CHOLESTEROL AND FAT METABOLISM IN RELATION TO NUTRITION AND DISEASE

First Session

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The chemistry and biochemistry of the sterols

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The sterols are naturally occurring alcohols which consist basically of the steroid skeleton (cyclopentanoperhydrophenanthrene ring system with two angular methyl groups) and which vary in the number of cyclic double bonds. To the ring system is attached an alkyl side-chain which also may have double bonds. The conventional representation of the sterol skeleton with numbering is shown in Fig. 1. The centres of asymmetry and the positions at which double bonds commonly occur are marked.
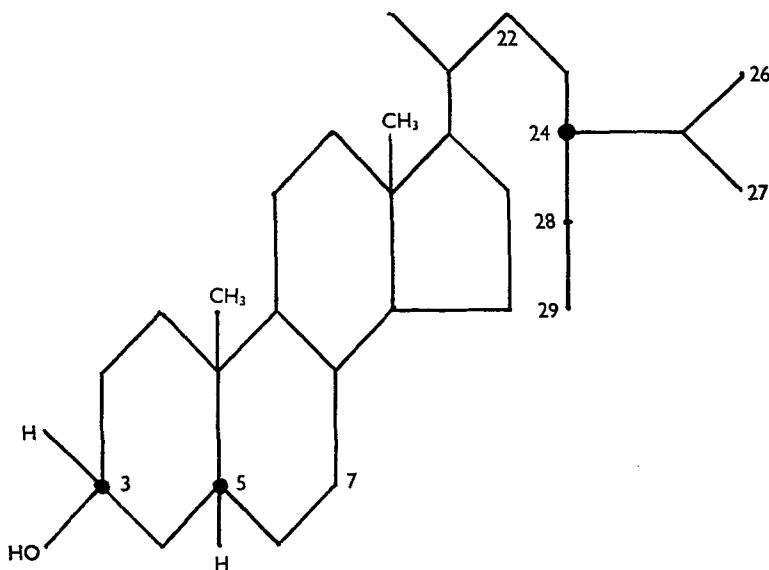

Fig. 1. Skeleton formula of the sterols.
●, main centres of asymmetry marked.

In the stereochemistry of sterols the convention is to represent solid lines for bonds assumed to lie above the plane of the ring system (β-oriented) and dotted lines for those in the opposite direction (a-oriented). An hydroxyl group is present in all sterols in position 3 and in most natural sterols it is β-oriented. The 3β-hydroxy sterols are precipitated by an ethanolic solution of digitonin and this property is used for estimating total sterol content.

In the stanols (saturated sterols) there is a centre of asymmetry at position 5, thus $5a$- (*allo* series) and 5β- (normal series) forms occur. Coprostanol, the principal sterol in the faeces of carnivores and omnivores, is a 5β-compound.

Three basic patterns of sterols containing twenty-seven, twenty-eight and twenty-nine carbon units are found. Cholestanol may be taken as the basic type of a C_{27} sterol. The point of attachment for the additional carbon atoms is at position 24 where in the C_{28} series a methyl group is attached and in the C_{29} series an ethyl group is present. The orientations at C_{24} may be a or b giving rise to two series in each of the C_{28} and C_{29} sterols.

The complex subject of the stereochemistry of the sterols is described more fully by Fieser & Fieser (1949) and by Barton (1953).

Bergmann (1952, 1953) has suggested that the sterols are best classified by the direction and extent of the optical rotations which are dependent upon the degree of unsaturation and location of the double bond. In Table 1 are given the main naturally occurring sterols classified by number of carbon atoms, degree of unsaturation and optical activity.

Table 1. *The main naturally occurring sterols*

No of C atoms	Configuration at C_{24}	1	2	3	4	5
27	–	Cholestanol	Cholesterol	—	Lathosterol (7)	7-Dehydrocholesterol
28	a	Campestanol	Campesterol	Chalinasterol	Stellastenols	—
	b	Ergostanol	—	Brassicasterol	Ergostenols	Ergosterol (22)
29	a	Poriferastanol	Clionasterol	Poriferasterol	Chondrillasterol (7,22)	—
	b	Stigmastanol	β-Sitosterol	Stigmasterol	Spinasterols	—

In column 1 the sterols are all saturated (stanols) with $[a]_D + 10°$ to $+ 30°$. Those listed are $5a$-stanols; 5β-stanols are found in faeces, e.g. coprostanol is the isomer of cholestanol.
In column 2 the sterols have a double bond at position 5 and have $[a]_D - 30°$ to $- 45°$.
In column 3 double bonds are present at positions 5 and 22, the $[a]_D$ is $- 50°$ to $- 70°$.
In column 4 double bonds are present at positions 7, 22 or both, the $[a]_D$ is $0°$ to $- 25°$.
In column 5 double bonds are present at positions 5 and 7, and at 22 in ergosterol, the $[a]_D$ is $< -90°$.

Occurrence and method of combination

Sterols are found in all living organisms with the exception of certain bacteria. In general C_{27} sterols are found in vertebrates whereas the C_{28} and C_{29} sterols are found in the vegetable kingdom. All types of sterols are found in invertebrates, which were extensively studied by Bergmann (1952).

The sterols are found in tissues, secretions and excretions as the free alcohols and as esters, normally with the higher saturated and unsaturated fatty acids. The

ether linkage is also found, particularly in plants where the sterols are combined with carbohydrates to form the so-called phytosterolins.

Role of the sterols

It is unwise perhaps to assess the metabolic and structural functions of the sterols apart from that of the other lipids such as the glycerides and phospholipids with which the free sterols and their esters are always associated. Moreover the lipids are attached to protein, forming the lipoproteins which play a part in affecting *inter alia* the solubility of these compounds. Unfortunately there is little available information on the nature and mode of combination of the protein component.

Metabolic functions. The presence of cholesteryl esters is usually taken as evidence of the importance of cholesterol in the transport of fatty acids. Sobotka (1938) pictures a relationship between the various lipids and considers that an exchange esterification may be brought about by the hydrolytic and synthetic activity of esterases. Such a mechanism would be needed in maintaining the normal balance of lipids, and disorders of it might be reflected in the development of lipidoses.

Precursor of other steroids. The basic steroid structure is found in a number of physiologically important compounds, and cholesterol has been assumed to be the precursor of these. There is good evidence that the bile acids are derived from cholesterol (for review see Bergström, 1953). Conversions of cholesterol to certain sex hormones and to adrenal cortical steroids have been demonstrated also.

On reflection, however, the position is by no means simple and such transformations represent dynamic equilibria of chemical compounds within the animal organism. To speculate it may be assumed that cholesterol forms a convenient storage equilibriant which can be transformed to more reactive compounds. A study of the factors regulating these changes would indeed be profitable.

Structural functions. The wide distribution of sterols in all tissues and the fact that they are not affected by extreme starvation show they are essential constituents forming part of the *élément constant*. Their exact function is a matter for surmise, but presumably the shape of the molecule fits it to form a basic part of the architecture of the cell, particularly the membrane.

A striking and unexplained feature of cholesterol is its high concentration as the free alcohol in the white matter of nervous tissue. Here it seems to lie outside the restless ebb and flow that occurs in other tissues. In the adult animal the cholesterol of the nervous tissue is in a static condition. The role generally attributed to it is that of an insulating agent.

Protection and lubrication. Sterols are found (with other lipids) in large amounts in the skin secretion or sebum of all animals (see review by Wheatley, 1952). It is considered that they have a conditioning action presumably related to the shape of the molecule. Such an action would perhaps account also for the high content of sterols in the faecal excretion.

Growth substances. Although it is now generally accepted that sterols are formed by biosynthesis from small units there is good evidence that in some animal species such as beetles the sterols are necessary for growth (see, e.g., Noland, 1954).

Numerous other functions have been ascribed to the sterols but the above may be taken as the most representative.

The absorption of sterols by animals

As sterols are found in all animal and vegetable tissues and hence in all foods, a knowledge of their absorption is of some importance. In Table 2 data on the absorption of the main sterols are given. The criterion of absorption normally taken is a loss of sterol after a balance experiment with evidence of deposition of sterol in the tissues of the animal. The use of isotopically labelled sterols is of great value in such studies.

Table 2. *Absorption of sterols by animals*

Sterol	Occurrence	Absorbability and reference
C_{27} sterols:		
Cholesterol $(3\beta$–ol)	Present in all animal tissues	Absorbed in presence of fat by man, various mammals and birds
Cholesterol $(3\alpha$–ol) (epicholesterol)	Synthetic product	Poorly absorbed by rats (Hernandez, Chaikoff, Dauben & Abraham, 1954)
Lathosterol	Accompanies cholesterol	Absorbed by rabbits (Lemmon, Pierce, Biggs, Parsons & Kritchevsky, 1954)
7-Dehydrocholesterol	Accompanies cholesterol	Absorbed by rabbits (Cook, Kliman & Fieser, 1954)
Cholestanol	Accompanies cholesterol	Absorbed by rabbits (Cook *et al.* 1954) Absorbed by rats (Dam & Brun, 1935) Not absorbed by man (Dam, 1934)
Coprostanol	Faeces	Not absorbed by man (Bürger & Winterseel, 1931) or mice (Breusch, 1938)
C_{28} sterols:		
Ergosterol	Yeast and certain fungi	Slightly absorbed by rats and hens (see Hanahan & Wakil, 1953). Absorbed after irradiation (Cruickshank, Kodicek & Armitage, 1954)
Chalinasterol (ostreasterol)	Bivalves (e.g. oyster)	Absorbed by mice (Sperry & Bergmann, 1937)
Brassicasterol (with other sterols) (see Bergmann & Ottke, 1949)	Mussel (*Modiolus*)	Some absorption by rabbits (Riddell & Cook, unpublished)
C_{29} sterols:		
'Sitosterol' (a mixture of stenols and stanols)	Fats of higher plants, particularly cereals	Apparently not absorbed by mice, rats or rabbits (Schoenheimer, 1931; Breusch, 1938). Tritium-labelled sitosterol slightly absorbed by man ($<1\%$) and rat (Gould, 1954). Mixed leaf sterols (^{14}C-labelled) slightly absorbed (*c.* 5%) by guinea-pigs (Duncan, 1954). Presence affects absorption of cholesterol (see text)
β-Sitosterol		Converted to β-coprositostanol by rats (Rosenheim & Webster, 1941)
Stigmasterol	Soya bean	Not absorbed by rats or mice (Breusch, 1931; Rosenheim & Webster, 1941)

Cholesterol is absorbed by all animals studied, but the extent varies with different species (see Cook, 1952). The rabbit possesses a marked capacity for absorbing

cholesterol, but in man the absorption is poor (see Cook, Edwards & Riddell, 1956). The 3α-ol-epimer (*epi*cholesterol) is but poorly absorbed, which suggests that esterification is an important process in the absorption of sterols.

It is often stated that the saturated sterols are not absorbed, but cholestanol is well absorbed by the rabbit and is as atherogenic as is cholesterol (Cook, Kliman & Fieser, 1954).

The C_{28} and C_{29} sterols are poorly absorbed. The faeces of herbivorous animals contain only these sterols which are presumably derived from herbage.

The interesting observations of Peterson and his colleagues (e.g. Peterson, Nichols & Schneour, 1952) that the administration of plant sterols decreases the absorption of exogenous cholesterol in chickens has been extended by Pollak (1953) to experiments on man. The effect in man is similar and has been confirmed by other workers. The mechanism of the action is obscure but may be related to a competitive inhibition of the esterification reaction.

In conclusion, some of the roles and pathways of cholesterol in organisms have been surmised but a clear-cut picture eludes us as yet. Cholesterol and related sterols present indeed a challenge to the biochemist.

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