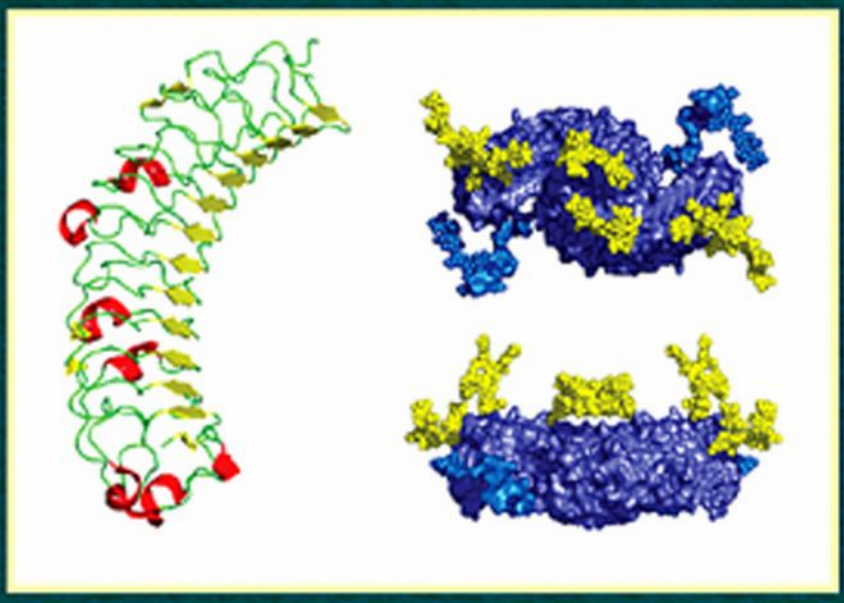
Carbohydrate Chemistry, Biology and Medical Applications



EDITED BY
Hari G. Garg • Mary K. Cowman
Charles A. Hales

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Dedication

To my wife, Mithlesh, and our children, Ashima and Arvin, for their loyal support and generous love.

Hari G. Garg

To my husband, Gene, and our son Rudd, for their loyal support and generous love.

Mary K. Cowman

To my wife, Mary Ann, and our sons, Sam, Chris, and John, for their loyal support and generous love.

Charles A. Hales

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Preface

Carbohydrates are one of four major classes of biologically important molecules, the others being nucleic acids, proteins, and lipids. Historically, carbohydrate studies have dealt mainly with the structure and role of monosaccharides and small oligosaccharides (such as glucose, fructose, sucrose, and lactose) in cellular metabolism and fermentation processes, and the roles of polysaccharides such as cellulose in cell wall organization, and starch and glycogen as storage forms of glucose. The last fifty years have seen an explosion of knowledge about complex carbohydrate structures and their biological functions. First came structural studies that elucidated the role of cellulose in plant cell walls and chitin in invertebrates, as fibrillar assemblies providing mechanical strength. The glycosaminoglycans, their proteoglycans, and other network-forming polysaccharides such as alginates were found to give support to the polysaccharide or protein fibrillar components of the extracellular matrices of both plant and animal tissues. Thus mechanical and physical properties (tensile strength, viscoelasticity, osmotic pressure) were understood to depend on polysaccharides. More recently, other important roles have been elucidated for oligosaccharides, polysaccharides, glycoproteins, glycolipids and other complex glycoconjugates. These roles depend on specific receptor-ligand interactions, and control not only the organization of the pericellular and extracellular matrices, but also a myriad of cellular activities such as changes in gene expression through signaling pathways. Pathogen-host interactions, response to growth factors, inflammation, wound healing, a number of genetically linked disorders, and many other physiological processes depend on specific carbohydrate structures and interactions. This book is intended to assist physicians, glycobiologists, pharmaceutical scientists, and graduate students to gain an understanding the complex nature and functions of carbohydrates. The 17 chapters in this volume, written by renowned scientists and physicians working in the carbohydrate field, provide a broad overview of the chemistry, biology, and medical applications of carbohydrates.

The first four chapters deal with different aspects of carbohydrate chemistry. In Chapter 1, Derek Horton discusses the development of carbohydrate chemistry and biology from antiquity to the present and beyond and summarizes the structures and methods for structural analysis of complex carbohydrates. In Chapter 2, Bo Xie and Catherine Costello review the state-of-art application of mass spectrometry to the structural analysis of complex carbohydrates. In Chapter 3, Zhongwu Guo briefly summarizes the types of glycosylation methods and synthetic strategies that are commonly used in the chemical synthesis of glycoconjugates. Enzymes have simplified the synthesis of some oligosaccharides, and in Chapter 4,

Doris Su *et al.* review the enzymatic synthesis of oligosaccharides and their conversion to glycolipids.

Chapters 5–10 focus on the GAGs and heavily glycosylated proteins, that is, PGs. Malfunction either in the synthesis or in the breakdown of these macromolecules is associated with numerous human diseases. In Chapter 5, Mara Ludwig describes the contribution of different PGs to lung biology. Chapter 6, which includes the PGs of intervertebral disk, is by Peter Roughley. In Chapter 7, Paul Scott focuses on skin and its small leucine-rich repeat PGs. In Chapter 8, Masahiro Zako and Masahiko Yoneda discuss the role of GAGs in ocular pathogenic conditions. In Chapter 9, Michael Roth *et al.* summarize the biological functions of GAGs. In Chapter 10, Jin Xie *et al.* describe the physiological, pathophysiological, and therapeutic roles of heparin and heparan sulfate.

Carbohydrates are critical for biological activity. Chapters 11–17 address the therapeutic and diagnostic medical applications of carbohydrates. In Chapter 11, Andrew Burd and Lin Huang describe the use of carbohydrate polymers in wound dressings. In Chapter 12, Günther Boehm *et al.* review oligosaccharides in human milk and infant formulas. In Chapter 13, Michiko Fukuda *et al.* describe the role of cell surface carbohydrates in development and disease. In Chapters 14 and 15, Endre Balazs and Philip Band, and Luis Avila *et al.*, respectively, detail the medical use of hyaluronan-based therapeutic products and drug delivery and medical applications of chemically modified hyaluronan. Chapters 16 and 17 by Xichun Zhou *et al.*, and Tim Horlacher *et al.*, respectively, describe carbohydrate microarrays, which are being used to address specific challenges in carbohydrate research to provide novel medical diagnostic approaches and to unravel the functions of carbohydrates in health and disease.

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Chapter 1

The Development of Carbohydrate Chemistry and Biology

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I. Early History

A major proportion of the organic matter on Earth is plant tissue ("biomass") and is composed of carbohydrates, principally cellulose. This is the structural support polymer of land plants and the material used since ancient times in the form of cotton and linen textiles, and later as paper. Chitin is a polymer related to cellulose that has skeletal function in arthropods and fungi. Other polymeric carbohydrates constitute the structural support framework for marine plants and the cell walls of microorganisms. The sweet carbohydrate of sugar cane, now termed sucrose, has been a dietary item for at least 10 millennia.

Ranking alongside cellulose in abundance is starch, a biopolymer that is the food-reserve carbohydrate of photosynthetic plants, and the closely related glycogen, the storage carbohydrate in the animal kingdom. Starch occurs as microscopic granules in plant storage tissue (cereal grains, tubers), and the process for its isolation was clearly described by Cato the Elder (1): steeping the grains in cold water to swell them, straining off the husks, and allowing the milky suspension to settle to afford, after drying, a white powder. This procedure is essentially the same as the modern corn wet-milling process, and the resultant starch powder is essentially pure carbohydrate whose molecular formula can be expressed as $C_6(H_2O)_5$, hence the term carbohydrate. It was used as early as 4000 BCE in Egypt as an adhesive with the cellulosic fiber of the papyrus plant to make writing material, and early in the first millennium CE for sizing paper and to stiffen cloth (2).

The photosynthetic apparatus in the green plant utilizes solar energy to effect the reduction of atmospheric carbon dioxide in a complex sequence of reactions (3,4) whose net result is the formation of glucose, a simple sugar (monosaccharide)

having the molecular formula $C_6H_{12}O_6$. Subsequent *in vivo* conversions afford carbohydrate polymers (polysaccharides), notably starch and cellulose, along with many related polymers formed from other monosaccharide sugars. In 1811, it was demonstrated (5) that acid hydrolysis of starch led to near-quantitative conversion into glucose, and later (6,7) it was shown that hydrolysis of cellulose likewise afforded glucose.

In the early nineteenth century, individual sugars were often named after their source, for example grape sugar (Traubenzucker) for glucose and cane sugar (Rohrzucker) for saccharose (the name sucrose was coined much later). The latter sugar was subsequently obtained from the juice of the sugar beet. During that century, a number of other simple sugars (monosaccharides) were isolated from acid hydrolyzates of other polysaccharide sources and were given names with the ending "-ose"; these include mannose, xylose, arabinose, and fucose. A nitrogen-containing sugar obtained by hydrolysis of chitin was termed glucosamine, and hydrolysis of milk sugar (lactose) led to galactose.

The name glucose was coined by Dumas in 1838 for the sugar obtained from honey, grapes, starch, and cellulose; 20 years later its molecular formula of $C_6H_{12}O_6$ was established, and subsequently it was shown to be a linear six-carbon aldehyde having hydroxyl groups on each of the chain carbon atoms. Polarimetric studies led Kekulé in 1866 to propose the name "dextrose" because glucose is dextrorotatory, and the levorotatory "fruit sugar" (Fruchtzucker, fructose) obtained by hydrolysis of cane sugar (sucrose) was for some time named "levulose." The French word "cellule" for cell and the "-ose" suffix led to the term cellulose, long before its structure was known. The term "carbohydrate" (French "hydrate de carbone," German "Kohlenhydrate") was applied originally to monosaccharides in recognition of the fact that their empirical composition can be expressed as $C_n(H_2O)_m$. However, the term is now used generically in a wider sense.

II. The Contribution of Emil Fischer

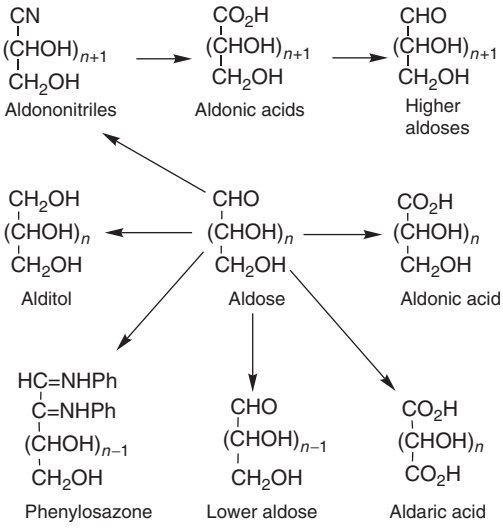
During the last two decades of the nineteenth century, Emil Fischer (8) began his fundamental studies on carbohydrates, showing that phenylhydrazine reacts with glucose, mannose, and fructose to give the same crystalline phenylosazone, and he utilized the reaction introduced by Kiliani, the addition of hydrogen cyanide to a sugar, to give two isomeric acids. In his 1890 address to the German Chemical Society (9), he showed that "Traubenzucker" is a 2,3,4,5,6-pentahydroxyhexanal and that "Fruchtzucker" is a 1,3,4,5,6-pentahydroxy-2-hexanone.

The concept of stereochemistry, developed since 1874 by Van't Hoff and Le Bel, had a great impact on carbohydrate chemistry because it could easily explain isomerism. From extensive chemical manipulations conducted with great skill, coupled with brilliant reasoning, Fischer correlated the families of sugars, and within 10 years, he was able to assign the relative configurations of most known sugars and to synthesize many additional examples (8). He introduced the "lock and key" hypothesis to interpret the action of an enzyme on a glycosidic substrate,

and his monumental achievements inspired a whole generation of researchers in the field of natural products (10).

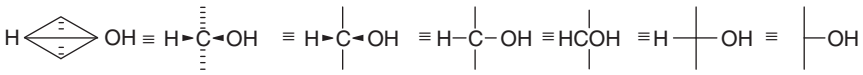
To name the various compounds, Fischer and others laid the foundations of a terminology still in use, based on the terms triose, tetrose, pentose, and hexose. He endorsed Armstrong's proposal to classify sugars into aldoses and ketoses, and proposed the name fructose for levulose because he found that the sign of optical rotation was not a suitable criterion for grouping sugars into families.

The major transformations of the aldoses utilized by Fischer are illustrated in Scheme 1, wherein aldoses are converted by mild oxidation (bromine water) into aldonic acids, by reduction (originally sodium amalgam in ethanol, nowadays sodium borohydride) into alditols, by reaction with phenylhydrazine to form phenylosazones, and by vigorous oxidation (nitric acid) into aldaric acids. Reaction of an aldose with hydrogen cyanide creates a new asymmetric center and affords a pair of isomeric nitriles (termed epimers), convertible by a sequence of transformations (Fischer–Kiliani chain-ascent reaction) into a pair of higher aldoses. A reaction sequence (Ruff degradation) that essentially effects the reverse process converts an aldose into the corresponding lower aldose having one fewer carbon atom in the chain.



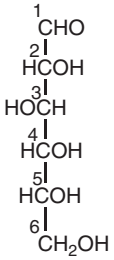
Scheme 1 Major transformations of aldoses.

Emil Fischer introduced the classical projection formulas for sugars, with a standard orientation (carbon chain vertical, carbonyl group at the top, Scheme 2); as he used models with flexible bonds between the atoms, he could easily "stretch" his sugar models into a position suitable for projection.



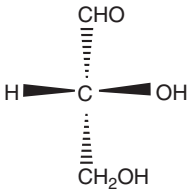
Scheme 2 The Fischer projection formula for a tetrahedrally substituted carbon atom.

He assigned to the dextrorotatory glucose (via the derived glucaric acid) the projection having the OH group at C-5 pointing to the right (Scheme 3), well knowing that there was a 50% chance that this was wrong. Much later, Bijvoet (11) proved Fischer's arbitrary assumption to be correct in the absolute sense, by using a special X-ray technique.



Scheme 3 D-Glucose, Fischer projection.

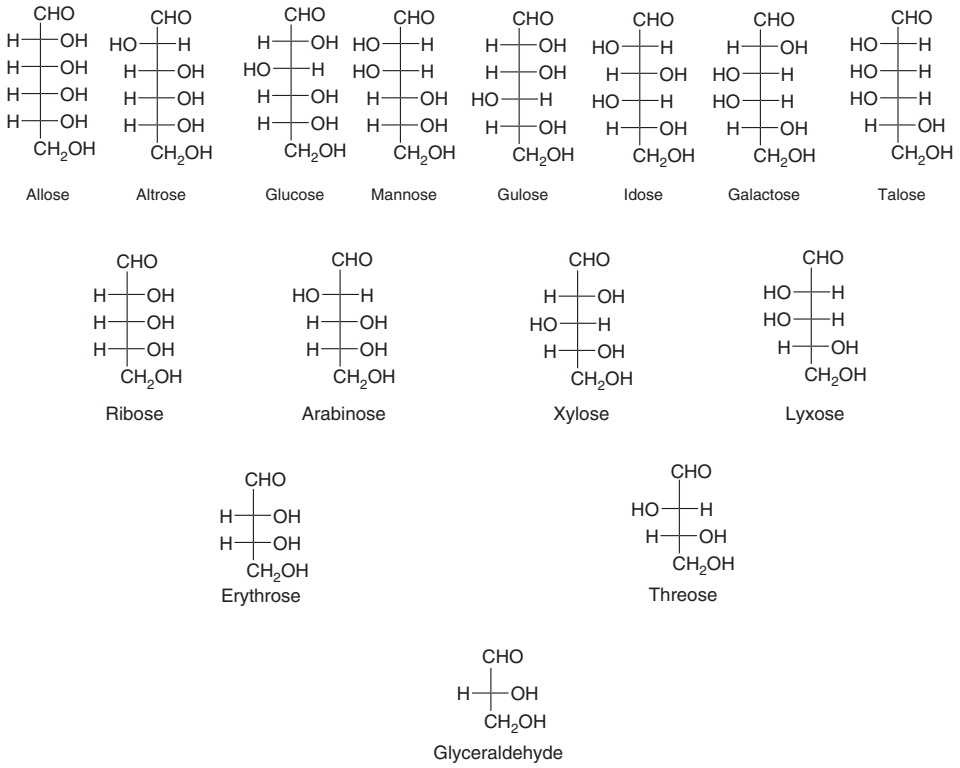
Rosanoff in 1906 (12) selected the enantiomeric glyceraldehydes as the point of reference; any sugar derivable by chain lengthening from what is now known as D-glyceraldehyde belongs to the D series, a convention still in use (Scheme 4).



Scheme 4 D-Glyceraldehyde.

For a sugar having n stereocenters, there are 2^n isomers, so that there are $2^4=16$ aldohexoses, 8 in the D series and 8 in the L series. The names of the D-aldoses and their stereochemical relationships are illustrated in Scheme 5. These names form the basis of the group-configurational designators: *allo*, *altro*, *gluco*,

manno, *gulo*, *ido*, *galacto*, and *talo* for four stereocenters; *ribo*, *arabino*, *xylo*, and *lyxo* for three stereocenters; and *erythro* and *threo* for two stereocenters.



Scheme 5 The D family of aldoses.

The Cahn–Ingold–Prelog *R*,*S* system of stereodesignators (13), introduced much later for naming other natural products, is not used for sugars as it would lead to unwieldy names.

III. Cyclic Forms

Toward the end of the nineteenth century, it was realized that the free sugars exist as cyclic hemiacetals or hemiketals. Individual sugars react with methanol under acid catalysis to give stable products termed methyl glycosides, which are mixed full acetals. These have a new asymmetric center at the original carbonyl atom and were thus isolated as pairs of isomers that were designated as the α and β forms, later termed anomers. In the D series, the α anomer was defined as the one having the more-positive specific rotation, and in the L series, the α anomer