, Martin
Lipton, Brian R. Moyer, and Yukio Yano
Discussion: James B. Bassingthwaite 217

Part 2

Critical Review of Correlation and Validation Studies for Evaluating Atherosclerosis

- Introduction 223
William Insull, Jr. and C. Richard Minick
- 11 Correlation of Lesion Configuration with Functional
Significance 227
David S. Sumner
Discussion: Don P. Giddens 258
- 12 Correlation of Antemortem Angiography
with Pathology 265
C. Miller Fisher
Discussion: James A. DeWeese 280
- 13 Correlation of Postmortem Angiography with Pathologic
Anatomy: Quantitation of Atherosclerotic Lesions 283
Christopher K. Zarins, Michael A. Zatina, and
Seymour Glagov
Discussion: M. Gene Bond 304
- 14 Correlation of Doppler Ultrasound with Arteriography in the
Quantitative Evaluation of Atherosclerosis 307
Christopher P. L. Wood
Discussion: Merrill P. Spencer 346

- 15 Correlation of B-Mode Ultrasound of the Carotid Artery with Arteriography and Pathology 351
Anthony J. Comerota
Discussion: Robert S. Lees 364
- 16 Correlation of Morphological and Biochemical Components of Atherosclerotic Plaques 369
C. Richard Minick, Domenick J. Falcone, and David P. Hajjar
Discussion: William Insull, Jr. 387
- 17 Multicenter Trial for Assessment of B-Mode Ultrasound Imaging 389
James F. Toole and Alan Berson
Discussion: Robert W. Barnes 395

Part 3

Critical Review of Measurements of Change in Atherosclerosis Progression and Regression

- Introduction 401
Assaad S. Daoud and William P. Newman III
- 18 Pathobiology of Atherosclerosis 405
Assaad S. Daoud, Katherine E. Fritz, and John Jarmolych
Discussion: Mark L. Armstrong 433
- 19 Animal Studies of Atherosclerosis Progression and Regression 435
M. Gene Bond, Janet K. Sawyer, Bill C. Bullock, Ralph W. Barnes, and Marshall R. Ball
Discussion: William Hollander 450
- 20 Human Studies of Progression and Regression 453
William P. Newman III
Discussion: Colin J. Schwartz 471
- 21 Coronary Angiography Quality Control in the CASS Study 475
J. Ward Kennedy, Lloyd D. Fisher, and Thomas Killip
Discussion: Lloyd D. Fisher 491
- 22 Vessel Injury, Thrombosis, and the Progression and Regression of Atherosclerotic Lesions 493
J. Fraser Mustard, Raelene L. Kinlough-Rathbone, and Marian A. Packham
A Discussion of Platelet Thrombi in Atherogenesis:
M. Daria Haust 513

23	Review of Clinical Studies on the Quantification and Progression of Atherosclerosis	517
	Michael B. Mock	
	Discussion: David H. Blankenhorn	533
24	Experimental Design Problems: Interpretation of Statistical Arithmetic	537
	Elmer C. Hall	
	Discussion: C. Alex McMahan	545
Part 4		
Summary		
25	Universal Reference Standards for Measuring Atherosclerotic Lesions: The Quest for the "Gold Standard"	551
	William Insull, Jr.	
26	Recommendations	561
	David H. Blankenhorn	
Index		571