PROGRESS in CLINICAL and BIOLOGICAL RESEARCH VOLUME 219

RECENT ADVANCES IN ARTERIAL DISEASES

Atherosclerosis, Hypertension, and Vasospasm

EDITORS: Thomas N. Tulenko
Robert H. Cox

ALAN R. LISS, INC., NEW YORK

RECENT ADVANCES IN ARTERIAL DISEASES

Atherosclerosis, Hypertension, and Vasospasm

Proceedings of the A.N. Richards Symposium
Held in Philadelphia, Pennsylvania, May 10–11, 1984

Editors

Thomas N. Tulenko
Department of Physiology-Biochemistry
Medical College of Pennsylvania
Philadelphia, Pennsylvania

Robert H. Cox
Department of Physiology
University of Pennsylvania
Lockus Research Institute
The Graduate Hospital
Philadelphia, Pennsylvania

ALAN R. LISS, INC. • NEW YORK

Address all Inquiries to the Publisher
Alan R. Liss, Inc., 41 East 11th Street, New York, NY 10003

Copyright © 1986 Alan R. Liss, Inc.

Printed in the United States of America

Under the conditions stated below the owner of copyright for this book hereby grants permission to users to make photocopy reproductions of any part or all of its contents for personal or internal organizational use, or for personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per-copy fee through the Copyright Clearance Center, Incorporated, 27 Congress Street, Salem, MA 01970, as listed in the most current issue of "Permissions to Photocopy" (Publisher's Fee List, distributed by CCC, Inc.), for copying beyond that permitted by sections 107 or 108 of the US Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

Library of Congress Cataloging in Publication Data

Main entry under title:

A.N. Richards Symposium (1984 : Philadelphia Pa.)
Recent advances in arterial diseases.

(Progress in clinical and biological research ; v. 219)
Includes index.
1. Arteries—Diseases—Congresses. 2. Atherosclerosis —Congresses. 3. Hypertension—Congresses. 4. Coronary vasospasm—Congresses. I. Tulenko, Thomas N. II. Cox, Robert H. III. Title. IV. Series. [DNLM: 1. Arteriosclerosis—Congresses. 2. Cerebral Ischemia, Transient —Congresses. 3. Coronary Vasospasm—Congresses. 4. Hypertension—Congresses. WI PR668E v.219 / WG 550 A103 1984r]
RC691.A22 1984 616.1'3 86-10558
ISBN 0-8451-5069-3

PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH

Series Editors

Nathan Back, Vincent P. Eijsvoogel, Kurt Hirschhorn, Sidney Udenfriend
George J. Brewer, Robert Grover, Seymour S. Kety, Jonathan W. Uhr

RECENT TITLES

Vol 163: **Prevention of Physical and Mental Congenital Defects,** Maurice Marois, *Editor.* Published in 3 volumes: Part A: *The Scope of the Problem.* Part B: *Epidemiology, Early Detection and Therapy, and Environmental Factors.* Part C: *Basic and Medical Science, Education, and Future Strategies*

Vol 164: **Information and Energy Transduction in Biological Membranes,** C. Liana Bolis, Ernst J.M. Helmreich, Hermann Passow, *Editors*

Vol 165: **The Red Cell: Sixth Ann Arbor Conference**, George J. Brewer, *Editor*

Vol 166: **Human Alkaline Phosphatases,** Torgny Stigbrand, William H. Fishman, *Editors*

Vol 167: **Ethopharmacological Aggression Research**, Klaus A. Miczek, Menno R. Kruk, Berend Olivier, *Editors*

Vol 168: **Epithelial Calcium and Phosphate Transport: Molecular and Cellular Aspects,** Felix Bronner, Meinrad Peterlik, *Editors*

Vol 169: **Biological Perspectives on Aggression,** Kevin J. Flannelly, Robert J. Blanchard, D. Caroline Blanchard, *Editors*

Vol 170: **Porphyrin Localization and Treatment of Tumors,** Daniel R. Doiron, Charles J. Gomer, *Editors*

Vol 171: **Developmental Mechanisms: Normal and Abnormal,** James W. Lash, Lauri Saxén, *Editors*

Vol 172: **Molecular Basis of Cancer,** Robert Rein, *Editor*. Published in 2 volumes: Part A: *Macromolecular Structure, Carcinogens, and Oncogenes.* Part B: *Macromolecular Recognition, Chemotherapy, and Immunology*

Vol 173: **Pepsinogens in Man: Clinical and Genetic Advances,** Johanna Kreuning, I. Michael Samloff, Jerome I. Rotter, Aldur Eriksson, *Editors*

Vol 174: **Enzymology of Carbonyl Metabolism 2: Aldehyde Dehydrogenase, Aldo-Keto Reductase, and Alcohol Dehydrogenase,** T. Geoffrey Flynn, Henry Weiner, *Editors*

Vol 175: **Advances in Neuroblastoma Research,** Audrey E. Evans, Giulio J. D'Angio, Robert C. Seeger, *Editors*

Vol 176: **Contemporary Sensory Neurobiology,** Manning J. Correia, Adrian A. Perachio, *Editors*

Vol 177: **Medical Genetics: Past, Present, Future,** Kåre Berg, *Editor*

Vol 178: **Bluetongue and Related Orbiviruses,** T. Lynwood Barber, Michael M. Jochim, *Editors*

Vol 179: **Taurine: Biological Actions and Clinical Perspectives,** Simo S. Oja, Liisa Ahtee, Pirjo Kontro, Matti K. Paasonen, *Editors*

Vol 180: **Intracellular Protein Catabolism,** Edward A. Khairallah, Judith S. Bond, John W.C. Bird, *Editors*

Vol 181: **Germfree Research: Microflora Control and Its Application to the Biomedical Sciences,** Bernard S. Wostmann, *Editor*, Julian R. Pleasants, Morris Pollard, Bernard A. Teah, Morris Wagner, *Co-Editors*

Vol 182: **Infection, Immunity, and Blood Transfusion,** Roger Y. Dodd and Lewellys F. Barker, *Editors*

Vol 183: **Aldehyde Adducts in Alcoholism,** Michael A. Collins, *Editor*

Vol 184: **Hematopoietic Stem Cell Physiology,** Eugene P. Cronkite, Nicholas Dainiak, Ronald P. McCaffrey, Jiri Palek, Peter J. Quesenberry, *Editors*

Vol 185: **EORTC Genitourinary Group Monograph 2,** Fritz H. Schroeder, Brian Richards, *Editors.* Published in two volumes: Part A: *Therapeutic Principles in Metastatic Prostatic Cancer.* Part B: *Superficial Bladder Tumors*

Vol 186: **Carcinoma of the Large Bowel and Its Precursors,** John R.F. Ingall, Anthony J. Mastromarino, *Editors*

Vol 187: **Normal and Abnormal Bone Growth: Basic and Clinical Research,** Andrew D. Dixon, Bernard G. Sarnat, *Editors*

Vol 188: **Detection and Treatment of Lipid and Lipoprotein Disorders of Childhood,** Kurt Widhalm, Herbert K. Naito, *Editors*

Vol 189: **Bacterial Endotoxins: Structure, Biomedical Significance, and Detection With the Limulus Amebocyte Lysate Test,** Jan W. ten Cate, Harry R. Büller, Augueste Sturk, Jac Levin, *Editors*

Vol 190: **The Interphotoreceptor Matrix in Health and Disease,** C. David Bridges, *Editor*, Alice J. Adler, *Associate Editor*

Vol 191: **Experimental Approaches for the Study of Hemoglobin Switching,** George Stamatoyannopoulos, Arthur W. Nienhuis, *Editors*

Vol 192: **Endocoids,** Harbans Lal, Frank LaBella, John Lane, *Editors*

Vol 193: **Fetal Liver Transplantation,** Robert Peter Gale, Jean-Louis Touraine, Guido Lucarelli, *Editors*

Vol 194: **Diseases of Complex Etiology in Small Populations: Ethnic Differences and Research Approaches,** Ranajit Chakraborty, Emöke J.E. Szathmary, *Editors*

Vol 195: **Cellular and Molecular Aspects of Aging: The Red Cell as a Model,** John W. Eaton, Diane K. Konzen, James G. White, *Editors*

Vol 196: **Advances in Microscopy,** Ronald R. Cowden, Fredrick W. Harrison, *Editors*

Vol 197: **Cooperative Approaches to Research and Development of Orphan Drugs,** Melvin Van Woert, Eunyong Chung, *Editors*

Vol 198: **Biochemistry and Biology of DNA Methylation,** Giulio L. Cantoni, Aharon Razin, *Editors*

Vol 199: **Leukotrienes in Cardiovascular and Pulmonary Function,** Allan M. Lefer, Marlys H. Gee, *Editors*

Vol 200: **Endocrine Genetics and Genetics of Growth,** Costas J. Papadatos, Christos S. Bartsocas, *Editors*

Vol 201: **Primary Chemotherapy in Cancer Medicine,** D.J. Theo Wagener, Geert H. Blijham, Jan B.E. Smeets, Jacques A. Wils, *Editors*

Vol 202: **The 2-5A System: Molecular and Clinical Aspects of the Interferon-Regulated Pathway,** Bryan R.G. Williams, Robert H. Silverman, *Editors*

Vol 203: **Testicular Cancer,** Saad Khoury, René Küss, Gerald P. Murphy, Christian Chatelain, James P. Karr, *Editors*

Vol 204: **Tumor Markers and Their Significance in the Management of Breast Cancer,** Thomas Dao, Angela Brodie, Clement Ip, *Editors*

Vol 205: **Comparative Endocrinology: Developments and Directions,** Charles L. Ralph, *Editor*

Vol 206: **Genetic Toxicology of the Diet,** Ib Knudsen, *Editor*

Vol 207: **Monitoring of Occupational Genotoxicants,** Marja Sorsa, Hannu Norppa, *Editors*

Vol 208: **Risk and Reason: Risk Assessment in Relation to Environmental Mutagens and Carcinogens,** Per Oftedal, Anton Brøgger, *Editors*

Vol 209: **Genetic Toxicology of Environmental Chemicals,** Claes Ramel, Bo Lambert, Jan Magnusson, *Editors*. Published in two volumes: Part A: *Basic Principles and Mechanisms of Action.* Part B: *Genetic Effects and Applied Mutagenesis*

Vol 210: **Ionic Currents in Development,** Richard Nuccitelli, *Editor*

Vol 211: **Transfusion Medicine: Recent Technological Advances,** Kris Murawski, Frans Peetoom, *Editors*

Vol 212: **Cancer Metastasis: Experimental and Clinical Strategies,** D.R. Welch, B.K. Bhuyan, L.A. Liotta, *Editors*

Vol 213: **Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological, and Structure–Activity Relationships,** Vivian Cody, Elliott Middleton, Jr., Jeffrey B. Harborne, *Editors*

Vol 214: **Ethnic Differences in Reactions to Drugs and Xenobiotics,** Werner Kalow, H. Werner Goedde, Dharam P. Agarwal, *Editors*

Vol 215: **Megakaryocyte Development and Function,** Richard F. Levine, Neil Williams, Jack Levin, Bruce L. Evatt, *Editors*

Vol 216: **Advances in Cancer Control: Health Care Financing and Research,** Lee E. Mortenson, Paul F. Engstrom, Paul N. Anderson, *Editors*

Vol 217: **Progress in Developmental Biology,** Harold C. Slavkin, *Editor.* Published in two volumes.

Vol 218: **Evolutionary Perspective and the New Genetics,** Henry Gershowitz, Donald L. Rucknagel, Richard E. Tashian, *Editors*

Vol 219: **Recent Advances in Arterial Diseases: Atherosclerosis, Hypertension, and Vasospasm,** Thomas N. Tulenko, Robert H. Cox, *Editors*

Please contact the publisher for information about previous titles in this series.

此为试读,需要完整PDF请访问: www.ertongbook.com

Recent Advances in Arterial Diseases

Atherosclerosis, Hypertension, and Vasospasm

Contributors

A. Barnett, Department of Pharmacology, Schering Corporation, Bloomfield, NJ 07003 **[133]**

Carl Baron, Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104 **[103]**

T. Baum, Department of Pharmacology, Schering Corporation, Bloomfield, NJ 07003 **[133]**

Peter C. Block, Director, Cardiac Catheterization Laboratory, Massachusetts General Hospital, Boston, MA 02114 **[51]**

D.F. Bohr, Department of Physiology, University of Michigan, Ann Arbor, MI 48109 **[225]**

Raymond Broderick, Department of Physiology-Biochemistry, Medical College of Pennsylvania, Philadelphia, PA 19129; present address: Pennsylvania Muscle Institute, University of Pennsylvania, Philadelphia, PA 19146 **[75]**

C. Cauvin, Department of Pharmacology, University of Miami School of Medicine, Miami, FL 33101 **[157]**

Samuel Chacko, Department of Pathology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA 19104 **[169]**

P.J.S. Chiu, Department of Pharmacology, Schering Corporation, Bloomfield, NJ 07003 **[133]**

Ronald F. Coburn, Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104 **[103]**

D.M. Cohen, Warner-Lambert/Parke Davis, Pharmaceutical Division, Ann Arbor, MI 48105 **[281]**

Richard A. Cohen, Department of Clinical Research, Boston University Medical Center, Boston, MA 02118 **[353]**

P. Macke Consigny, Departments of Physiology, Biochemistry and Radiologic Science, Medical College of Pennsylvania, Philadelphia, PA 19129 **[59]**

Robert H. Cox, Department of Physiology, University of Pennsylvania, Bockus Research Institute, The Graduate Hospital, Philadelphia, PA 19104 **[xiii, 187]**

The number in brackets is the opening page number of the contributor's article.

D.B. Evans, Warner-Lambert/Parke Davis, Pharmaceutical Division, Ann Arbor, MI 48105 **[281]**

William S. Fillers, Department of Pathology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA 19104 **[169]**

Stephen F. Flaim, Department of Biological Research, McNeil Pharmaceutical, Spring House, PA 19477 **[311]**

P.B. Furspan, Department of Physiology, University of Michigan, Ann Arbor, MI 48109 **[225]**

William Halpern, Department of Physiology and Biophysics, University of Vermont College of Medicine, Burlington, VT 05405 **[211]**

David R. Harder, Departments of Neurology and Physiology, Medical College of Wisconsin, Milwaukee, WI 53193 **[245]**

Richard J. Heaslip, Department of Pathology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA 19104 **[169]**

Allan W. Jones, Department of Physiology, University of Missouri, Columbia, MO 65212 **[265]**

Edward A. Kaminski, Department of Pathology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA 19104 **[169]**

H.R. Kaplan, Warner-Lambert/Parke Davis, Pharmaceutical Division, Ann Arbor, MI 48105 **[281]**

B.R. Krause, Warner-Lambert/Parke Davis, Pharmaceutical Division, Ann Arbor, MI 48105 **[281]**

David Kritchevsky, Wistar Institute, Philadelphia, PA 19104 **[39]**

F.S. Lamb, Department of Physiology, University of Michigan, Ann Arbor, MI 48109 **[225]**

P. Leyten, Department of Pharmacology, University of Miami School of Medicine, Miami, FL 33101 **[157]**

N. Lodge, Department of Pharmacology, University of Miami School of Medicine, Miami, FL 33101 **[157]**

M. Rene Malinow, Laboratory of Cardiovascular Diseases, Oregon Regional Primate Research Center, Beaverton, OR 97006 **[31]**

R.S. Newton, Warner-Lambert/Parke Davis, Pharmaceutical Division, Ann Arbor, MI 48105 **[281]**

George Osol, Department of Physiology and Biophysics, University of Vermont College of Medicine, Burlington, VT 05405 **[211]**

M. Tzimas Papadopoulos, Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104 **[103]**

P.V. Ross, Department of Physiology, University of Michigan, Ann Arbor, MI 48109 **[225]**

M.J. Ryan, Warner-Lambert/Parke Davis, Pharmaceutical Division, Ann Arbor, MI 48105 **[281]**

K. Saida, Department of Pharmacology, University of Miami School of Medicine, Miami, FL 33101 **[157]**

Richard W. St. Clair, Department of Pathology, Bowman Gray School of Medicine, Winston-Salem, NC 27103 **[1]**

William P. Santamore, Bockus Research Institute, The Graduate Hospital, Philadelphia, PA 19146; present address: Cardiology Division, Bowman Gray School of Medicine, Winston-Salem, NC 27103 **[363]**

David Scott, Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104 **[103]**

Jacquelyn M. Smith, Department of Physiology, University of Missouri, Columbia, MO 65212 **[265]**

E.J. Sybertz, Department of Pharmacology, Schering Corporation, Bloomfield, NJ 07003 **[133]**

Thomas N. Tulenko, Department of Physiology-Biochemistry, Medical College of Pennsylvania, Philadelphia, PA 19129 **[xiii, 75]**

C. van Breemen, Department of Pharmacology, University of Miami School of Medicine, Miami, FL 33101 **[157]**

S. Vemulapalli, Department of Pharmacology, Schering Corporation, Bloomfield, NJ 07003 **[133]**

R.W. Watkins, Department of Pharmacology, Schering Corporation, Bloomfield, NJ 07003 **[133]**

R.C. Webb, Department of Physiology, University of Michigan, Ann Arbor, MI 48109 **[225]**

George B. Weiss, Research Department, Ciba-Geigy Corporation, Summit, NJ 07901 **[123]**

Preface

For the purpose of this text, we brought together experts in the area of vascular physiology and pathophysiology to discuss their views concerning the etiology of various vascular disease states. The need to better understand the nature of diseased blood vessels is underscored by the fact that nearly 43 million Americans have one or more forms of heart or blood vessel disease, accounting for more deaths (51%) than all other causes combined. Furthermore, these figures do not include the dibilitating vasculopathy associated with diabetes melitus, a disease affecting an additional 10 million Americans. Aside from the severe morbidity and mortality rates, the economic costs of these diseases are by far the largest for any single diagnostic group of diseases and accounted for an estimated $80 billion in 1979 alone. In organizing this monograph, it was our intent to explore hypotheses relating to three major underlying blood vessel disease states: atherosclerosis, hypertension and vasospasm. We did not try to put together an up to the moment state of the art review. Instead, it was our goal to integrate new information into the existing conceptual basis of our understanding of how blood vessels become diseased, and what might be done once the disease process has established itself. The book is divided into three major sections:

Section I deals with problems associated with the role of lipids in vascular function and includes information on the development and regression of atherosclerosis and pharmacological approaches to lowering blood lipid levels. In addition, the use of transluminal angioplasty in restoring blood flow in plaque occluded vessels is reviewed along with the short- and long-term impact of this procedure of arterial wall function.

Included in this section are in-depth discussions of the role of various lipids in arterial smooth muscle function, apart from their role in the genesis of atherosclerosis. The effects of cholesterol enrichment on cell membranes and smooth muscle contractility is presented along with discussions on the role of membrane phosphatidylinositol metabolism in excitation-contraction coupling, as well as calcium binding to smooth muscle cell membrane phospholipids. In addition, a potential role for platelet activating factor (AGEPC or PAF) in circulatory hemodynamics is presented.

Section II addresses the mechanistic basis of smooth muscle function and how it might be altered in hypertension. The role of calcium in excitation-contraction coupling in normal smooth muscle as well as calcium interactions with smooth muscle membranes in hypertension is developed. Chapters presenting biochemical and physiologic approaches taken to help clarify our understanding of the manner in which the contractile proteins mediate vasconstriction in normal and hypertensive arteries are also reviewed. In addition, electrophysiological alterations associated with hypertension are described as are alterations in calcium dependent ion fluxes across the smooth muscle membranes. Lastly, the use of and directions for new research for antihypertensive drug therapy is presented, including a review of calcium antagonists and their mechanism of actions.

Section III entertains possible models which might explain the mechanistic basis for arterial vasospasm describing smooth muscle, endothelial and neuronal factors as well as noncellular factors which could contribute to the development of this potentially life-threatening condition.

This book is therefore directed to the vascular biologist, whether a physician-scientist or basic scientist, young or old, in the hope that it may stimulate new ideas for future progress in this most vital area of medicine.

Because this monograph was compiled from the proceedings of the A.N. Richards Symposium sponsored by the Physiological Society of Philadelphia, the editors wish to express their gratitude to the Society for making this work possible. We are also grateful to those who participated in the symposium and authored the various chapters, not only for their efforts but also for their cooperation and patience in helping to complete this task. In addition, we would also like to thank Miss Maxine Blob for her secretarial assistance.

On behalf of the Physiological Society of Philadelphia, we wish to gratefully acknowledge the financial support of the following corporate sponsors: Wallace Laboratories, Stuart Pharmaceuticals, Hoffmann-LaRoche, Inc., Revlon Health Care Group, Smith Kline & French Laboratories, Bristol-Meyers Company, McNeil Pharmaceutical, Sandoz, Inc., American Critical Care, Schering Corporation, The Upjohn Company, and Wyeth Laboratories.

Thomas N. Tulenko, Ph.D.
Robert H. Cox, Ph.D.
Philadelphia, Pa.

此为试读,需要完整PDF请访问: www.ertongbook.com

Contents

Recent Advances in Arterial Diseases: Atherosclerosis, Hypertension, and Vasospasm, pages 1-29
© 1986 Alan R. Liss, Inc.

PATHOGENESIS OF THE ATHEROSCLEROTIC LESION: CURRENT CONCEPTS OF CELLULAR AND BIOCHEMICAL EVENTS

Richard W. St. Clair, Ph.D.

Department of Pathology
Bowman Gray School of Medicine
Winston-Salem, North Carolina 27103

Atherosclerosis and its principal clinical sequelae, coronary heart disease and stroke, were not recognized as significant health problems until about the beginning of the 20th century. This is no doubt due to a variety of factors including enhanced awareness of these diseases by medical personnel, eradication of many acute infectious diseases, increased life span, changing life styles and dietary patterns, and an actual increase in the incidence of atherosclerosis (Working Group on Arteriosclerosis of NHLBI 1981). Atherosclerosis is not new to modern times as it has been found in severe form in the oldest Egyptian mummies (Leibowitz 1970; Ruffer 1911). The era of experimental atherosclerosis dates back to the early 1900's to the work of Anitschkow (1933) on cholesterol-induced atherosclerosis in rabbits.

Atherosclerosis is a complex pathologic process affecting a number of arteries, some more than others. These changes initially involve the intimal layer of the arterial wall in which there is focal accumulation of a variety of complex lipids, proteins and carbohydrates; cellular components such as smooth muscle cells and macrophage-like cells; blood and blood constituents and, in more advanced lesions, high concentrations of mineral, particularly calcium.

Although some debate exists, the first pathologic change in atherosclerosis is generally agreed to be the fatty streak (Working Group on Arteriosclerosis of NHLBI

1981; McGill 1977). Fatty streaks contain both intracellular (foam cells) and extracellular lipids, principally in the intima. This results in only a slight elevation of the normal intimal surface, but because of the fat content gives the surface a yellow, streaked appearance upon gross observation, resulting in the term fatty streak. Since it is not possible to observe the same artery multiple times over the lifetime of an individual, the natural history of atherosclerosis can only be deduced from autopsy studies carried out on individuals of a variety of ages who have died of natural or accidental causes. By far, the most comprehensive of these is the Geographic Pathology Study conducted in the 1950's and 1960's (McGill 1968). This study compared the extent and severity of atherosclerosis in 19 countries with individuals of widely different ethnic, racial and socioeconomic background and revealed that fatty streaks develop to a similar extent in all populations during the first two decades of life. These so-called juvenile fatty streaks, consisting principally of cholesteryl-ester-laden foam cells, develop in the coronary arteries at sites where more advanced lesions, fibrous plaques, are found in older individuals. In the aorta, however, juvenile fatty streaks are most prevalent in the proximal portion while fibrous plaques are most extensive in the abdominal segment (McGill 1977). When this information is coupled with the fact that fatty streaks at all sites are more severe in blacks and females, while the extent and severity of atherosclerosis is greatest in white males, it suggests that under certain conditions some fatty streaks progress to fibrous plaques while others remain stationary or may even regress (McGill 1977). Alternatively, some fibrous plaques may develop from nonfatty streak precursors.

Fibrous plaques develop in the abdominal aorta and coronary arteries after the age of about 20 and in the thoracic aorta and cerebral arteries after age 30 (Eggen, Solberg 1968; Solberg et al 1968; Solberg, Eggen 1971; Solberg, McGarry 1972). This represents about a 15- to 20-year delay from the first appearance of fatty streaks to the appearance of fibrous plaques. Whereas there is little difference among geographic locations in the extent of fatty streaks that develop up to about age 20, the extent and severity of fibrous plaques varies widely among populations and closely parallels the clinical incidence

of coronary heart disease (Eggen, Solberg 1968; Solberg et al 1968; McGill 1968; Solberg, Eggen 1971; Solberg, McGarry 1972; Kagan et al 1976). As a result, the factors that are responsible for the progression of certain fatty streaks to fibrous plaques (or the development of fibrous plaques from other precursor lesions) are of key importance in understanding the pathogenesis of atherosclerosis. Autopsy studies have shown that known risk factors such as elevated plasma cholesterol concentrations, high blood pressure, cigarette smoking and low HDL cholesterol levels are associated with accelerated fibrous plaque formation (Solberg, Strong 1983). Together, however, all of these risk factors can explain only about 25% of the individual variability in atherosclerosis as measured at autopsy (Holme et al 1981). This suggests either that there are other yet-to-be-identified risk factors or that local factors at the level of the arterial wall play an important role in the pathogenesis of atherosclerosis. The importance of the arterial wall itself in determining susceptibility to atherosclerosis is supported by studies with animal models such as the pigeon, in which major differences exist in susceptibility and resistance to atherosclerosis between breeds that otherwise have identical risk factors (St. Clair 1983a). These local factors clearly do not act in isolation, but instead interact in an as yet poorly-understood fashion with a variety of environmental and genetically-mediated risk factors.

It is the purpose of this paper to review some of the principal biochemical and cellular changes in atherosclerotic arteries and to summarize the current concepts of the pathogenesis of atherosclerosis. Particular emphasis will be placed on our current understanding of the interaction of blood constituents, such as lipoproteins, with the cells of the arterial wall. It must be kept in mind, however, that understanding of the pathogenesis of atherosclerosis is rapidly developing, and many of our current concepts may have to be altered as new information is obtained.

BIOCHEMICAL CHANGES IN THE ATHEROSCLEROTIC ARTERY

The principal biochemical changes characteristic of atherosclerotic lesions are well known (St. Clair 1976)

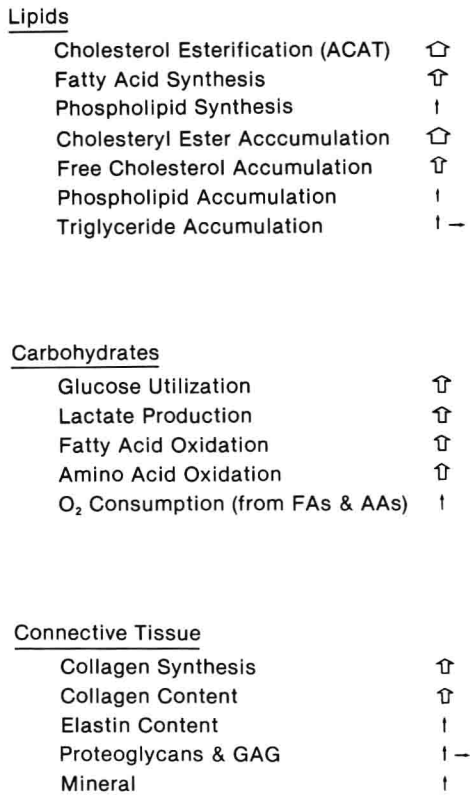

Fig. 1: Major biochemical changes in the atherosclerotic lesion.

and are summarized in Fig. 1. The size of the arrows in Fig. 1 denotes the relative magnitude of the change. The hallmark of atherosclerosis is the accumulation of cholesterol in the arterial wall. In cholesterol-fed animals, or in fatty streak lesions from human beings, cholesteryl oleate is the major form of cholesterol that accumulates (Day, Wahlqvist 1970; Geer, Guidry 1964; Geer, Malcolm 1965; Küinert, Krug 1971; Smith et al 1967; St. Clair 1976). Initially, cholesteryl esters accumulate within foam cells, but as the lesions become more fibrous and necrotic, large amounts of extracellular cholesteryl esters are also found. The cholesteryl ester composition

此为试读,需要完整PDF请访问: www.ertongbook.com