Biochemistry of cholesterol

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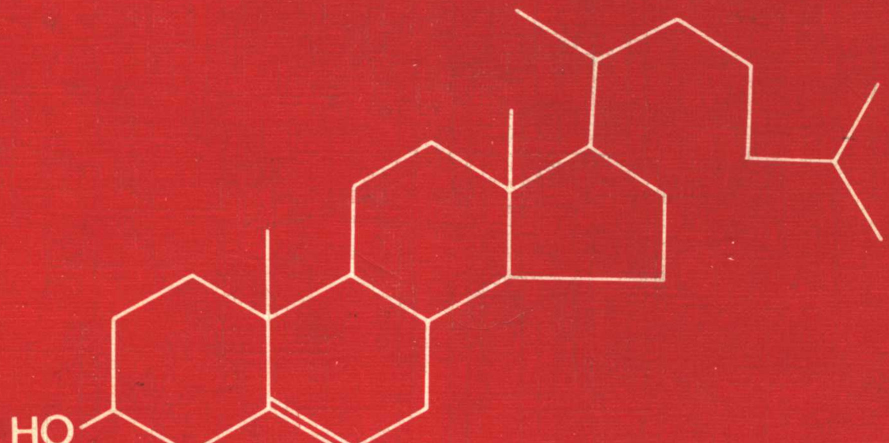

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Preface

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 atherosclerosis. 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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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,