

Hormones and Atherosclerosis

Robert W. Stout, MD, FRCP
Professor of Geriatric Medicine
The Queen's University of Belfast



MTP PRESS LIMITED · LANCASTER · BOSTON · THE HAGUE
International Medical Publishers

Published in the UK and Europe by
MTP Press Limited
Falcon House
Lancaster, England

British Library Cataloguing in Publication Data

Stout, Robert W.

Hormones and Atherosclerosis.

1. Atherosclerosis 2. Hormones

I. Title

616.1'36071 RC692

ISBN-13: 978-94-011-6266-1

e-ISBN-13: 978-94-011-6264-7

DOI: 10.1007/978-94-011-6264-7

Published in the USA by
MTP Press
A division of Kluwer Boston Inc
190 Old Derby Street
Hingham, MA 02043, USA

Library of Congress Cataloging in Publication Data

Stout, Robert W.

Hormones and atherosclerosis.

Bibliography: p.

Includes index.

1. Atherosclerosis—Etiology. 2. Hormones—

Physiological effect. I. Title. [DNLM:

1. Hormones. 2. Arteriosclerosis—Etiology.

WG 550 S925h]

RC692.S74 1982 616.1'3 82-12696

ISBN-13: 978-94-011-6266-1

Copyright © 1982 R. W. Stout

Softcover reprint of the hardcover 1st edition 1982

All rights reserved. No part of this publication may be reproduced,
stored in a retrieval system, or transmitted in any form or by any means,
electronic, mechanical, photocopying, recording, or otherwise,
without prior permission from the publishers.

Hormones and Atherosclerosis

Contents

Preface	vi
Acknowledgements	viii
1 Introduction	1
2 The pathogenesis of atherosclerosis	5
DIABETES MELLITUS	
3 Diabetes mellitus and atherosclerosis	19
4 Risk factors for atherosclerosis in diabetes	35
5 Lipid metabolism in diabetes	51
6 Insulin and atherosclerosis	69
7 Vascular disease and experimental diabetes	77
8 Diabetes and atherosclerosis – conclusions	93
SEX HORMONES	
9 Atherosclerosis in males and females	97
10 Oestrogens, progestogens and cardiovascular disease	113
11 Sex hormones, lipid and carbohydrate metabolism	129
12 The effects of sex hormones on the arterial wall	143
13 Sex hormones and atherosclerosis – conclusions	153
THYROID	
14 Thyroid function and atherosclerosis	157
15 Thyroid function and lipid metabolism	167
OTHER HORMONES	
16 Growth hormone	177
17 Renin	181
18 Corticosteroids	187
19 Cyclic AMP	191
CONCLUSIONS	
20 Conclusions	197
Appendix	199
Index	201

Preface

As the acute infectious diseases recede in importance, and as the number of people surviving into middle and old age increases, the chronic 'degenerative' diseases assume greater importance as causes of death and disability. Of these diseases, atherosclerosis is by far the most prevalent and its consequences the most devastating. The search for the cause of atherosclerosis is consuming large amounts of resources of both money and research talent. As yet, the cause remains unknown.

Much of the research effort into atherosclerosis has been concerned with lipid metabolism. This is based on the knowledge that abnormalities of certain lipids and lipoproteins predispose to cardiovascular disease. Often the research has not been directly related to atherosclerosis and it is only recently that widespread attention has been paid to the artery. The development of methods of growing vascular endothelial and smooth muscle cells in culture has made possible detailed studies of the biology of the arterial wall.

There are a number of reasons why investigations of lipid metabolism alone will not identify the cause of atherosclerosis. First, only a minority of patients with cardiovascular disease have abnormal circulating lipids and lipoproteins. Second, there are three major predisposing factors for atherosclerosis which cannot be entirely explained by abnormal lipid metabolism – age, sex, and diabetes mellitus. Third, it is now clear that lipid is only one component of the atheromatous plaque, and incorporation of lipid may be a late feature of the development of the lesion.

Of the three predisposing factors mentioned above, sex and diabetes are associated with changes in hormone secretion. Other endocrine disorders, including abnormalities in thyroid hormone and growth hormone secretion, have also been associated with an increased frequency of cardiovascular disease. This book is an attempt to discuss the association of hormones and atherosclerosis.

The emphasis of the book is on atherosclerosis defined by the World Health Organization as 'a variable combination of changes of the intima of the arteries (as distinct from arterioles) consisting of the focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits and associated with medial changes'. Other types of vascular disease are not discussed, nor is thrombosis except where it closely relates to atherosclerosis. The emphasis is also on the major hormones and

the clinical syndromes associated with their abnormalities. Other more recently discovered hormones, including the arachidonic acid metabolites associated with platelet function, are discussed in relation to the major hormones.

The literature on atherosclerosis is vast. Only references which are relevant to the topic discussed are included, although overlap with other topics is difficult to avoid and some pertinent reports may have been inadvertently omitted. I have concentrated on the recent literature and, with rare exceptions, have avoided citing abstracts. I hope that the reviews of the association of hormone secretion with atherosclerosis, and of the experimental evidence of hormone action on the arterial wall are comprehensive. The sections on lipid metabolism and other risk factors are inevitably more selective.

My interest in hormones and atherosclerosis was first stimulated 15 years ago by Professor John Vallence-Owen's suggestion that high insulin levels may predispose to vascular disease. With his active encouragement and support, I involved myself in experimental work in this topic in the Department of Medicine, The Queen's University of Belfast. The department was soon joined by Professor Keith Buchanan with whom I also enjoyed fruitful collaboration. In 1971 I was awarded an Eli Lilly Foreign Educational Fellowship by the Medical Research Council and spent 18 months at the University of Washington School of Medicine, Seattle, USA. There I had the good fortune to work in the Division of Gerontology and Metabolism which was headed by Dr Edwin Bierman, and which included Drs Daniel Porte, William Hazzard and John Brunzell. I also had the opportunity to work with Dr Russell Ross in the Department of Pathology. More recently Dr Hugh Taggart has investigated oestrogens and atherosclerosis in my own department. While I have quoted the published work of all these investigators, it is impossible to assess the impact on my thinking of the ideas formulated in many fruitful and enjoyable discussions. I acknowledge with gratitude the contributions of these friends and colleagues. I, of course, accept full responsibility for all that is written in this book.

Much of the basic work of this book was carried out while I was a visiting scientist at the University of Washington School of Medicine in spring 1981. I am grateful to the Wellcome Trust for financial assistance which made this visit possible. Libraries are of course essential for writers of a book of this type and I received great assistance from the Medical Library of the Queen's University of Belfast. I am particularly grateful to Dr Keith Lewis, assistant librarian, for considerable help. Mrs Melanie Hilary and Miss Andree Best typed the manuscript with great skill and patience. Lastly I thank my wife and family for their forbearance over many months when I shut myself in my study and was generally unsociable.

Acknowledgments

I am grateful to the following for permission to use copyright illustrations:

Figure 2.1 From *Diabetes, its Physiological and Biochemical Basis*, edited by J. Vallance-Owen, by kind permission of MTP Press, Lancaster.

Figure 4.1 From Chait, A., Bierman, E. L. and Albers, J. J. (1979). Low density lipoprotein receptor activity in fibroblasts cultured from diabetic donors. *Diabetes*, **28**, 914–18, by kind permission of Dr Alan Chait, and the American Diabetes Association Inc.

Figure 5.1 From Chait, A., Bierman, E. L. and Albers, J. J. (1978). Regulatory role of insulin in the degradation of low density lipoprotein by cultured human skin fibroblasts. *Biochim. Biophys. Acta*, **529**, 292–9, by kind permission of Dr Alan Chait and Elsevier Biomedical Press, Amsterdam.

Figure 6.1 From Stout, R. W. (1979). Diabetes and atherosclerosis – the role of insulin. *Diabetologia*, **16**, 141–50, by kind permission of Springer-Verlag, Heidelberg.

Figure 7.2. From Stout, R. W., Buchanan, K. D. and Vallance-Owen, J. (1972). Arterial lipid metabolism in relation to blood glucose and plasma insulin in rats with streptozotocin-induced diabetes. *Diabetologia*, **8**, 398–401, by kind permission of Springer-Verlag.

Figure 7.3 From Stout, R. W., Bierman, E. L. and Ross, R. (1975). Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells. *Circ. Res.*, **36**, 319–28, by kind permission of the American Heart Association.

Figure 15.1 From Chait, A., Bierman, E. L. and Albers, J. J. (1979). Regulatory role of triiodothyronine in the degradation of low density lipoprotein by cultured human skin fibroblasts. *J. Clin. Endocrinol. Metab.*, **48**, 887–9, by kind permission of Dr Alan Chait and the Editor in Chief, *Journal of Clinical Endocrinology and Metabolism*.