Textbook of Pharmacology

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SECOND EDITION

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Preface

We were pleased by the success of the first edition; however, it was not without its deficiencies. We were sufficiently impressed by the kind and constructive criticisms made by many of our readers to take heed of their comments, most of which have been incorporated in this volume. It is now more than a decade since the first edition was published. In the intervening years, pharmacology has advanced to an extent that has necessitated the addition of much new material and radical revision of the previous text. In addition we have changed the structure of the book.

Our experience of teaching and examining in the subject, not only in Australia and the UK, but also in other English-speaking countries in Africa and Asia, has given us a profound and humble respect for the enthusiasm and interest of students and their teachers, and for the depth of their knowledge. Obviously, in the relatively short duration of a first degree, it is impossible for any student to become an expert in all aspects of the subject, but each University attempts to engender enthusiasm by teaching some facets in depth. Our attempt to cater for all has resulted in a much larger and more comprehensive treatise than the first edition. All components have been expanded, some, such as endocrinology, the chemotherapy of infections and of cancer, and pharmacokinetics, greatly so. A number of new subjects have been added, including drugs used in skin disorders, drugs of abuse and dependence, and pharmacologically active constituents of food.

One of the problems of pharmacology for students, and even for professional pharmacologists, is that the subject matter may be presented simply as boring lists of drugs and their properties. Such lists, in the form of pharmacopoeias, formularies and prescriber's handbooks, provide valuable and indeed essential repositories of information about drugs. However, attempts to teach or to learn the subject in this way have stultifying effects on both teachers and students, and divorce it from other closely related subjects. Our approach to pharmacology is to give it a central place within the nexus of the biomedical sciences such that there are no clear lines of demarcation with, for example, biochemistry, physiology, pathology and microbiology. Accordingly, we have written about drugs and their effects in the context of a background of the relevant portions of related biomedical sciences. We believe that this approach makes pharmacology more interesting to learn and provides a more solid foundation of knowledge for the understanding of the mechanisms of action of drugs and the rationale of drug use. Furthermore, since new drugs are continuously being developed, we hope that a broad approach to the subject will provide a fair degree of understanding of drugs that are yet to be discovered.

There may be sufficient biochemistry, physiology, microbiology and pathology in this book to satisfy the basic requirements of undergraduates studying pharmacology within a pharmacy course. This may especially be the case in those pharmacy schools in which teaching in the related biomedical sciences is largely the responsibility of the pharmacologists. However, we do not pretend to have produced a textbook which is adequate for any subject other than pharmacology. For institutions other than pharmacy schools, and especially in medical schools where the main biomedical sciences are generally taught separately, we hope to have provided a framework for integration that will help the student, at least, and possibly the teachers in the other subjects. We also hope that this book will be found useful by those engaged in research into various aspects of pharmacology, either as the central theme of their research or as a peripheral offshoot of research which is primarily in another discipline. Finally, we hope that our pharmacologist colleagues all over the world will find the book of interest and our approach to the subject of some use to them.

We did not write this book without important assistance from our colleagues which has ranged through constructive criticisms of manuscripts, helping with proof corrections and, in some cases, actual contributions of material. In particular, we would like to thank Professors G. Burnstock, P. Chang, A. E. Doyle, W. M. Hutchison, P. I. Korner, W. J. Louis, J. R. Parratt and C. Raper, and Drs Mary K. Clegg, W. F. Dryden, G. J. Dusting, B. L. Furman, A. L. Green, A. L. Harvey, J. Jackson, Kathleen A. Kane, F. J. Laska, E. Malta, I. G. Marshall, R. J. Marshall, L. Roller, M. Martin-Smith, Marian W. McCulloch, M. W. Nott, M. Parker, J. L. Paterson, K. Paterson, Jocelyn N. Pennefather, G. T. Roberts, I. W. Rodger, Anne Stafford, D. F. Story, R. M. Wadsworth, N. G. Waton and I. J. Zeitlin for their valuable contributions. A number of other contributions are acknowledged in Table headings and Figure legends. We are also very grateful to Margaret H. Perry and Ilse Rand for uncomplainingly typing and retyping successive drafts of the manuscript, to Dr. David Story for devising a computer programme for indexing, to Elaine Sonerson and Kate Osborn for typing the computer tapes and the index, to Nigel Palmer, Linda Adler and Rosemary Walton of Blackwell Scientific Publications for their help and for their tolerance and forbearance, and to Per Saugman, Chairman and Managing Director of Blackwell Scientific Publications without whose interest and encouragement the book would not have been published.

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Chapter 1
Constituents of Tissues

The chemical substances of which tissues are composed are, at the most fundamental level, the sites of drug action. The chemical reactions between drugs and the components of the biological system on which they act have resultant effects which may be more or less complicated, depending on the particular interlocking biochemical and physiological mechanisms that are modified as a result of the reactions. With some drugs the nature of the chemical reactions underlying their effects are unknown or are a matter of conjecture, but the reactions of many drugs with constituents of biological systems are known. This chapter contains an account of some of the more important constituents of mammalian tissues, and particularly of the human body, which are the chemical partners to the drugs in the reactions leading to the biological effect.

THE ELEMENTAL COMPOSITION OF LIVING MATTER

Living matter contains fewer than one-third of the chemical elements (Fig. 1.1). Only hydrogen, carbon, nitrogen and iodine are found in higher concentrations in the human body than in the earth's crust. Six other elements are found in roughly the same proportions: oxygen, phosphorus, sulphur, chlorine,

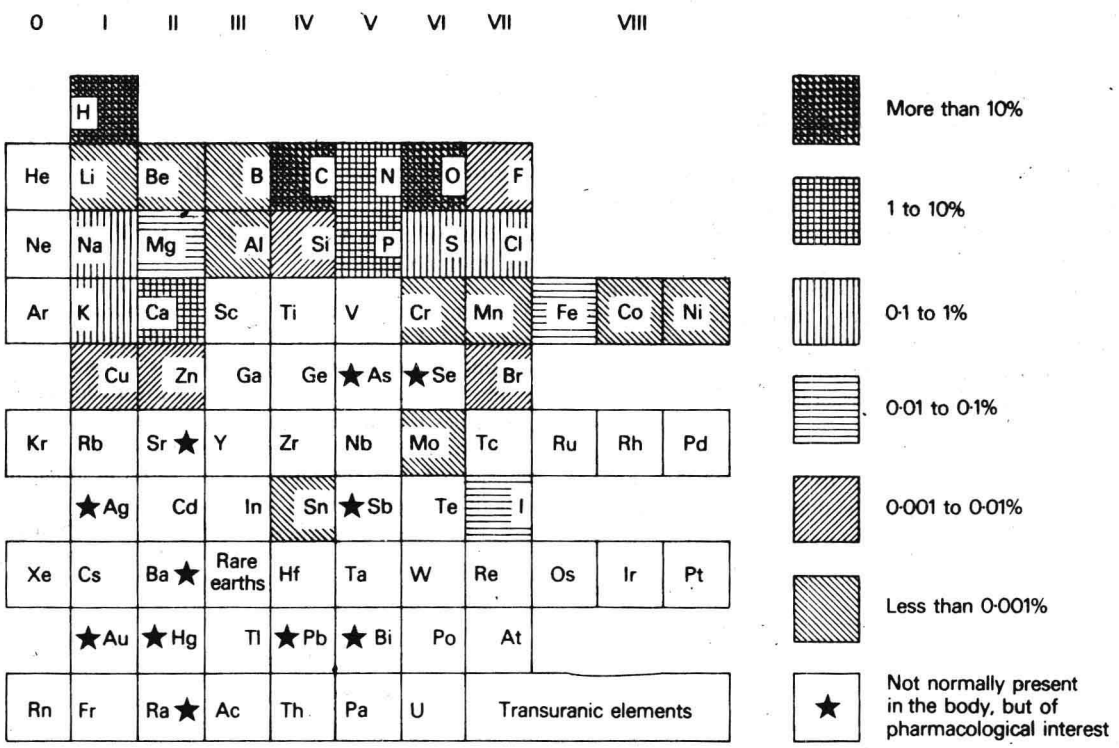


FIG. 1.1. A periodic table of the elements showing their relative abundance in the human body.

potassium and calcium. The remaining elements are at least ten times more abundant in the earth's crust than in the body. The relative abundance of an element in the body is no guide to its importance; some elements which are present in trace amounts of 10 parts per million (0.001 %) or less may be essential for health if not for life itself.

Some of the elements that are designated in Fig. 1.1 as 'not normally present' in the body may in fact be present in some circumstances, particularly if they are taken up from the environment into the body from food, drink and the air. Exposure to mercury, lead, arsenic or selenium, for example, may occur because of a naturally high level due to the geological features of a region or they may be the result of pollution in certain areas: if sufficiently high amounts of these elements are accumulated they may cause serious toxic effects.

Certain organisms may accumulate considerable amounts of elements that do not normally occur in the human body. Thus the ascidians (sea squirts) contain vanadium, niobium, tantalum, chromium and tungsten as well as the heavy metals occurring in the human body. In the ascidians, these metals appear to be involved in the analogous physiological processes in which iron plays a role in higher animals, namely, oxygen transport and electron transfer reactions. Selenium is known to be an essential trace element for sheep, although excess is toxic; it is thought by some to be essential for man.

Apart from hydrogen, oxygen is the element present in the human body in the greatest amount, comprising about 65% of the total (by weight). Most is combined with hydrogen as water. It is generally recognized that the primeval life forms developed in the waters of the earth and the evolution of animals progressed a considerable distance in the sea before terrestrial forms emerged. The heritage of our remote origins is still contained within us—the most abundant compound constituting the human body is water which contributes 45 to 75% by weight. The exact amount depends principally on age, sex and build: relatively, infants have more than adults, men more than women, and the lean more than the obese; there may also be considerable differences between health and disease and the water content of the body may be affected by drugs.

The next most common element is carbon which accounts for about one-half of the dry weight of tissues (other than bone). The unique nature of living matter is due to its organic constituents—that is, compounds based on a carbon skeleton. In fact, the word organic is derived from the outmoded idea that complex carbon-containing compounds require the vital processes of life for their formation. As will emerge later, the uniqueness of life arises directly from the complexity of the organic constituents.

There are important inorganic constituents of the body, in addition to water. Sodium, potassium and chlorine are present as the ions, and so is part of the calcium, magnesium, iodine and bromine. Other important ions occurring in living matter, apart from those formed from organic acids and bases, are bicarbonate, ammonium, phosphate and sulphate. The bony skeleton and the teeth are composed of calcium and magnesium phosphates and the teeth contain lithium fluoride as well. Additional important inorganic compounds include carbon dioxide and oxygen. Most of the nitrogen, sulphur and iodine, and the heavy metals, are incorporated into or linked to organic molecules. About one-tenth of the phosphorus is combined with organic compounds which are largely concerned with the storage and transfer of energy (see pages 1.34–35).

Living matter may therefore be considered as a matrix of insoluble organic compounds and minerals which supports and contains an aqueous medium containing organic colloids, dissolved organic compounds, gasses and electrolytes.

The bulk of the organic substances of living matter may be classified into three major divisions: carbohydrates, lipids, and amino acids and their complexes (principally proteins). These divisions by no means exhaust the variety of organic substances that are present in the tissues, but they serve as convenient starting points.

The relative amounts of the major groups of substances in four tissues are shown in Table 1.1.

CARBOHYDRATES AND RELATED SUBSTANCES

The term carbohydrate originally signified substances having the empirical formula $(CH_2O)_n$ and comprised the substances commonly known as sugars and their polymers. This meaning is too restrictive since there are many biologically important molecules having significant physiological roles and properties of pharmacological interest which can, for convenience, be considered together with carbohydrates although they are not strictly 'carbon hydrates'. There are a number of terminologies, none of which is entirely satisfactory in defining the group.

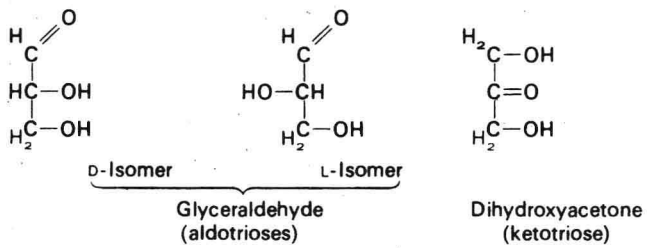
TABLE 1.1. Approximate relative proportions of the major constituents of some mammalian tissues (percentages of total by weight)

	Water	Inorganic constituents	Carbohydrates	Lipids	Proteins	Other organic compounds
Muscle	75	1	0.6	3	19	1
Blood	79	0.9	0.1	1	19	0.2
Brain	78	1	0.1	12	8	1
Bone	22	45	Low	Low	30	Low

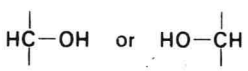
Thus, simple sugars or their derivatives may be termed *saccharides* and their polymers are *polysaccharides*. The term *glycose* may be used for any monosaccharide, and the polymers are *glycans*.

GLYCOSES

The simplest carbohydrates contain 3-carbon atoms and are known as *trioses*. There are three:

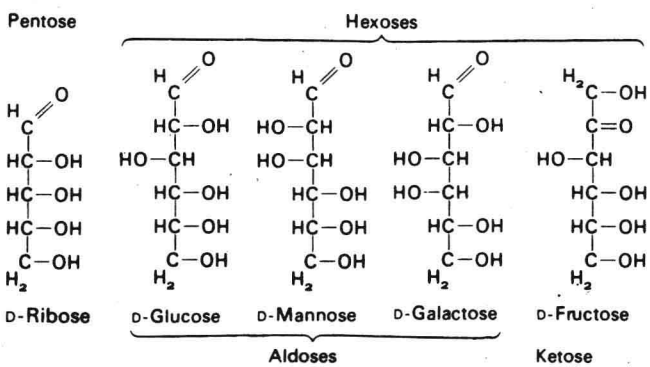


The glycoses with longer carbon chains may be considered as derivatives of the trioses that are formed by inserting the groups



between the carbon carrying the carbonyl oxygen, which may be an aldehyde or a ketone group, and the carbon below it. This gives rise to two families; the *aldoses* and the *ketoses*. The generic name of a glycose also includes a reference to the numbers of carbons in the chain; there are *tetroses*, *pentoses*, *hexoses* and *heptoses* in ascending order.

Aldotriose contains an asymmetric carbon atom and gives rise to two series, the D-aldoglycoses and the L-aldoglycoses. Each additional group is also asymmetric, so there are four aldotetroses, eight aldopentoses and sixteen possible aldohexoses. In the ketose series, the first asymmetric group appears with the tetroses, so there are four ketopentoses and eight ketohexoses. All of these simple sugars (or glycoses) are known, but the five whose formulae are given below are the most commonly occurring and the most important; they are all in the D-series. The most familiar property of sugars is their sweet taste; of the glycoses, the sweetest is fructose.



Optical isomers

The presence in an organic molecule of an asymmetric carbon atom, that is, one to which four different groups are joined, gives rise to optical activity. As with the triose glyceraldehyde mentioned above, there are two isomers which are related to each other as mirror images. A solution of an optically active isomer causes the rotation of the plane of polarization when polarized light is passed through it. The direction of rotation is designated *d* or (+) if it is dextro-rotatory and *l* or (−) if it is laevorotatory. With any pair of optical isomers the sign of rotation differs, one will be *d* and the other *l*, but the degree of rotation is the same for each. The configuration of the isomers may also be designated in terms of the absolute structures; by convention, the absolute configuration is determined by the relationship of a particular isomer to the isomers of glyceraldehyde, to which the prefixes D- or L- were arbitrarily assigned. In order to understand this, it is necessary to visualize the three-dimensional structure of the molecules as represented in Fig. 1.2. In the projection formula of the glycoses, the convention is to represent the molecule in such a way that the —H and —OH groups on the asymmetric carbon furthest from the aldo- or keto-group are projecting upwards at an angle out of the plane of the paper. The configuration of the groups on this carbon determines whether a compound is in the D- or L-series of glycoses, by reference to the

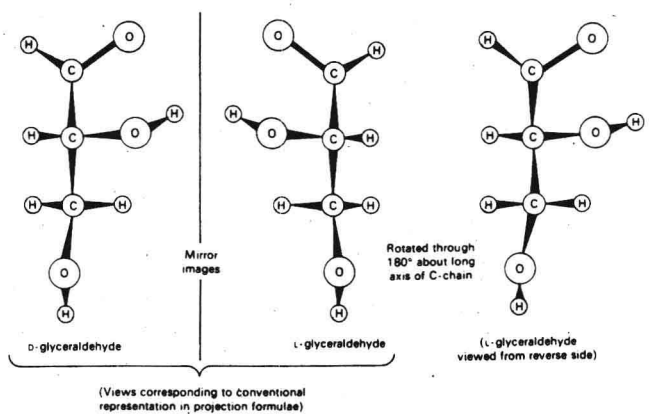


FIG. 1.2. Optical isomers of glyceraldehyde. The bonds represented as ▬ are not in the plane of the paper; the broader end is slanting towards the reader, the thinner away from him.

configurations of D- and L-glyceraldehyde. These absolute configurations need not correspond to the *d* or (+) and *l* or (−) which indicate the direction of rotation of polarized light, and both concepts may be included in the name of a compound, as in D-(+)-glyceraldehyde or D-(+)-glucose, but note that the commonest naturally occurring form of fructose is D-(−)-fructose.

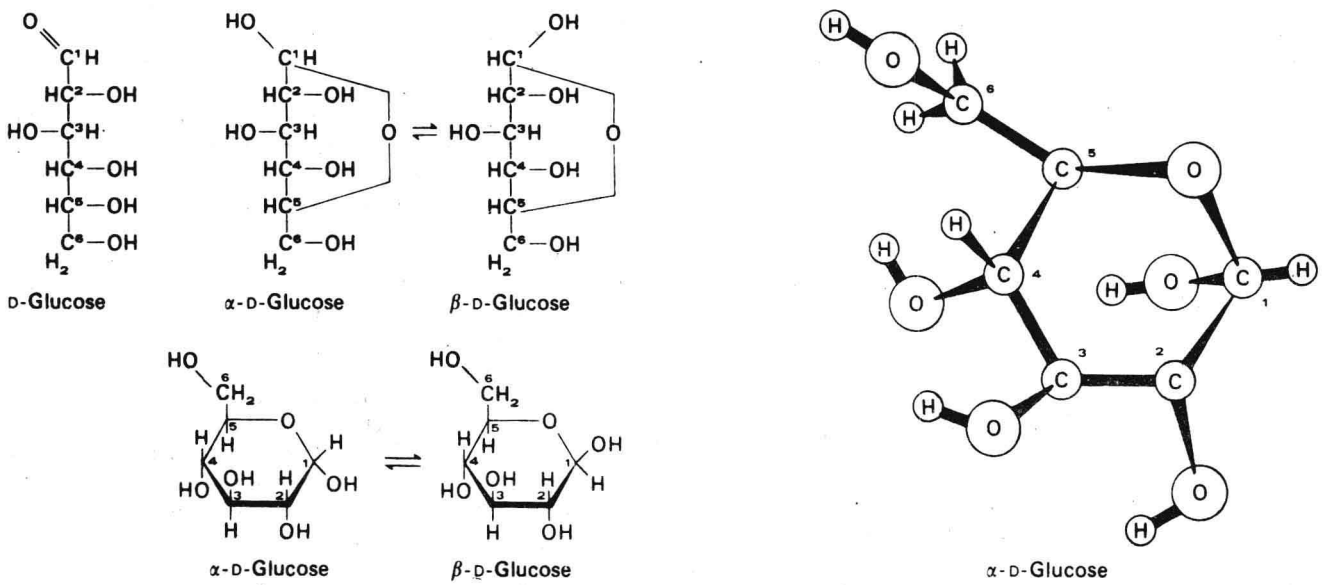
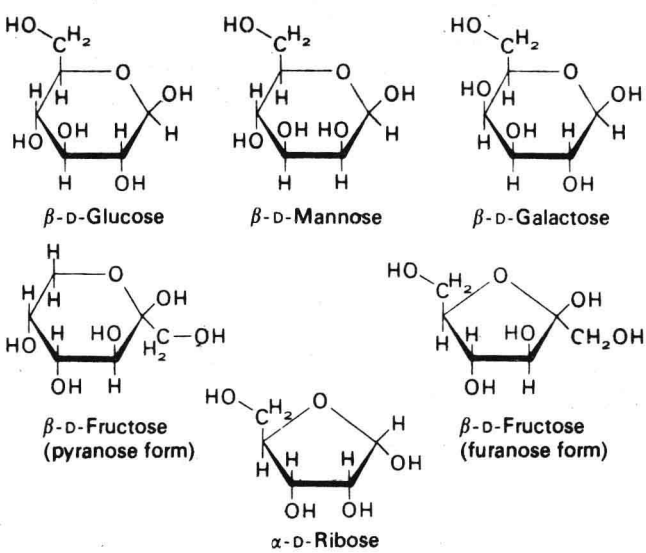


FIG. 1.3. Representations of the structural formula of glucose. Corresponding carbon atoms in the various formulae may be identified by the index numbers 1 to 6.

Configuration of glycoses

Glucose and other glycoses were represented as straight chain compounds in the formulae given above for convenience in showing the relationship between the aldo- and keto-series and the D- and L-forms. There are a number of other representations, each having some heuristic value. These are summarized in the case of glucose in Fig. 1.3. The straight chain representation of the formulae of the glucose molecule is known as a Fischer projection model, after the chemist who was mainly responsible for elucidating the primary structure of the glucose isomers, and the one shown is in the D-series because of the conformation about C-5. The molecule contains an internal oxygen bridge between C-1 and C-5, and this introduces a further centre of asymmetry on C-1, the isomers being designated α and β. Providing the hydroxyl oxygen on C-1 is not involved in bonding to another molecule, there is an equilibrium mixture of the α and β forms which are said to constitute an anomeric pair. If one of the forms is prepared, it slowly changes to the equilibrium mixture in solution. The representation of the carbon chain with the oxygen bridge as a ring structure was originally due to Haworth. In the Haworth formula, the ring is considered to be projecting forward from the plane of the paper, groups pointing upward from carbon atoms are (more or less) above the plane of the ring, and those pointing downwards are below. In the D-series, C-6 is represented as shown in the figure and in the L-series it is drawn within the ring. The anomeric pair may be represented by drawing the substituents on C-1 at angles. The ball-and-stick model of the glucose formula shows that the ring is not in fact planar, but is buckled. It should be remembered that there is free rotation of the carbon–oxygen bonds formed with the C-1, C-2, C-3, C-4 and C-6 atoms, so the hydrogen atoms of the hydroxyl groups do not necessarily take up the positions shown in the figure; similarly, the bond between C-5 and C-6 may rotate. The 6-membered oxygen-containing ring structure for glucose is known as the *pyranose* form. The other aldohexoses also assume a pyranose form, but the aldopentoses (e.g. ribose) are in a 5-membered ring known as the *furanose* form. The ketohexoses (e.g. fructose) may be in either the pyranose or the furanose form. The Haworth representations of the more important glycoses are shown below:

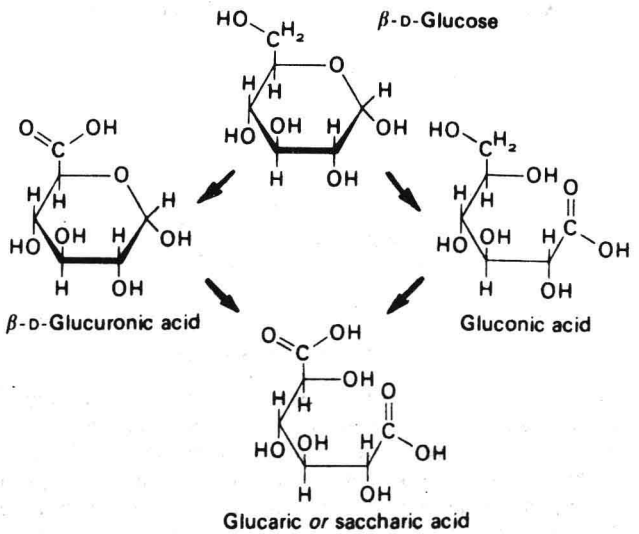


Derivatives of monosaccharides

Some of these derivatives and polymers containing them are of considerable pharmacological importance.

Acid derivatives

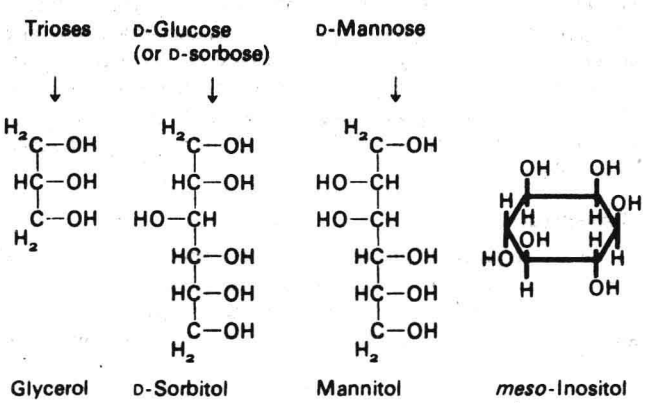
Oxidation of the aldehyde group on C-1 of the aldohexoses, or of the alcohol group on C-6, or of both groups gives rise to acids. Taking glucose as an example the three acid derivatives are as follows:



Similarly, galactose gives rise to galacturonic acid and the dicarboxylic galactaric (or mucic) acid. The acids with the carboxyl group on C-6 are known as *uronic acids* because of their presence in urine, generally as conjugates with other substances, including many drugs.

Polyhydric alcohols

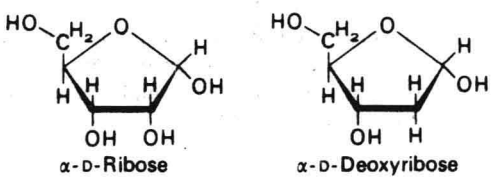
Reduction of the aldose or ketose group of glycoses yields polyhydric alcohols. Some examples are given below:



Glycerol is considered in more detail later as a constituent of lipids. It retains water and is used in many pharmaceutical preparations for application to the skin as an emollient. It has a soothing sweet taste and is used as a demulcent in preparations taken by mouth; it has a mild laxative action due to water retention in the gut. Sorbitol has similar properties and uses. It occurs naturally in many fruits. Being less well utilized metabolically than sucrose and fairly sweet (about half as sweet as sucrose), D-sorbitol is used as a sweetener in diabetic diets. Mannitol is not metabolized; it is given by injection as an osmotic diuretic and to facilitate the osmotic removal of fluid from the eyeball in glaucoma. Cyclic polyhydric alcohols have the same empirical formulae as carbohydrates. One of them, *meso*- or *myo*-inositol, is present in muscle and nervous tissue. It is thought to be an essential growth factor and may be classified as a vitamin (page 43.18); it functions as a coenzyme in lipid and carbohydrate metabolism.

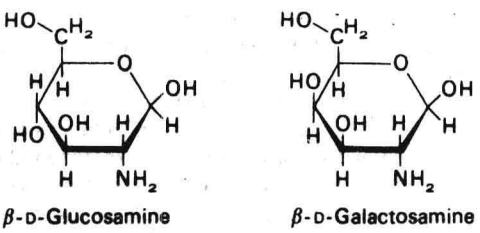
Deoxyglycoses

These are formed by reduction of a hydroxyl group. The most important is deoxyribose; it is present in DNA, that is deoxyribonucleic acid (page 3.1). Its relationship to ribose, the sugar in RNA or ribonucleic acid, is shown below:



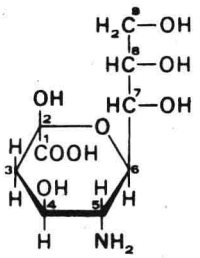
Aminoglycoses

Replacement of a hydroxyl by an amino group yields a glycosamine:

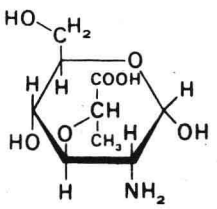


Glucosamine and galactosamine and their *N*-acetyl derivatives are widely distributed in polymeric constituents of tissues of structural and functional importance. Certain other derivatives of aminoglycoses are also important, particularly as constituents of cell membranes. *Muramic acid* and glucosamine, as their *N*-acetals, are present in bacterial cell walls (page 34.3 *et seq*). *Neuraminic acid* is derived from a nonose (a 9-carbon glycose). Its *N*- and *O*-acetyl derivatives, which are known as *sialic acids*, and their *N*-glycol derivatives are widely distributed in tissues where

they occur as constituents of glycolipids, gangliosides and glycoproteins. These are present in mucus secretions, milk, and in cell membranes where they are thought to be the sites at which viruses attach and penetrate into the cell. Aminoglycoses are present in some antibiotics (pages 3.19 and 34.40). The structures of neuraminic and muramic acids are shown below:



Neuraminic acid
(Note: the pyranose ring is shown, for convenience, from the opposite of the usual side, as indicated by numbering of carbon atoms)



Muramic acid

Glycose esters

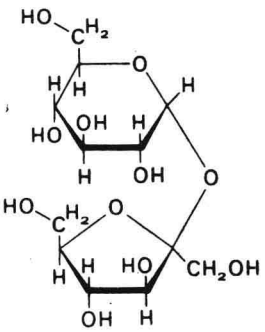
Esters of trioses, glucose and fructose with phosphoric acid are concerned in carbohydrate metabolism (see page 2.13 *et seq*). Esters of glucose and galactose with sulphuric acid are constituents of many polysaccharides.

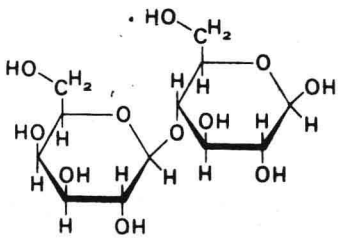
Glycosides

The glycoses and their derivatives can form ether-type links through the oxygen attached to C-1 with a hydroxyl group of another glycose or with alcoholic hydroxyl groups of other molecules, the nonglycose portion being termed the *aglycone*. Glycosides of pharmacological importance include the cardiac glycosides (see page 22.74) in which the glycone is steroidal and the glycoses are often of relatively rare occurrence. A number of vitamin-like compounds belonging to the *vitamin P* group (see page 43.18) are glycosides. *Phlorizin* is a poisonous glycoside found in the roots of certain fruit trees which blocks some of the actions of insulin and is used to produce experimental diabetes. *Amygdalin*, a glycoside which occurs in almonds and other plant material, yields benzyl cyanide on hydrolysis and has been the cause of poisoning in livestock. Glucuronic acid forms glycoside links with many normal products of metabolism and with some drugs. These compounds are termed *glucuronides* (page 26.14).

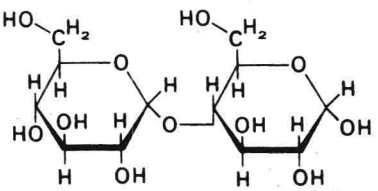
Disaccharides

The disaccharides are formed by a glycoside link between two glycoses. The most important are sucrose, lactose and maltose:





Lactose
(β-1-D-galactosyl-4-D-glucose)



Maltose
(α-1-D-glucosyl-4-D-glucose)

Sucrose is the sugar of commerce and is the sweetest tasting of the disaccharides. The α-glucosyl glycoside link is readily attacked by digestive enzymes. Lactose is present in milk and is also known as milk sugar: it is commonly used as an excipient in pharmaceutical preparations and as a dummy substance (placebo) in drug trials. Maltose is formed in the digestive tract from the breakdown of starches and glycogen.

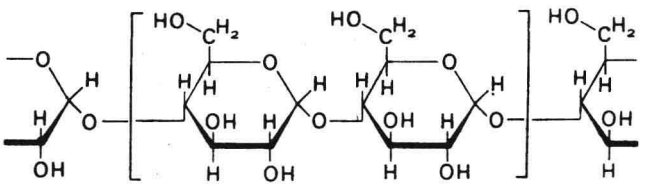
POLYSACCHARIDES OR GLYCANS AND RELATED POLYMERS

Carbohydrates containing from two to ten glycose units per molecule are sometimes termed *oligosaccharides* (*oligo* = a few), the term polysaccharide being reserved for polymers containing more than ten glycose units. Simple polysaccharides, or *homoglycans* as they are also known, contain only one type of glycose unit. Those containing more than one type, and which generally contain some units of glycose derivatives, are termed complex polysaccharides or *heteroglycans*; these include the *glycosaminoglycans* (containing glycosamine units) and other *mucopolysaccharides* with sulphate or sulphate and amino groups attached to glycose units.

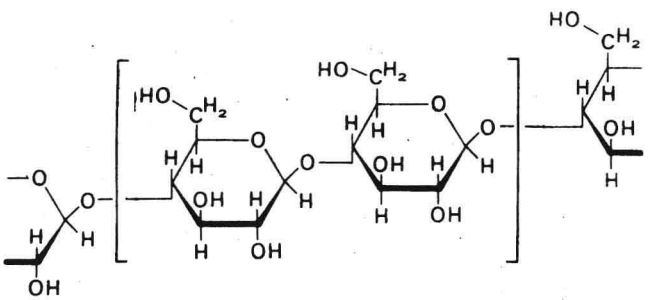
Homoglucans

These are polymers of glucose. The most common in nature are the starches based on α-1-4 links and cellulose based on β-1-4 links. The distinction is important since the digestive enzymes of animals can attack starches but not cellulose, although the

digestive tracts of most herbivorous animals contain symbiotic microorganisms which break down cellulose to constituents utilizable by the host. The repeating units of starch and cellulose are shown below:



Portion of starch chain with glucose residues linked through the α-1 and 4 positions (maltose units shown in square brackets)



Portion of cellulose chain with glucose residues linked through the β-1 and 4 positions (cellobiose units shown in square brackets)

Starches

These may be regarded as storage depots of glucose in plant tissues. They constitute the major carbohydrate portion of the diet. The various forms differ in molecular weight and in the number and arrangements of side chains. Plants also contain *amyloses* and *amylopectins*. Amyloses consist of 200–300 glucose units in a straight chain whereas amylopectins have more than 1000 units including side chains formed through 1-α-6 links. *Dextrins* are formed by partial hydrolysis of starches.

Glycogen

This is the storage form of glucose in animal tissues. The human body contains about 0.5 kg, of which about half is in the liver and most of the remainder is in muscle. The molecular weight of muscle glycogen is about 10^6 and that of liver is 5×10^6 to 10^9. There is much branching of the chain through 1-α-6 links. The polymer molecule forms an elongated ovoid with branching on every 3rd to 5th glycose unit in the centre reducing to every 10th to 14th on the periphery.

Cellulose and some cellulose derivatives

The cellulose polymer functions chiefly as a structural component of plant tissues. Its importance as a constituent of human food is in providing bulk in the diet. Some cellulose derivatives have pharmaceutical and pharmacological importance. Products formed by the addition of methyl or carboxymethyl groups to cellulose preparations, to form *methylcellulose* and *carboxymethylcellulose* have the property of swelling in water. They are included in some tablets and capsules to facilitate disintegration and dispersal of drugs. They are also used to provide bulk in low-calorie diets and as bulk laxatives (see page 25.33). Yet another use is to stabilize liquid preparations of insoluble drugs. *Cellulose nitrate* dissolved in an ether–ethanol mixture is *collodion*. When it is applied to the skin the solvent evaporates to leave a tough protective film which is used to protect superficial injuries. *Oxycellulose* is a substance in which some of the primary hydroxyl groups (on C-6) have been oxidized to carboxylic groups. It is used as a haemostatic; that is, to arrest bleeding. When the material is exposed to a fluid containing calcium ions, such as the blood plasma, cross-linkages are formed between the $-COO^-$ groups and Ca^{2+} ions, the oxycellulose forming in effect an artificial clot (see page 21.23).

Dextrans

These are glucosans formed through 1-α-6 links and having molecular weights of 10^4 to 10^7. They are made industrially by bacterial action on a sucrose substrate. Solutions of dextrans with viscosity and colloid osmotic pressure similar to that of plasma are used as blood substitutes (see pages 28.14–15). Derivatives of dextrans which have been cross-linked are known by the trade name of *Sephadex*®. The solid polymer forms cages with dimensions approximately those of macromolecules of biological interest, including polypeptides, proteins, and polysaccharides. Mixtures of substances of different molecular weights may be separated by filtration through an appropriate Sephadex® when the molecules larger than the cage size pass through readily, but smaller molecules which can enter the cages are entrapped. Sephadex® has been termed a 'molecular sieve'. *Dextran sulphate* acts like heparin, which it resembles in molecular weight and ionic charge (see below).

Other homoglycans

Many polymers of glycoses other than glucose are known, but only two are of particular interest here:

Inulin

This is a fructan, the molecule being composed of about 35 fructofuranose units with 2-β-1 links. It occurs in tubers of dahlias and Jerusalem artichokes. Being readily soluble in water and not metabolized, it is used in diagnostic tests of renal function. It does not pass through cell membranes and is used experimentally to determine the extracellular space of tissues.

Agar

This may be regarded as a galactan being largely composed of D- and L-galactose units. It occurs in certain seaweeds. It forms a gel with water and is used to provide a base for media in bacteriological experiments. It is not digested and is used as a bulk laxative (page 25.33).