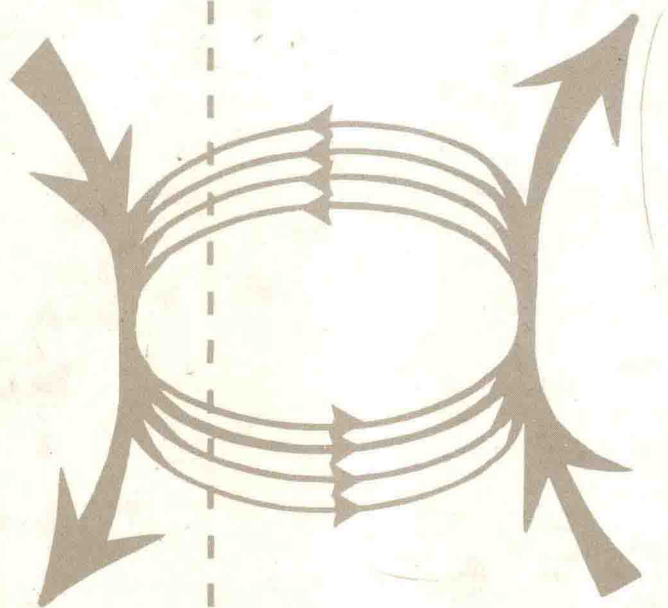


# Cholesterol



John R. Sabine

# CHOLESTEROL

---

John R. Sabine

*Waite Agricultural Research Institute  
The University of Adelaide  
Glen Osmond, South Australia  
Australia*

MARCEL DEKKER, INC. New York and Basel

Library of Congress Cataloging in Publication Data

Sabine, John R  
Cholesterol.

Bibliography: p.  
Includes indexes.

1. Cholesterol metabolism. 2. Mammals--Physiology.  
I. Title. [DNLM: 1. Cholesterol--Metabolism.  
2. Cholesterol--Adverse effects. 3. Arteriosclerosis--  
Etiology. 4. Neoplasms--Etiology. 5. Cholelithiasis--  
Etiology. QU95 S116c]  
QP752.C582 574.1'9243 76-28905  
ISBN 0-8247-6516-8

COPYRIGHT © 1977 by MARCEL DEKKER, INC. ALL RIGHTS RESERVED

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

MARCEL DEKKER, INC.  
270 Madison Avenue, New York, New York 10016

Current printing (last digit):  
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

To

*Mary Ann*

—without whom little would be possible  
—and even less would be fun

## Preface

During the nearly twenty years since the last books on cholesterol were published, the scientific world has accumulated a vast storehouse of “facts” relative to this compound, particularly relative to its involvement in a number of serious diseases. Unfortunately, however, our true understanding of these facts, and our proper appreciation of their real significance to disease, seem not to have grown in the same proportion.

This present text is an attempt to integrate the vast, diverse literature concerning cholesterol into a comprehensive and comprehensible whole, an attempt to provide a coherent framework of our present knowledge and understanding, or lack of it, of cholesterol metabolism—in man and animals, in health and disease.

To this end, in the chapters that follow, I propose to do three things:

- (a) to present a summary of our knowledge to date of the role cholesterol plays in mammalian systems and of the mechanisms by which it gets into and out of these systems;
- (b) to discuss the various controls that operate to regulate this ingress and egress—both the physiological controls proposed by nature and the pharmacological controls devised by man;
- (c) to summarize the evidence implicating cholesterol in the etiology of several diseases—atherosclerosis, cancer, and cholelithiasis in particular.

In all of this a dominant theme will be: What next? That is, what are the significant gaps in present knowledge (the simplest and most obvious gaps will be apparent in many of the tables), and how can we best proceed to close these gaps?

The major problem for the future, however, is not “What are the facts?” but rather “What are the questions?” We must learn to ask the right questions if we ever hope to increase our understanding and not just our knowledge.

If students (secondary, tertiary, or quaternary), scientists (biological or physical), medical practitioners or veterinary practitioners, and interested laymen or women find this informative or enjoyable or both, then I shall be even happier than I am now—and this will be sufficient reward.

John R. Sabine  
Adelaide

## Acknowledgments

In the total production effort of this book I am indebted to many people for many things. If I try, however, to acknowledge individually all those who have helped me so much then I know I shall surely offend by missing some. So, my general thanks and gratitude to one and all, and I sincerely hope that you will all receive some reward by sharing with me my pleasure in whatever success the book, our book, might achieve.

But nevertheless some individual acknowledgments are indeed necessary, and above all I record my deep appreciation for the unfailing support and encouragement of my wife, Mary Ann, and of my children. Without their ready and cheerful acceptance of my need to work long hours away from family activity I could not have continued my task for long, let alone finished it.

At the technical level I am deeply grateful to my various research assistants, especially Miss Judy Scott, for their consistent and considerable help in the massive task of physically finding and recording my reference material and in the innumerable minor and major tasks associated with assembling the manuscript. For Judy's generous and cheerful assistance in all of this I am particularly grateful. I also readily and willingly acknowledge my indebtedness to Miss S. Jean Susman and the girls of the Waite Institute library for their unfailing help with reference material, to my colleagues in the Department of Animal Physiology for their considerable tolerance of my low level of participation in departmental activities over several years, to my graduate students for their help in frequently clarifying my ideas during many discussions and for their patient suffering of my severe, but I hope not fatal, neglect of their welfare, to various friends who have read part of the manuscript and who have removed some of the more glaring errors, to my several typists for their uncomplaining cooperation, and in this context particularly to Miss Jan Peavy, whose rapid and skillful conversion of my initial handwritten manuscript into presentable typescript made the subsequent tasks of revision and rewriting so much easier, to a particularly obliging and cooperative Mrs. Betty Steedman and her photocopying machine, without which invention the whole exercise might have been for me technically impossible, and especially to Miss Lynne

Cobiac for her skill and imagination in drawing my graphs and charts and in converting my hazy initial ideas into most acceptable, and at least to me, very pleasing cartoons. In this last context I hope that Mr. Norman Lindsay would consider that Bunyip Bluegum, from his "The Magic Pudding," has been adapted to an acceptable use.

Cholesterol research in my own laboratory is being and/or has been generously supported by the research funds of the University of Adelaide and by several grants—from the Australian Research Grants Committee, the Anti-Cancer Foundation of the University of Adelaide, and especially the National Heart Foundation of Australia. A small grant from the University's Animal Products Research Foundation helped to cover some of the book's production costs.

And finally I must acknowledge a beginning and an end. As a beginning it was the late Professor I. L. Chaikoff and his colleagues of the University of California at Berkeley who first introduced me to cholesterol research. And for this current end point, this book, I am thankful for the continued assistance and encouragement of the staff of Marcel Dekker, Inc.—who were responsible for its initial conception, who have tolerated its long and protracted gestation, and who have ultimately combined to ensure its successful delivery as a healthy and I hope both pleasing and productive offspring.



# Contents

PREFACE	v
ACKNOWLEDGMENTS	vii
1 THE PROBLEM WITH CHOLESTEROL	1
I In the Body	1
II In the Laboratory	2
2 THE ROLE OF CHOLESTEROL IN MAMMALIAN SYSTEMS	5
I Distribution of Cholesterol	6
II Cholesterol in Membranes	10
III Cholesterol Not in Membranes	26
3 METHODS IN CHOLESTEROL RESEARCH	29
I Early Chemistry	31
II Detection and Analysis	32
III The Appropriate Experimental Animal?	35
IV Metabolic Studies	36
V Membranes—Natural and Artificial	49
VI Cholesterol Not in Membranes	54
4 DIGESTION/ABSORPTION/TRANSPORT/STORAGE	57
I Sterols in the Diet	58
II Digestion	58
III Absorption	62
IV Transport	71
V Cellular Uptake and Storage	73
VI Diseases of Absorption, Transport, and Storage	75

5	BIOSYNTHESIS	79
	I The Pathway of Cholesterol Biosynthesis	80
	II Sites and Rates of Synthesis	102
	III Cholesterol and the Fetus	103
6	PHYSIOLOGICAL CONTROL OVER BIOSYNTHESIS	105
	I Endogenous Controls	106
	II $\beta$ -Hydroxy- $\beta$ -methylglutaryl Coenzyme A Reductase as the Physiologically Important Enzyme?	108
	III Dietary Feedback Control Over Liver Synthesis	110
	IV Control During Fasting and the Effects of Diet	114
	V The Circadian Rhythm	119
	VI Hormonal Influences	121
	VII Bile Salt Status and Cholesterogenesis	125
	VIII Interrelation Between Cholesterol and Ubiquinone	128
	IX Control of Cholesterogenesis During Development	130
	X Control of Cholesterogenesis in Tissue Culture Cells	132
	XI Obesity and Other Diseases	134
	XII Are Other Factors Physiological?	134
7	PHARMACOLOGICAL CONTROL OVER BIOSYNTHESIS	137
	I Is There an Ideal Inhibitor?	139
	II A Classification of Active Agents	140
	III Inhibitors of Cholesterol Synthesis	142
	IV Stimulators of Cholesterol Synthesis	151
	V Detergents	155
8	METABOLISM AND EXCRETION	157
	I Pathways of Removal	158
	II Total Turnover	160
	III Metabolism to Bile Acids	164
	IV Metabolism to Steroid Hormones	176
	V Other Metabolic Routes	180
	VI Cholesterol Excretion	184
	VII Metabolism of Plant Sterols	190

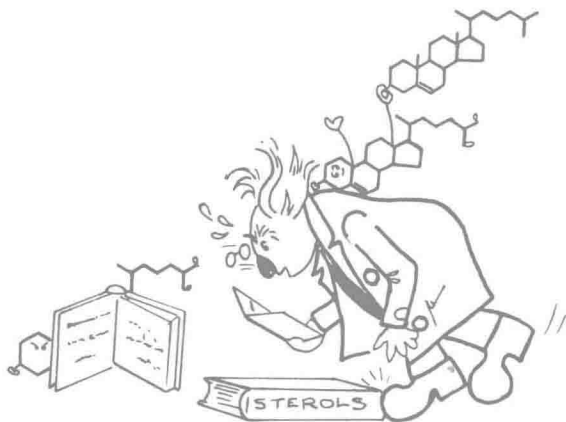
9	CHOLESTEROL IN THE BLOOD	191
	I The Role of Blood Cholesterol	192
	II Distribution	194
	III Turnover (LCAT)	204
	IV Factors Influencing Concentration	208
	V What Else Correlates with Blood Cholesterol?	243
10	CHOLESTEROL AND ATHEROSCLEROSIS	245
	I Introduction	246
	II Cardiovascular Disease in Man	247
	III Atherosclerosis in Experimental Animals	259
	IV Cholesterol Metabolism in the Arterial Wall	265
	V A Summary—With Some Thoughts for the Future	274
11	CHOLESTEROL AND CANCER	277
	I Why Cholesterol?	277
	II Blood Cholesterol and Cancer	278
	III Defective Cholesterol Metabolism in Cancerous and Precancerous Liver	280
	IV Cholesterol and Cancer Cells in Culture	286
	V Carcinolipin	288
12	CHOLESTEROL AND GALLSTONE DISEASE	289
	I Incidence	290
	II Stages in Stone Formation	291
	III Factors Influencing Stone Formation	298
	IV Stone Dissolution	302
	V Plasma Cholesterol Changes Accompanying Cholestasis	302
13	CHOLESTEROL AND THE NERVOUS SYSTEM	305
	I Cholesterol in Adult Nervous Tissue	307
	II Synthesis and Turnover of Nervous Tissue Cholesterol	309
	III The Role of Cholesterol in Nervous Tissue	314
	IV Agents Affecting Nervous System Cholesterol	315
	V Involvement of Cholesterol in Disorders of the Nervous System	320

14	THE PROBLEM REVISITED	327
	I The Patient	327
	II The Experiment	328
	III The Public	328
	IV Myself	329
	REFERENCES	331
	AUTHOR INDEX	423
	SUBJECT INDEX	463

# 1

## The Problem with Cholesterol

---



---

I. IN THE BODY	1
II. IN THE LABORATORY	2

The problem is simple—there is just too much cholesterol!

### I. In the Body

The average adult male, if such existed, would weigh approximately 70 kg, of which just over 0.2%, or about 145 g, would be cholesterol, with approximately 5½% of this amount, or 8 g, contained in his plasma.

This average man, if he lived in North America, Western Europe, or Australasia, would consume every day close to 0.5 g of cholesterol, plus assorted amounts of related sterols. His average daily synthesis of cholesterol, working at only a fraction of full capacity, might be another 1.0 g, giving a total each day of 1.5 g. His average daily metabolic requirement should be no more than 350 mg, even less if he recycled efficiently.

Man's plight is even worse than this many-fold excess of intake plus production over requirement. Not only does every cell of his body both contain cholesterol and have ready access to a large extracellular supply, but every cell (with the possible exception of the mature red blood cell) can also make cholesterol. In other words every cell contains, and therefore must synthesize and maintain control over, the some 26 enzymes responsible for converting acetyl coenzyme A to cholesterol. Such extravagance, on so grand a scale, is virtually unknown elsewhere in the mammalian world.

And, final irony, all this cholesterol may mean the death of our average man, or at least of our average Western man. At the end of his three score years and ten, or very often much sooner, his body will somewhere contain more cholesterol than it should, and the excess may kill him.

## II. In the Laboratory

There is also too much cholesterol in the literature.

The index to *Biological Abstracts* for a recent 6-month period [1] lists 487 items\* under the heading Cholesterol—and my guess is that two-thirds of these either flatly contradict, or at least provide an alternative observation to or explanation for, the corresponding number of the previous six months.

The number of papers published that are relevant to cholesterol metabolism is huge, because the rewards are very great and the basic technology very simple. If you can maintain an animal, and if you can bleed it, then you can do cholesterol research. The determination of blood cholesterol,  $\pm$  say 5%, is a simple procedure for the most primitive laboratory. And the prizes (both scientific and financial) for obtaining the right answers, e.g., to, why does blood cholesterol go up? and, why won't it come down? are very substantial indeed.

But the number of irrelevant papers is likewise huge, only marginally less than the total number, since all but a very few are asking questions to which there is really only one answer: it all depends. It all depends on the species or the breed or the strain, or on age or sex or nutritional status (past and present), or on the temperature or the time of day or the season of the year, or on a dozen other variables. If you know the answer for the African elephant, someone will want it for the Indian. If the liver does it, what about the lung or the left leg (their cells all need, absorb, make and excrete cholesterol)? If the mung bean is good, what about the broad bean, and were they both sprayed with the same insecticide and fed the same fertilizer?

\*Don't worry, I haven't read them all, let alone referred to them all here.

There is no lack of pertinent variables to try—or of people wanting to try them. What are lacking, sadly lacking, are explanations, comprehensive and coherent cellular and molecular mechanisms, upon which can be hung logical hypotheses for the wide variations observed. As the cholesterol story unfolds in the following chapters it should become obvious that some great work has been done. The structure and biosynthetic derivation of the cholesterol molecule, the basic enzyme pathways leading to cholesterol and from it to bile salts and the steroid hormones, the physicochemical explanation for the formation of cholesterol gallstones, and the distribution pattern of cholesterol in human blood; these are areas in which the broad patterns are clear, even though all the finer details might not be. But beyond these, and a few others, there is as yet no hint, no semblance of a pattern. And the vast bulk of current work is unlikely ever to uncover a pattern.

For example, in this text I have referenced some hundreds of articles in which the results include values for blood cholesterol, and my files contain at least as many more again. Yet in not one of these papers have the authors wondered why there is any cholesterol in blood at all, let alone why half the world's population should have more cholesterol in their blood plasma than they have glucose.

I have seen expressed somewhere the concept that “if something can be done, someone will try to do it.” I wish people would stop doing cholesterol research simply because it can be done.

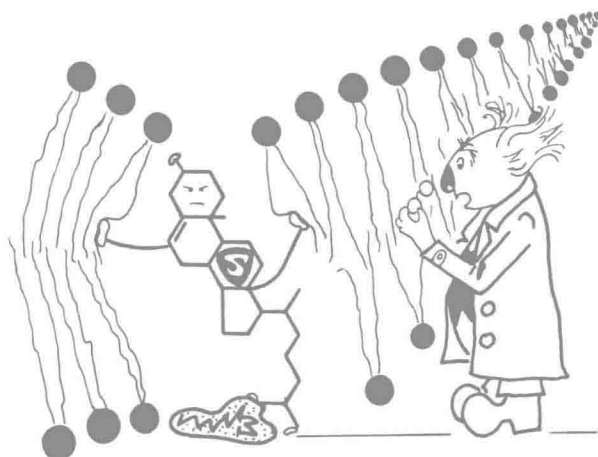




# 2

## The Role of Cholesterol in Mammalian Systems

---



I. DISTRIBUTION OF CHOLESTEROL	6
II. CHOLESTEROL IN MEMBRANES	10
A. What is a Membrane?	10
B. Cholesterol and Membrane Structure	12
C. Cholesterol and Membrane Permeability	18
D. Cholesterol and Membrane Fusion	21
E. Cholesterol and Membrane Electrical Activity	22
F. Cholesterol and Membrane Metabolic Activity	23
1. Enzyme Activity	24
2. Protein Synthesis	25
3. Receptors	25
G. Cholesterol and Membranes in Summary	26
III. CHOLESTEROL NOT IN MEMBRANES	26

Cholesterol is both an end and a beginning.

As the end product of a long and intricately regulated biosynthetic pathway, its predominant role appears to be as a constituent of membranes. Every mammalian membrane contains some cholesterol and some membranes contain a great deal.