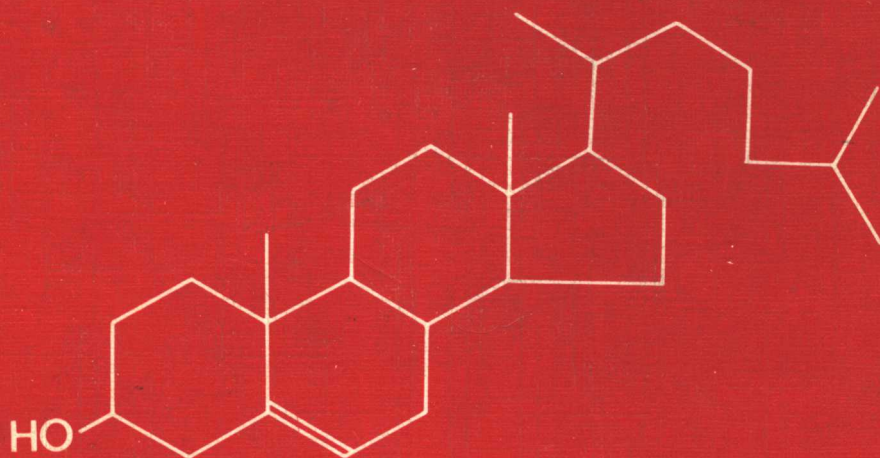


# Biochemistry of cholesterol

G.F. GIBBONS, K.A. MITROPOULOS AND N.B. MYANT



Elsevier Biomedical

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1982

Elsevier Biomedical Press  
Amsterdam · New York · Oxford

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ISBN 0-444-80348-3

Published by:  
Elsevier Biomedical Press B.V.  
PO Box 211  
1000 AZ Amsterdam, The Netherlands

Sole distributors for the USA and Canada:  
Elsevier Science Publishing Company Inc.  
52 Vanderbilt Avenue  
New York, NY 10017, USA

Printed in the Netherlands

# Preface

One of the things which many students of natural products enjoy most is musing on the question of why a particular organism biosynthesises a particular compound, rather than other, related, compounds of slightly different structure. Is it a question of the natural selection of a unique molecular structure which, above all others, performs a certain biological function most effectively? Of the large number of known sterols and related triterpenoids, the almost exclusive presence of cholesterol as the major sterol of every vertebrate (and many invertebrate) animals suggests that this hypothesis is correct. It is reasonable therefore to ask questions relating the molecular structure and chemical behaviour of cholesterol to its biological role at the molecular level. These relationships are emphasised throughout this book.

To do this effectively we have had to use concepts which, although usually taken for granted by chemists, are sometimes confusing to those whose primary interests lie in the so-called biomedical field. To bridge this communications gap we have tried to explain the necessary chemical (and particularly stereochemical) concepts, in a simple, but not oversimplified, manner. These aspects are dealt with in Chapter 2, entitled 'Chemistry', and we suggest that this chapter be read first. The chemistry of cholesterol is a vast subject and the topics described have been selected partly because they are recent developments, partly because they are of importance in relating structural features to biological function, and partly because they are of practical value in investigating aspects of cholesterol biochemistry, notably its biosynthesis, metabolism and analysis.

With respect to the biosynthesis of cholesterol, we now know in intricate detail the way in which cells assemble the cholesterol molecule from small precursors and this has been one of the major achievements of biological chemists over the last 30 years or so. Much of this work is already well documented and in the chapter on 'Biosynthesis' (Chapter 5) we have concentrated on more recent developments including discussion of the enzymic mechanisms involved in several of the steps. These have been described in the context of earlier work. In the chapter on 'Regulation of synthesis and further metabolism' (Chapter 8) we have tried to integrate the vast literature into a comprehensive whole and to identify the areas in which future research may be particularly fruitful. At present, however, the molecular mechanism responsible for the regulation of cholesterol biosynthesis is not completely understood although it may be related to the movement of cholesterol into and out of the cell. Apart from its intrinsic interest, research in this field has gathered momentum as a result of clinical interests, particularly as it may have an important bearing on determining the plasma cholesterol concentration. In recent years a great deal has been written about the plasma cholesterol in health and disease, particularly in relation to human athero-

sclerosis. In Chapter 7 we have tried to provide the reader with a brief account of the biochemistry of the plasma lipoproteins, the vehicles in which all the cholesterol in plasma is carried.

A rapidly developing and potentially important field in cholesterol research concerns the role of cholesterol in determining the properties of biological membranes. Our understanding of the function of cholesterol in cellular membranes is in its infancy and this is the direction in which future research into cholesterol may well proceed. Finally, it has been our intention to write a book that will be useful to the teacher or postgraduate research worker already working in the sterol field and to the beginner with no special knowledge of sterols.

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London  
December, 1981*

# Acknowledgements

Several people assisted in the preparation of this book without whose help its already lengthy gestation period would have been further extended. We would like to thank Professor D. N. Kirk, Westfield College, University of London, for his useful criticism of Chapter 2 and for numerous helpful suggestions. Dorothy Buyers and Jean De Luca typed their way uncomplainingly through successive drafts and Katarzyna Richards prepared the figures and formulae. One of us (GFG) was introduced to sterol biochemistry several years ago by Dr John Goad, University of Liverpool. He thanks him for his patience and encouragement during that period and for his continued friendship.

# Contents

Preface .....	v
Acknowledgements .....	vii

## Chapter 1 Introduction

Cholesterol, past, present and future .....	1
Why cholesterol? .....	2
Sterols in plants and animals .....	2
Cholesterol in disease .....	3
Too much cholesterol? .....	3

## Chapter 2 Chemistry

What is a steroid? .....	5
Stereochemical concepts and conventions .....	6
Use of molecular models .....	6
Conformation and configuration .....	6
$\alpha$ and $\beta$ configuration: axial and equatorial bonds .....	9
Valency angles and torsion angles .....	9
Enantiomers and epimers .....	10
Ring junctions: <i>cis</i> and <i>trans</i> : <i>syn</i> and <i>anti</i> .....	11
Specification of absolute configuration .....	11
Fischer convention and Fischer projection .....	11
Plattner convention .....	12
<i>R</i> - and <i>S</i> -notation .....	12
<i>Z</i> - and <i>E</i> -notation .....	13
Nomenclature .....	14
Fundamental structures .....	16
Stereochemical modifications (IUPAC rule 2S-5) .....	16
Double bonds (IUPAC rule 2S-4) .....	16
Other substituents .....	17
Ring contraction, ring enlargement and ring fission (IUPAC rules 2S-7 and 2S-8) .....	17
Correlation of trivial and systematic names .....	17
Structure of cholesterol .....	17

Establishment of the structural formula . . . . .	18
Establishment of relative stereochemistry . . . . .	19
Absolute configuration . . . . .	19
Structural implications of the C-5,6 double bond. . . . .	20
Conformation of the cholesterol side-chain . . . . .	21
Overall shape of the cholesterol nucleus . . . . .	22
Conformational analysis . . . . .	22
General considerations . . . . .	22
Stereoelectronic factors . . . . .	25
Reactions controlled by steric effects . . . . .	26
Prediction of stereochemical outcome . . . . .	28
Determination of steroidal conformation by X-ray and force-field analysis . .	28
Conformational transmission and other long-range effects . . . . .	29
Reactions involving cholesterol and related sterols . . . . .	33
Reactions of the 3 $\beta$ -hydroxyl group . . . . .	33
Esterification and etherification . . . . .	33
Dehydration . . . . .	33
Nucleophilic substitution and 'i-steroid' formation . . . . .	34
Oxidation . . . . .	34
Reaction with digitonin . . . . .	35
Reactions involving the C-5,6 double bond. . . . .	35
<i>Trans</i> -diaxial addition versus <i>cis</i> addition . . . . .	35
Epoxide formation . . . . .	36
Catalytic reduction . . . . .	37
Oxidation of cholesterol . . . . .	37
Allylic oxidation . . . . .	37
Photochemical and auto-oxidation of cholesterol . . . . .	38
Oxidation of the extra-nuclear methyl groups . . . . .	39
Desaturation and double bond rearrangement . . . . .	40
Synthesis of cholesterol precursors . . . . .	40
4,4,14 $\alpha$ -Trimethyl sterols (C <sub>30</sub> ) and 4,4-dimethyl sterols (C <sub>29</sub> ) . . . . .	40
4 $\alpha$ -Methyl sterols (C <sub>28</sub> sterols) . . . . .	45
4-Demethyl sterols (C <sub>27</sub> sterols) . . . . .	45
Side-chain unsaturated cholesterol precursors . . . . .	45
Oxygenated cholesterol precursors . . . . .	46
Long-range functionalization of steroids . . . . .	46
Partial synthesis of steroids . . . . .	47
Biogenetic-type synthesis . . . . .	47
Hydroxylated vitamin D derivatives . . . . .	52



## Chapter 3      Methods of analysis

The principle of additivity in structural analysis . . . . .	60
Preparative chromatography . . . . .	60
Uses in sterol analysis . . . . .	60
Basic principles . . . . .	61
Column chromatography . . . . .	61
Adsorption . . . . .	61
Argentation . . . . .	62
Thin-layer chromatography . . . . .	62
Adsorption . . . . .	62
Argentation . . . . .	64
Partition (reversed phase) . . . . .	65
Detection of radioactive sterols after TLC . . . . .	65
Gas chromatography . . . . .	65
Basic principles . . . . .	65
Practical aspects . . . . .	67
Columns and stationary phases . . . . .	67
Detectors . . . . .	67
Sample preparation and derivative formation . . . . .	69
Effect of molecular size, shape and substituent configuration on retention time . . . . .	69
Additivity of the effect of structural features on sterol retention time . . . . .	70
Quantitative analysis . . . . .	71
Preparative gas chromatography . . . . .	71
High performance liquid chromatography . . . . .	72
Basic principles . . . . .	72
Uses in steroid and sterol analysis . . . . .	72
Detection of labelled and unlabelled sterols . . . . .	73
Mass spectrometry . . . . .	74
Basic principles . . . . .	74
The instrument . . . . .	74
The sample . . . . .	74
Applications . . . . .	74
Molecular weight determination . . . . .	74
Structural studies . . . . .	74
Combined gas chromatography—mass spectrometry . . . . .	79
Ultraviolet spectroscopy . . . . .	81
Basic principles . . . . .	81
Constant contribution of structural features to the absorption maximum . . . . .	81
Location of the position of isolated double bonds . . . . .	82

Infrared spectroscopy . . . . .	83
Basic principles . . . . .	83
Infrared spectrum of cholesterol . . . . .	86
Use of infrared in structural analysis . . . . .	87
Determination of the position of double bonds in natural sterols . . . . .	87
In sterol synthesis . . . . .	87
Effect of configuration on position of absorption bands . . . . .	87
Nuclear magnetic resonance spectrometry . . . . .	88
Introduction . . . . .	88
The chemical shift . . . . .	88
Spin-spin coupling . . . . .	89
The proton-NMR spectrum of cholesterol . . . . .	89
Methyl group chemical shifts as indicators of sterol structure . . . . .	90
Side-chain stereochemistry . . . . .	90
<sup>13</sup> C-Nuclear magnetic resonance . . . . .	91
Optical rotation, optical dispersion and circular dichroism . . . . .	91
Origin of chiroptical phenomena . . . . .	91
Specific rotation . . . . .	92
Analysis of ORD and CD curves . . . . .	92
The 'octant' rule . . . . .	93
Determination of configuration of hydroxyl groups . . . . .	94
Long-range effects in ORD and CD . . . . .	94
Systematic quantitative and qualitative analysis of cholesterol, its precursors and other sterols in biological material . . . . .	95
Introduction . . . . .	95
Quantitative analysis of cholesterol present as the sole sterol . . . . .	95
Isolation procedures . . . . .	95
Quantification procedures . . . . .	96
Qualitative and quantitative analysis of sterol mixtures . . . . .	100

## Chapter 4      The distribution of cholesterol and other related steroids in nature

Vertebrates . . . . .	109
General . . . . .	109
Liver and bile . . . . .	110
Skin . . . . .	111
Nervous tissue . . . . .	112
Fat, connective tissue and artery . . . . .	113
Intestinal wall and faeces . . . . .	114
Milk . . . . .	115
Serum . . . . .	115

Subcellular distribution . . . . .	115
Invertebrates . . . . .	118
General . . . . .	118
Insects and other arthropods . . . . .	118
Marine invertebrates . . . . .	119
General . . . . .	119
Echinoderms . . . . .	119
Porifera . . . . .	121
Coelenterates . . . . .	121
Molluscs . . . . .	121
Higher plants . . . . .	121
General . . . . .	121
Some phytosterols . . . . .	122
Methylated sterols . . . . .	123
Other steroids of higher plants . . . . .	123
Algae . . . . .	127
Fungi and lichens . . . . .	127

## Chapter 5      Biosynthesis

Cholesterol as a biological isoprene polymer . . . . .	131
Presentation of the chapter . . . . .	131
Historical background . . . . .	132
Principles used in elucidating the biosynthetic pathway . . . . .	133
Analogies in organic chemistry . . . . .	133
Biogenetic relationships suggested by structural similarity . . . . .	133
Criteria for obligatory intermediacy . . . . .	134
Techniques involved in the investigation of the biosynthetic pathway . . . . .	135
Use of enzyme systems . . . . .	135
In vivo studies . . . . .	135
Tissue slices . . . . .	135
Crude cell-free systems ('Bucher homogenates'). . . . .	136
Single-enzyme preparations . . . . .	136
Particulate enzymes . . . . .	136
The use of isotopic tracers . . . . .	137
Principle . . . . .	137
Methodology . . . . .	137
Detection of short-lived biosynthetic intermediates . . . . .	137
The pathway to cholesterol . . . . .	138
The origin of cholesterol carbon . . . . .	138
The nature and metabolic source of the 'biologically active' acetate . . . . .	139

The pre-isoprenoid segment of the pathway: conversion of acetyl-CoA to mevalonic acid . . . . .	140
Compartmentation in the early stages of cholesterol biosynthesis . . . . .	143
Formation of the biological isoprene unit: conversion of mevalonic acid to isopentenyl pyrophosphate . . . . .	144
Coupling of the C <sub>5</sub> units: formation of farnesyl pyrophosphate . . . . .	146
Squalene synthesis: coupling of the farnesyl pyrophosphate units. . . . .	148
Formation of the steroid skeleton: squalene to lanosterol . . . . .	151
Enzymic modification of the sterol skeleton: conversion of lanosterol into cholesterol . . . . .	155
Removal of methyl groups . . . . .	157
Nuclear double bond rearrangement . . . . .	161
Saturation of the $\Delta^{24}$ bond . . . . .	163
Probable sequence of events in the transformation of lanosterol into cholesterol . . . . .	163
Sterol carrier protein . . . . .	165
Stereochemistry of cholesterol biosynthesis . . . . .	166
Formation and isomerisation of isopentenyl pyrophosphate . . . . .	169
Formation of farnesyl pyrophosphate . . . . .	170
Formation of squalene . . . . .	172
Post-lanosterol phases . . . . .	172
Reduction of the $\Delta^{24}$ bond . . . . .	173
Introduction and saturation of the $\Delta^{14}$ bond . . . . .	173
Isomerization of the $\Delta^8$ bond to $\Delta^7$ . . . . .	174
Introduction of the $\Delta^5$ bond . . . . .	174
Saturation of the $\Delta^7$ bond . . . . .	174
An alternative pathway of mevalonic acid metabolism: the <i>trans</i> -3-methylglutaconyl shunt . . . . .	174
Sterol biosynthesis in plants . . . . .	176
Side-chain modification . . . . .	176
Other differences from mammalian sterol biosynthesis . . . . .	177
Other triterpenoids formed from squalene-2,3-oxide and squalene in plants and unicellular organisms . . . . .	179

## Chapter 6 Further metabolism

Bile acids . . . . .	189
Structure and comparative aspects . . . . .	189
Physiology and biological functions . . . . .	192
Enterohepatic circulation . . . . .	192
Physiological functions . . . . .	193
Biosynthesis of primary bile acids . . . . .	194
Historical background . . . . .	194
The sequence of steps leading to the biosynthesis of cholic acid . . . . .	195

The sequence of steps leading to the biosynthesis of chenodeoxycholic acid . . . . .	199
The intracellular localization and stereospecificity of 26-hydroxylase . . . .	201
Conjugation, deconjugation and esterification . . . . .	202
Further metabolism . . . . .	202
Steroid hormones . . . . .	203
Progestogens . . . . .	204
Origin and function . . . . .	204
Biosynthesis . . . . .	205
Adrenocortical steroids . . . . .	206
Isolation and function . . . . .	206
Biosynthesis . . . . .	208
Androgens . . . . .	208
Isolation and function . . . . .	208
Biosynthesis . . . . .	210
Estrogens . . . . .	212
Isolation and function . . . . .	212
Biosynthesis . . . . .	215
Synthesis in pregnancy . . . . .	217
Metabolism and excretion of steroid hormones . . . . .	217
Ecdysones . . . . .	219
Isolation, structure and function . . . . .	219
Biosynthesis . . . . .	220
Vitamin D . . . . .	221
Introduction . . . . .	221
Metabolism of calciferols . . . . .	221
25-hydroxylation . . . . .	222
1 $\alpha$ -hydroxylation . . . . .	222
24-hydroxylation . . . . .	223
Regulation of vitamin D metabolism and function . . . . .	223
Metabolism of cholesterol by plants . . . . .	225

## Chapter 7      Plasma cholesterol

Classification . . . . .	235
Human plasma lipoproteins . . . . .	235
Animal plasma lipoproteins . . . . .	237
Chemical composition and structure . . . . .	237
Composition . . . . .	237
Structure . . . . .	240
Biogenesis and metabolism . . . . .	241

Triglyceride-rich particles . . . . .	241
Formation and secretion . . . . .	241
Metabolism in the circulation . . . . .	243
Metabolism of LDL . . . . .	243
HDL . . . . .	244
Formation . . . . .	244
Metabolism . . . . .	246
Turnover and metabolism of plasma cholesterol . . . . .	246
General . . . . .	246
Cholesterol exchange . . . . .	247
LCAT and the function of the LCAT reaction . . . . .	247
HDL and reverse transport of cholesterol . . . . .	250

## Chapter 8 Regulation of synthesis and of further metabolism

Methods of study . . . . .	255
In vivo . . . . .	255
In vitro . . . . .	256
General . . . . .	256
Measurement of the overall rate of synthesis and degradation . . . . .	257
Significance of rate-limiting steps . . . . .	258
Regulation of cholesterol biosynthesis . . . . .	258
The rate-limiting step in cholesterol biosynthesis . . . . .	258
Other regulated steps in the biosynthesis of cholesterol . . . . .	259
Factors that influence the activity of hydroxymethylglutaryl-CoA reductase and the rate of cholesterol biosynthesis . . . . .	261
Diurnal variation . . . . .	261
Development changes . . . . .	263
Hormones . . . . .	263
Cholesterol . . . . .	265
Other sterols . . . . .	271
Phosphorylation and dephosphorylation . . . . .	273
Bile acids . . . . .	276
Abnormal regulation of cholesterol biosynthesis . . . . .	277
Neoplastic cells . . . . .	277
Familial hypercholesterolaemia . . . . .	279
Regulation of bile acid biosynthesis . . . . .	280
The rate-limiting step in bile acid biosynthesis . . . . .	280
Other steps subject to regulation . . . . .	281
Factors that influence the activity of cholesterol 7 $\alpha$ -hydroxylase and the rate . . . . .	

of bile acid biosynthesis . . . . .	282
Origin and availability of substrate . . . . .	282
The enterohepatic circulation of bile acids . . . . .	285
The diurnal rhythm and hormonal control . . . . .	287
Other factors . . . . .	289
Regulation of cholesteryl ester formation . . . . .	290
Regulation of acyl-CoA-cholesterol acyltransferase . . . . .	291
Regulation of steroid hormone biosynthesis . . . . .	291

## Chapter 9      Sterols in membranes

Protein–lipid–water interactions in relation to membranes . . . . .	305
Distribution of sterols in biomembranes . . . . .	306
The structure of the major sterols . . . . .	306
Phospholipid–sterol interaction . . . . .	308
The bilayer . . . . .	309
The stoichiometry of cholesterol–phospholipid association . . . . .	312
Lateral phase separation . . . . .	313
Non-bilayer lipid structures . . . . .	314
Relation between sterol structure and membrane function . . . . .	315
Liposomes and vesicles . . . . .	316
Black lipid membranes . . . . .	317
Lipid monolayers . . . . .	318
Biomembranes . . . . .	319
The function of cholesterol in biomembranes . . . . .	321
Membrane integrity, permeability and shape . . . . .	321
Membrane fusion . . . . .	322
Membrane asymmetry . . . . .	324
Mobility of lipids within membranes . . . . .	326
Membranes and cellular metabolic activity . . . . .	327
Enzyme activity . . . . .	327
Plasma-membrane receptors . . . . .	331
The evolution of the sterol molecule as a component of membranes . . . . .	333
Subject index . . . . .	343

# Chapter 1

## Introduction

In view of the extraordinary amount of attention devoted to the study of cholesterol over the years in fields as diverse as physics and surgery, one may reasonably ask the question 'What's so special about cholesterol?' The answer is that cholesterol is special, or unusual, in two important respects. First, it is a natural product, almost ubiquitously distributed, available in large quantities and of sufficient complexity to whet the appetite of enterprising chemists and physicists who wanted to understand its structure. In short, it gave these people something to sharpen their research tools on. Second, although these same properties motivated biochemists to investigate how organisms produce it, this sphere of cholesterol research has continually received more than academic interest in view of the association between cholesterol and atherosclerosis which, in the industrialised West, is the largest single cause of death in middle-aged men.

### Cholesterol, past, present and future

In every branch of science, for no apparent reason, certain aspects arise from obscurity and, for a time, become fashionable areas of study. The period over which a research fad remains popular is directly proportionate to the amount of information, useful and otherwise, which can be squeezed from it using techniques currently available. For the fledgling organic chemists of the late eighteenth and early nineteenth centuries one such obsession was the study of human and animal calculi. The simplicity of contemporary techniques ensured a lengthy popularity for these investigations.

It was from one such study of human gallstones that a new substance, cholesterol, appeared on the scene. This discovery is usually attributed to Chevreul, who in 1815 named it 'cholesterine', according to its source and its appearance (Chevreul, 1815). However, some fifty years earlier, Poulletier de la Salle described some properties of material obtained from the alcohol-soluble part of human gallstones. Later, Fourcroy, one of whose more amusing pastimes was examining the fat of putrified corpses in Parisian cemeteries, recognised this 'gras de cadavre' as being similar to the gallstone material and also to spermaceti. This group of substances he called 'adipocire'. It was then left to Chevreul to distinguish chemically between these three substances.

Since that time, the history of research into cholesterol can be divided into three overlapping eras, each characterised by the type of question which was asked of the substance. These were, in chronological order, 'What is it?', 'How is it made and what regulates its production?' and, finally, 'What is its function?'.

The first question, spanning a period of about 150 years, has been answered almost completely, largely by chemical means but owing much to the X-ray crystallographic



studies of Bernal and Crowfoot (Chapter 2). The second question started to be investigated around the turn of the present century and altogether we now know, in fine detail, the way in which the cholesterol molecule is assembled biochemically (Chapter 5). The problem of what regulates its production remains a very active and exciting field of research (Chapter 8). With respect to the final question, we have long been aware of the precursor role of cholesterol in the formation of bile acids and steroid hormones. What, however, is the role of cholesterol *per se*? In this regard, all we have at present are some rather vague ideas about the requirement for cholesterol in maintaining an integral membrane structure. This is the direction in which future cholesterol research is pointing and recent sophisticated work on the fine structure of sterols (Chapter 2) may contribute to our understanding of the way in which cholesterol interacts with other membrane constituents (Chapter 9).

## Why cholesterol?

A useful theoretical approach to the problem of cholesterol function may be to ask the question 'Why does the exact geometry of cholesterol fulfil, uniquely, the structural role required of it?' and this is discussed in Chapters 2 and 9. During the evolution of life, environmental pressures ensured the selective biosynthesis of molecules which were exactly tailored for a particular function. In this respect, cholesterol and its homologues have been around for a long time, and are probably almost as old as life itself. This is evidenced by the discovery of steranes (including cholestane) with the correct stereochemistry in certain pre-Cambrian shales which are 2.7 billion years old. They have also been detected in the Fig tree shale, which is older by 0.4 billion years (Eglinton and Calvin, 1967; Calvin, 1969). The primitive forms of life which inherited the earth at this point in its history probably had little use for bile acids or steroid hormones. Thus sterols were most probably selected initially for their structural function only, as were carotenoids and hopanoids whose role in the membranes of primitive organisms is discussed in Chapter 9. However, one of the most striking features of the steroids is their amazing biochemical versatility, a property they share with porphyrins which have also been associated with the early stages of life. This functional malleability of cholesterol – it is used for the production of bile acids, a variety of hormones, and pheromones as well as having a structural role – has probably ensured its retention from these early times, since evolutionary advantage may be obtained simply by modification of the molecule itself, rather than by *de novo* synthesis.

## Sterols in plants and animals

One of the most intriguing problems in comparative biochemistry, the answer to which may shed some light on the structural role of sterols, is why animals generally contain cholesterol whereas plants contain other sterols. This may relate to the number of functional roles which a sterol plays in a particular organism; the greater the number,